Preemptive light sedation in intensive care unit may reduce pulmonary complications in geriatrics receiving pancreaticoduodenectomy

Tien-Hua Chen[a,b,c], Cheng-Hsi Su[d], Chen-Yuan Hsiao[e,f], Shih-Yi Kao[g], Pei-Jiun Tsai [a,b,h,*]

[a]Institute of Anatomy and Cell Biology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [b]Trauma Center, Department of Surgery, Taipei Veterans General Hospital, Taiwan, ROC; [c]Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, Taiwan, ROC; [d]Department of Surgery, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [e]Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, ROC; [f]Landseed International Hospital, Taoyuan, Taiwan, ROC; [g]Ten-Chan General Hospital Zhongli, Taoyuan, Taiwan, ROC; [h]Department of Critical Care Medicine, Taipei Veterans General Hospital, Taiwan, ROC

Abstract

Background: Patients undergoing pancreaticoduodenectomy (PD) for periampullary lesions are usually elderly with a high risk of postoperative morbidity and mortality. This retrospective cohort study investigated whether postoperative preemptive light sedation aids in recovery of elderly patients following PD.

Methods: Ninety-nine geriatric patients undergoing PD at one hospital were enrolled from 2009 to 2018. Patients in the sedation group received mechanical ventilation support and preemptively light sedation with fentanyl and propofol or dexmedetomidine in the first 5 days postoperatively in the intensive care unit (ICU). Patients in the control group underwent early extubation and received morphine for pain control but no postoperative sedatives in the ordinary ward. Patients in the two groups were matched 1:1 using propensity scoring. The postoperative complication rate, surgical mortality, and postoperative hospital length of stay (LOS) were recorded. We also tested inflammation in an immortal human bronchial epithelial cell line.

Results: After 1:1 matching, 40 patients in the sedation group were compared with 40 patients in the control group. The sedation group had a significantly lower pulmonary complication rate and fewer patients with postoperative gastroparesis. Both groups had similar postoperative hospital LOS and identical surgical mortality rates. Patients in the sedation group had significantly better postoperative quality of life, including less pain and less heartbeat variation. In vitro cell experiments supported the above clinical observations, showing that adequate use of sedatives could significantly elevate the cell viability rate, protect cells from damage, decrease interleukin-6 production, and reduce inflammation.

Conclusion: Postoperative preemptive light sedation in the ICU in geriatric patients following PD may not only reduce the rates of postoperative pulmonary complications and gastroparesis but also improve postoperative quality of life without prolonging the postoperative hospital LOS.

Keywords: Intensive care unit; Pancreaticoduodenectomy; Postoperatively preemptive light sedation;Pulmonary complication; Surgical stress response

1. INTRODUCTION

Cancer of the pancreas is one of the most common cancers worldwide. Tumors in the head of the pancreas and periampullary tumors are usually highly fatal, and >95% of patients die from these cancers.[1] Surgical resection of the head of the pancreas and adjacent regions, a pancreaticoduodenectomy (PD or Whipple operation), is the only potentially curative treatment, but patients with periampullary cancer are usually elderly and may not be eligible for surgery. For example, in Taiwan, 81.2% of males and 84.3% of females with periampullary cancers were older than 65 years.[2] Before the early 1990s, pancreatic resection was considered unsuitable for patients older than 70 years because of the increased morbidity and mortality in this age group. In particular, older patients undergoing surgical procedures for life-threatening illnesses tend to have prolonged intensive care unit (ICU) stays and higher long-term crude mortality.[3–5] Such patients are also at increased risk of deterioration of functional abilities and require greater postdischarge institutional care.[1,6]

A 2003 study examined outcomes for 16 patients 80+ years who received PD. The overall mortality rate was 13%, the morbidity rate was 51% and 69% of patients required care in a surgical ICU for a median 8 days.[2] In 2006, Scurtu et al[7] investigated

* Address correspondence. Dr. Pei-Jiun Tsai, Department of Critical Care Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: pjtsai@vghtpe.gov.tw (P.-J. Tsai).

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70 elderly patients (aged 70–84 years) who underwent PD and were then transferred to an ICU for 6 days. The mortality rate was 0% in patients <75 years and 6.2% in those ≥75 years. The mean hospital stay was longer in patients ≥75 years (19 days), but not significantly so (17 days for those <75 years). The postoperative morbidity rate was also lower in patients <75 years (36.8%), but again this was not significantly different from the older patients (50.0%). In 2009, Hardacre et al.[8] reported the outcomes of 32 patients aged 80 years and older (median age: 82 years) who underwent pancreatectomies. There were no operative deaths, but 66% of patients had at least one complication and the median hospital length of stay (LOS) was 11 days. Furthermore, 59% of these patients stayed in the surgical ICU postoperatively for a median 2.5 days.

The most common surgical complications associated with PD are pancreatic fistula, delayed gastric emptying, intra-abdominal abscess, bleeding that requires transfusion or reoperation, wound infection, and pleural effusion requiring drainage.[9] The most common medical problems associated with PD are cardiac, pulmonary, neurologic, or urinary events.[10] Elderly candidates for PD require careful preoperative evaluation and rigorously controlled postoperative conditions. In general, intensive care can improve the postoperative monitoring and management of physiological status.[10,11] Thus, we hypothesized that postoperative intensive care with preemptive light sedation could ameliorate the surgical stress response and facilitate recovery after PD. Therefore, we conducted a single institution retrospective cohort study to compare the efficacy and safety of postoperative sedation versus usual care in geriatric patients following PD. We also conducted cellular analysis to confirm our findings.

2. METHODS

2.1. Clinical patient data

The hospital Institutional Review Board approved this retrospective cohort study. Patients who had periampullary lesions and received PD from 2009 to 2018 in our medical center were categorized into the sedation group and control group according the postoperative care strategy. The PD procedure is commonly performed in this institution. All enrolled patients were treated by the same pancreas surgery team. All surgical procedures were performed under surgeons with at least 10 years of experience with the PD procedure. The postoperative care for all enrolled patients was similar except for the use of sedation.

Patients in the sedation group were sent to the ICU with mechanical ventilator support immediately after the operation. A fentanyl citrate pump was prescribed as a postoperative analgesic in the ICU and the Behavioral Pain Scale (BPS), a valid and reliable BPS for use in the ICU,[12–15] was used by nurses to assess pain. Propofol and dexmedetomidine were used as the preemptive slight sedatives. A Richmond Agitation-Sedation Score (RASS) of –1 to –2 (light sedation) in the first 5 days after PD was considered optimal. Preemptive light sedation was discontinued at postoperative day 6 and the patient was weaned from the ventilator and extubated as soon as possible after adequate respiratory training. Patients experiencing unplanned endotracheal tube extubation within the first five postoperative days were excluded.

Patients in the control group underwent early extubation after careful evaluation by the anesthesiologist and received no postoperative sedative medication. Patients were excluded from the control group if they could not afford extubation immediately after the operation. An experienced anesthesiologist performed the evaluation process for postoperative extubation according to the perioperative hemodynamic status. Postoperative pain control included intravenous morphine and oral acetaminophen when the patient could tolerate oral intake.

The general exclusion criteria for all patients were as follows: age younger than 75 years, laparoscopic surgery, robot-assisted surgery, presence of an underlying neurological disorder, past history of head trauma, and long-term therapy with a psychiatric medication or sedative.

All major postoperative complications were recorded, including anastomotic leakage, intra-abdominal bleeding, intra-abdominal abscess, gastroparesis, cardiac events, and pulmonary events. Anastomotic leakage was defined as breakdown and subsequent leakage of digestive system fluid from pancreaticogastrostomy, choledochojejunostomy, or gastrojejunostomy. Intra-abdominal bleeding was defined as positive findings on angiography. Intra-abdominal abscess was defined as a pocket of infected fluid and pus (viscous interior) in the belly confirmed by both abdominal computed tomography and bacterial culture. Gastroparesis was defined as the presence of a nasogastric tube with >500 mL drainage by postoperative day 10. Postoperative cardiac events included newly developed arrhythmia and myocardial infarction. Postoperative pulmonary events comprised newly developed pneumonia, lung atelectasis, acute respiratory distress syndrome, and pulmonary edema found by chest plain film.

The primary endpoints were postoperative complication rate and surgical mortality, defined as postoperative 30-day mortality. The secondary endpoint was postoperative hospital LOS. In addition, delirium status assessed by nurses and patient self-reported pain scores (0-10) were recorded during the first 3 days in the ordinary hospital ward. The average heartbeat difference before and after surgery was also recorded.

Statistically significant between-group baseline characters were considered confounding variables. A propensity score was estimated using a logistic regression model and used to match subjects in each group. A 1:1 matching by propensity score was performed using the nearest neighbor method with a caliper width equal to 0.1 SDs. We also examined the balance in baseline covariates in the matched data using standardized differences.

2.2. Cell experiments

The 16HBE cell line (an immortal human bronchial epithelial cell) was cultured in a dish with RPMI-1640 medium (M&C Gene Technology, Beijing, China) which contained 10% fetal calf serum (Gibco, New York, NY, USA), 100 U/mL penicillin, and 100 mg/mL streptomycin (M&C Gene Technology, Beijing, China) in a humid atmosphere of 5% CO_2 and 95% air at 37°C.

16HBE cells were seeded at a density of 2.5×10^5 cells/100 μL/well in 96-well culture plates. The normal control group and different concentrations of H_2O_2 (100, 500, 1000, and 2000 μM) were placed for 60 minutes by group in six duplicate wells. Then 50-μL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 200 mg/mL) was added to each well. After incubation for 2.5 hours, 200 μL of culture medium and MTT were centrifuged and removed. Then, 180-μL dimethyl sulfoxide (DMSO) was added to each well and placed in the cell incubator for 5 to 10 minutes. After the purple crystals were completely dissolved, each sample was measured at 570 nm using a microplate reader. The above experiment was repeated three times, and the H_2O_2 concentration with the cell survival rate closest to 50% was selected as the optimal H_2O_2 concentration. Cell viability (%) = (average absorbance value of the H_2O_2-treated group[/average absorbance value of the normal control group) × 100%.

The 16HBE cells collected by centrifugation were planted in a 96-well culture plate at a density of 2.5×10^5 cells/100 μL/well and were randomly divided into 10 groups of six replicate wells in each group. Except for the normal control group, the other groups were pretreated with the corresponding dose of dexmedetomidine or propofol for 24 hours in the normal medium,

then 20 μL of H_2O_2 (2000 μM concentration) was added for 1 hour to each drug group. The experimental groups were as follows: (1) normal control group, no H_2O_2 treatment (C); (2) 2000 μM H_2O_2 injury group (H); (3) 10 ng/mL dexmedetomidine + 2000 μM H_2O_2 group (H + D 10); (4) 5 ng/mL dexmedetomidine + 2000 μM H_2O_2 group (H + D 5); (5) 1 ng/mL dexmedetomidine + 2000 μM H_2O_2 group (H + D 1); (6) 0.1 ng/mL dexmedetomidine + 2000 μM H_2O_2 group (H + D 0.1); (7) 10 μg/mL propofol + 2000 μM H_2O_2 group (H + P 10); (8) 5 μg/mL propofol + 2000 μM H_2O_2 group (H + P 5); (9) 1 μg/mL propofol + 2000 μM H_2O_2 group (H + P 1); (10) 0.1 μg/mL propofol + 2000 μM H_2O_2 group (H + P 0.1). The cell viability of the groups was determined by the MTT method. For all 10 treatment groups, the supernatant was tested for interleukin (IL)-6 levels by ELISA.

2.3. Statistical Analysis

Nominal variables were compared across groups by the chi-square test and Fisher's exact test. Continuous variables were reported as mean ± SD and compared using the independent *t* test (parametric values) or Mann-Whitney *U* test (nonparametric values). A p value of <0.05 was considered statistically significant. All analyses were done using SAS version 6.0 (SAS, Inc., Cary, NC, USA).

3. RESULTS

For 2009-2018, we identified 99 geriatric patients who underwent PD and met the inclusion criteria of the study. From the sedation group, 40 patients (100%) were matched with 40 patients in the control group (Fig. 1). The distribution of baseline covariates was adequately balanced in the matched data set (Table 1). The mean age of the sedation group was 79.6 years (range: 76-94 years) and that of the control group was 78.6 years (range: 75-84 years). The two groups had no significant differences after matching by preoperative demographic characteristics, including age, gender, body mass index (BMI) and weight loss in the previous 6 months. In addition, the groups did no significantly differ in Eastern Co-operative Oncology Group (ECOG) performance scores, preoperative American Society of Anesthesiologists (ASA) scores, intraoperative blood loss, operation time, or postoperative pathological diagnosis. The mean postoperative ICU LOS for patients in the sedation group was 7.2 ± 1.58 days (range: 6-13 days). The mean actual postoperative ventilation stay for patients in the sedation group was 6. 15 ± 1.58 days (range: 5-12 days).

Table 2 shows the concomitant diseases of patients in the matched data set. The percentage of patients with concomitant diseases was 85% (n = 34) in the sedation group and 77.5% (n = 31) in the control group, which were not significantly different. The two groups had no significant differences in most comorbidities. However, the sedation group had a significantly higher incidence of diabetes mellitus than the control group (50% vs 20%, p = 0.010).

Table 3 summarizes the clinical outcomes of the matched data set. The percentage of patients with overall complications was 25% (n = 10) in the sedation group and 47.5% (n = 19) in the control group (p = 0.063). Cardiac events, intra-abdominal abscess and intra-abdominal bleeding were slightly more common in the control group than in the sedation group, but the differences were not significant. The incidence of pulmonary events was significantly lower in the sedation group than in the control group (12.5% vs 40%, p = 0.011). Although the two patients with pulmonary complications in the sedation group progressed to respiratory failure, the overall reintubation rate was slightly lower in the sedation group (5% vs 20%, p = 0.091).

Further analysis of the clinical outcomes indicated gastroparesis in three patients in the sedation group and 13 patients in the control group (7.5% vs 32.5%, p = 0.012). In addition, one patient in the sedation group had a postoperative intestinal obstruction and underwent surgery for enterolysis on postoperative day 49. Patients in the sedation group had no postoperative events. The two groups had the same surgical mortality rate.

Table 4 shows the quality of life assessment of the matched data set. Patients in the control group had a significantly larger heartbeat difference before and after surgery (7.1 ± 5.3 vs 19.1 ± 8.7, p < 0.001). Patients in the sedation group had a significantly lower pain score in the first 3 days in the ordinary hospital ward compared with the control group (2.8 vs 6.1, p < 0.001). Although three patients in the sedation group had delirium in the first 3 days in the ordinary hospital ward, the two groups had no significant difference in the incidence of postoperative delirium (7.5% vs 2.5%, p = 0.615). Finally, the mean postoperative hospital LOS was similar between groups.

We tested the anti-inflammatory effect of the sedatives on cell function. H_2O_2 treatment significantly decreased cell viability of the 16HBE cell line and increased the IL-6 levels (Figs. 2 and 3). According to the MTT assays, the concentrations of propofol and dexmedetomidine produced no cytotoxicity and were avirulent to the 16HBE cell line. Exposure to 2000 μM of H_2O_2 for 60 minutes led to about 50% reduction in the cell viability rate. Pretreatment with propofol or dexmedetomidine for 24 hours significantly elevated the cell viability rate in a dose-dependent manner. Pretreatment with propofol or dexmedetomidine also significantly decreased the IL-6 production. The concentration of 5 μg/mL propofol and 1 ng/mL dexmedetomidine had the optimal protective effect.

4. DISCUSSION

Periampullary cancers are most common among geriatric patients and most patients with these cancers present with obstructive jaundice. Although biliary decompression before surgical intervention can relieve jaundice and biliary tract infection, most patients have infections when undergoing surgery. In general, elderly patients, particularly those older than 75 years, have more underlying diseases and have a higher risk of postoperative morbidity.[1,6] Geriatric patients also experience greater surgical stress, and this, along with cancer therapy, affects their recovery and postoperative quality of life. The surgical stress response is initiated with cytokines produced locally in response to nociceptive stimulation and other factors such as anxiety, fear, and tissue damage.[16–20] Postoperative recovery is smoother when the stress response is reduced, as with the use of adequate analgesia and sedation in critically-ill patients.[21–25] Thus, we hypothesized that postoperative intensive care with preemptive light sedation could ameliorate the surgical stress response in our patients. Our in vitro cell experiments confirmed that adequate use of sedatives could indeed protect the 16HBE cell line from H_2O_2 damage and reduce inflammation. Pretreatment of the cell line with propofol or dexmedetomidine significantly elevated the cell viability rate and significantly decreased IL-6 production after H_2O_2 damage.

We administered propofol or dexmedetomidine to patients in the sedation group to maintain a RASS of –2 (light sedation) for 5 days after surgery. The RASS can be administered in <20 seconds by many types of health care professionals, requires minimal training, and is highly reliable.[26] The RASS has an expanded set of scores at pivotal levels of sedation that are determined by responses to verbal and physical stimulation, which helps clinicians in the titration of medications. Extensive new methods[12] to assess agitation-sedation have markedly improved postoperative patient care. The sedatives

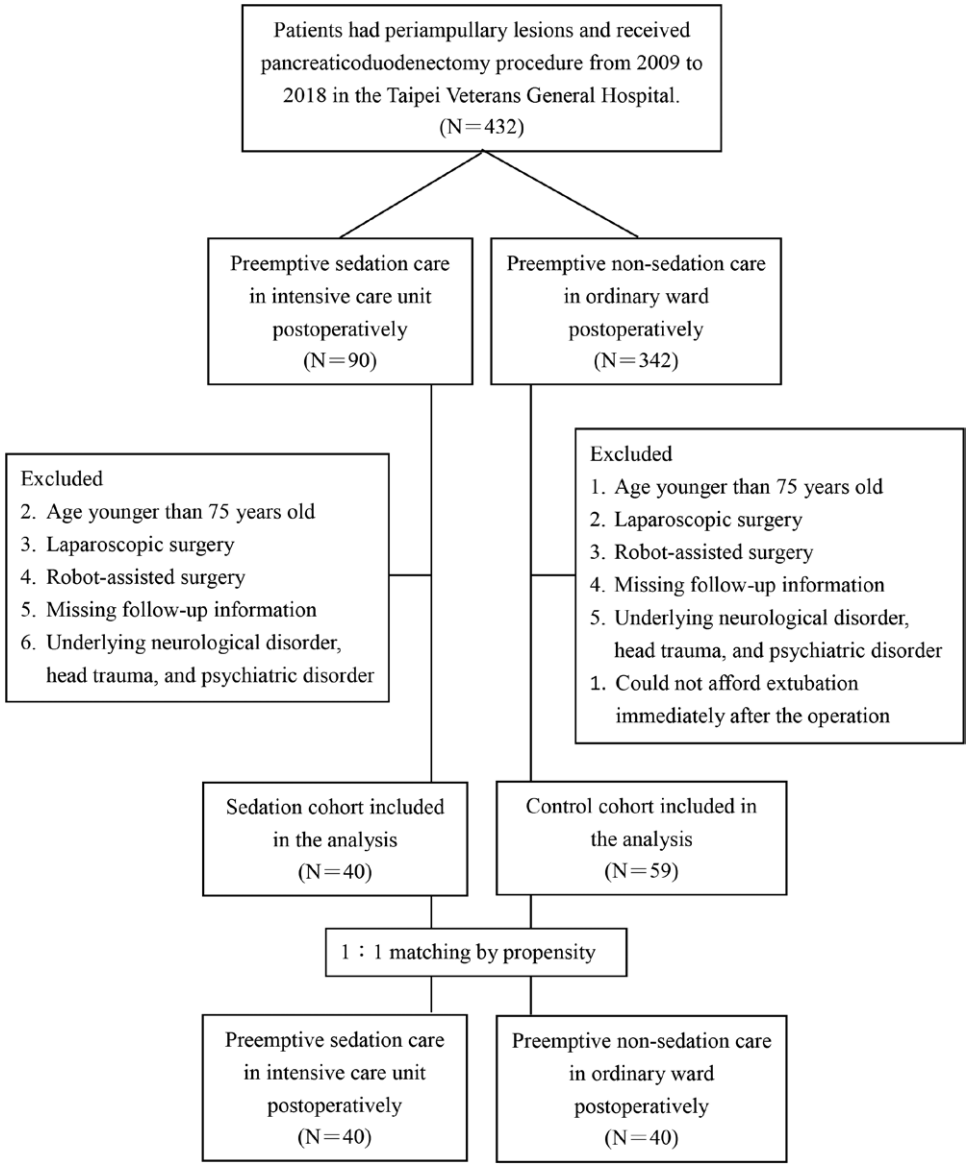

Fig. 1 Patient selection flow diagram.

used here, propofol and dexmedetomidine, are effective in providing a desired level of sedation, and the ease of weaning from them allows earlier extubation in patients receiving short-term sedation. We also controlled pain with a fentanyl citrate pump during the sedation period. According to the guidelines for ICU patients,[12–15] adequate analgesia and sedation should ensure that the patient is at an optimal level of comfort. The dose of fentanyl was adjusted based on the BPS (scored by bedside nurses) to prevent anything more than moderate pain.

In a 2003 report, of 16 patients aged 80+ years who underwent PD, 69% required surgical ICU care for a median of 8 days.[2] In 2006, Scurtu et al[7] investigated 70 patients aged 70 to 84 years who underwent PD and were transferred to the ICU for 6 days postoperatively. In our study, patients in the sedation group received preemptive sedation during the first five postoperative days. The "5-day rule" allows for supplementary nutritional support to sustain the metabolic response to injury, avoid malnutrition, and assist in host defense.[27]

In our study, the overall complication rate was lower in patients given 5 days of postoperative sedation. Although the sedation group had slightly higher ECOG performance status scores and were significantly more likely to develop diabetes (a well-known surgical risk factor), these results did not negatively affect overall outcomes. Furthermore, patients in the sedation group had significantly fewer pulmonary complications (12.5% vs 40%, p = 0.011). This effect may be related to benefits provided during the sedation and postsedation periods.

Age-related pulmonary changes may increase the risk of aspiration, atelectasis, and pneumonia in elderly patients after surgery.[28,29] Sedation, an integral part of critical care, has favorable effects on the cardiovascular and pulmonary systems.[30] Sedation and analgesia may also help reduce complications such as atelectasis, pneumonia, agitation, and accidental extubation. Successfully extubated patients may have better ambulation in the ordinary ward because of the greater comfort provided during ICU sedation. Improved ambulation

Table 1

Comparison of baseline characteristics between the sedation and control groups in the original and matched data sets

Variable	Original data sets			Matched data set		
	Sedation group (n = 40)	Control group (n = 59)	*p*	Sedation group (n = 40)	Control group (n = 40)	*p*
Preoperative variables						
Age, y	79.6 ± 4.2	77.6 ± 2.3	0.008	79.6 ± 4.2	78.6 ± 2.0	0.815
Gender			0.482			0.482
Male	28 (70%)	36 (61%)		28 (70%)	24 (60%)	
Female	12 (30%)	23 (39%)		12 (30%)	16 (40%)	
Body mass index (BMI)			0.307			0.821
<18	0	0		0	0	
18-24	24 (60%)	28 (47.5%)		24 (60%)	22 (55%)	
>24	16 (40%)	31 (52.5%)		16 (40%)	18 (45%)	
Smoking	10 (25%)	7 (11.9%)	0.153	10 (25%)	5 (12.5%)	0.252
Performance status (ECOG)			0.030			0.817
0	14 (35%)	35 (59.3%)		14 (35%)	16 (40%)	
1	26 (65%)	24 (40.7%)		26 (65%)	24 (60%)	
2	0	0		0	0	
Weight loss >10% in the past 6 months	12 (30%)	14 (23.7%)	0.643	12 (30%)	11 (27.5%)	1.000
Pathologic diagnosis			0.344			0.263
Malignant cancer	34 (85%)	54 (91.5%)		34 (85%)	38 (95%)	
Pancreas cancer	16	28		16	20	
Duodenal cancer	4	3		4	2	
Ampulla Vater cancer	10	18		10	12	
Distal CBD cancer	2	5		2	4	
Gastrointestinal stromal tumor	2	0		2	0	
Benign disease	6 (15%)	5 (8.5%)		6 (15%)	2 (5%)	
Chronic pancreatitis	1	2		1	1	
Benign CBD tumor	4	3		4	1	
Parasite infection	1	0		1	0	
Intraoperative variables						
ASA score			0.040			0.655
1	0	0		0	0	
2	18 (45%)	40 (67.8%)		18 (45%)	21 (52.5%)	
3	22 (55%)	19 (32.2%)		22 (55%)	19 (47.5%)	
Estimated blood loss, mL			0.307			0.180
<1000	16 (40%)	31 (52.5%)		16 (40%)	23 (57.5%)	
≥1000	24 (60%)	28 (47.5%)		24 (60%)	17 (42.5%)	
Operation time, h			0.595			0.655
<8	18 (45%)	31 (52.5%)		18 (45%)	21 (52.5%)	
≥8	22 (55%)	28 (47.5%)		22 (55%)	19 (47.5%)	

ECOG = Eastern Co-operative Oncology Group; CBD = common bile duct; ASA = American Society of Anesthesiologists

Table 2

Comorbidities of patients of the sedation and control groups in the matched data set

	Sedation group (n = 40)	Control group (n = 40)	*p*
No. of overall comorbidities			
0	6 (15%)	9 (22.5%)	0.169
1	16 (40%)	21 (52.5%)	
2 or more	18 (45%)	10 (25%)	
Specific comorbidities			
Diabetes mellitus	20 (50%)	8 (20%)	0.010*
Hypertension	25 (62.5%)	31 (77.5%)	0.223
Cardiac disease	8 (20%)	9 (22.5%)	1.000
Pulmonary disease	4 (10%)	3 (7.5%)	1.000
Hepatic disease	2 (5%)	2 (5%)	1.000

*$p < 0.05$ versus control.

during recovery is associated with fewer pulmonary complications such as atelectasis and pneumonia.[31,32] That association may explain the significant reduction in pulmonary morbidity in the sedation group.

Table 3

Clinical outcomes of patients of the sedation and control groups in the matched data set

Variable	Sedation group (n = 40)	Control group (n = 40)	*p*
Overall complications	10 (25%)	19 (47.5%)	0.063
Overall cardiac complication events	2 (5%)	7 (17.5%)	0.154
Myocardial infarction	1	1	
Arrhythmia with tachycardia	1	6	
Overall pulmonary events	5 (12.5%)	16 (40%)	0.011 *
Pneumonia	3	7	
Lung atelectasis	1	6	
ARDS	0	2	
Pulmonary edema	1	2	
Intra-abdominal abscess	3 (7.5%)	4 (10%)	1.000
Anastomotic leakage	6 (15%)	6 (15%)	1.000
Intra-abdominal bleeding	3 (7.5%)	4 (10%)	1.000
Gastroparesis	3 (7.5%)	13 (32.5%)	0.012*
Re-intubation	2 (5%)	8 (20%)	0.091
Surgical mortality	3 (7.5%)	3 (7.5%)	1.000

ARDS = acute respiratory distress syndrome.
*$p < 0.05$ versus control.

Table 4

Quality-of-life assessment of patients of the sedation and control groups in the matched data set

Variable	Sedation group (n = 40)	Control group (n = 40)	*p*
Average heartbeat difference before and after surgery, beat/min	7.1 ± 5.3	19.1 ± 8.7	<0.001*
Pain score in the ordinary ward	2.8 ± 1.2	6.1 ± 1.2	<0.001*
Delirium	3 (7.5%)	1 (2.5%)	0.615
Postoperative hospital length of stay, d	25.0 ± 16.8	27.3 ± 19.5	0.289

*$p < 0.05$ versus control.

Gastroparesis is one of the most common complications after pancreaticoduodenectomy related to the presence of other intra-abdominal complications such as leakage or abscess. Unfortunately, a retrospective analysis found that neither the method of pancreaticojejunostomy (Blumgart procedure or Kakita method) nor the route of gastroenteric reconstruction (anticolic or retrocolic) significantly prevented gastroparesis.[33] Surprisingly, our patients receiving postoperative sedation had a significantly lower incidence of delayed gastric emptying. The gastrointestinal tract plays a critical role in the body's immune system, containing half of all systemic immune cells.[34] Gut-associated lymphoid tissue is responsible for sampling foreign antigenic material within the intestines, and mounting

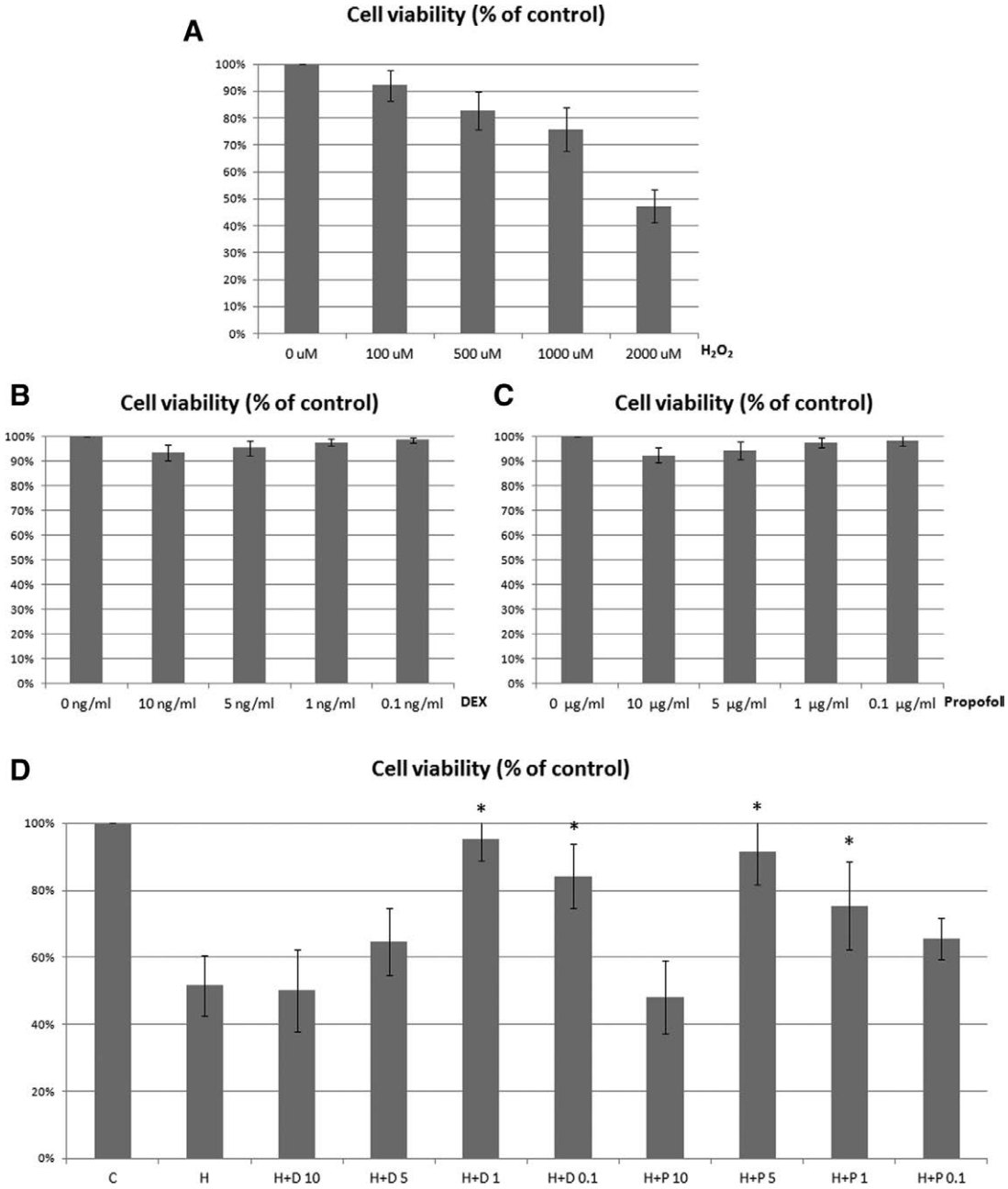

Fig. 2 Cell viability of the 16HBE cell line. H_2O_2 treatment significantly decreased cell viability of the 16HBE cell line. Pretreatment with propofol or dexmedetomidine for 24 h significantly elevated the cell viability rate in a dose-dependent manner. *$p < 0.05$. HBE = human bronchial epithelial cell.

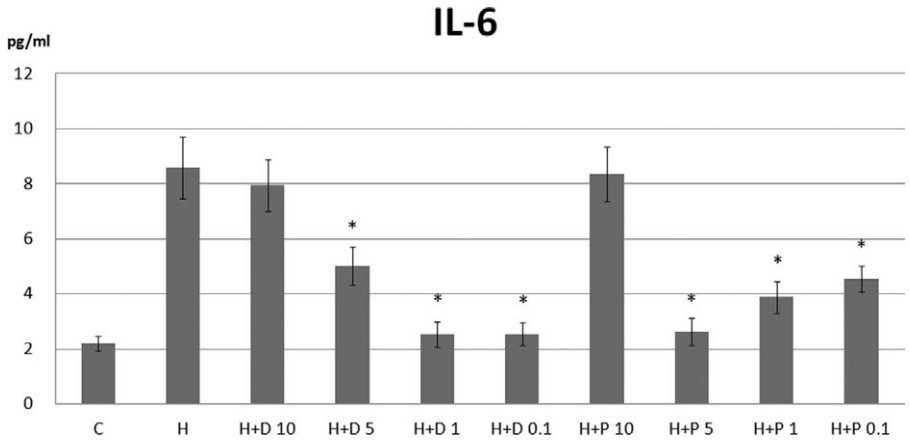

Fig. 3 IL-6 production of the 16HBE cell line. H_2O_2 treatment significantly increased the IL-6 levels of the 16HBE cell line. Pretreatment with propofol or dexmedetomidine significantly decreased IL-6 production. *$p < 0.05$. IL = interleukin; HBE = human bronchial epithelial cell.

cell-mediated and humoral responses as needed.[35] In critically-ill elderly subjects, a reduction in peristalsis, gastric acid secretion, and mucus production throughout the gut can lead to bacterial overgrowth, and potentially systemic bacterial circulation.[34,35] Surgical stress increases autonomic stimulation (mostly sympathetic) and the production of catecholamines. Preemptive postoperative sedation may reduce the surgical stress response, decrease the sympathetic tone, increase the parasympathetic tone, increase peristalsis and increase gastric acid secretion, and thereby improve recovery.

In terms of postoperative quality of life, patients in the sedation group faced a significantly smaller heartbeat variation before and after surgery (7.1 ± 5.3 vs 19.1 ± 8.7, $p < 0.001$). Greater heartbeat variation increases discomfort and decreases willingness to walk. Patient self-reported pain scores in the first 3 days in the ordinary hospital ward differed significantly between the sedation and control groups (2.8 vs 6.1, $p < 0.001$). Numerous scales can be used to estimate pain, but none objectively quantify pain intensity or relief. Typically, pain is self-assessed by the patient on a scale of 0 (no pain) to 10 (worst imaginable pain).[36–40] In our study, patients in the sedation group received fentanyl during the first few days of postoperative sedation and had less pain after weaning from sedation and transfer to an ordinary ward. This procedure presumably gave these patients a stronger desire for ambulation, more vitality, and fewer morbidities. By contrast, patients in the control group had high pain scores, with a relatively unstable condition, prolonged bedridden status, and more postoperative adverse events. The lower complication rate and lower pain scores in patients in the sedation group suggest that postoperative preemptive light sedation provides significant therapeutic benefits in critically-ill elderly patients.

The present study had two limitations. One was the relatively small sample size of the retrospective cohort study. More than 75% of patient who received PD in our hospital were younger than 75 years. Also, patients in the initial control group were excluded if they could not afford postoperative extubation. This safety measure excluded many patients and prolonged the case collection period. The other limitation was that this study was not a randomized controlled study. Randomized controlled multicenter trials are needed to validate our findings.

In conclusion, the present study indicated that geriatric patients receiving PD had superior clinical outcomes when given postoperative preemptive light sedation for 5 days. In particular, preemptive sedation reduced the rate of postoperative pulmonary complications and gastroparesis, improved postoperative quality of life, but had no effect on postoperative hospital LOS. Our in vitro cell experiments also demonstrated that adequate treatment with sedatives could protect cells from damage and reduce inflammation. Thus, in experienced institutions, postoperative light sedation in the ICU setting may be a safe and feasible strategy for improving outcomes in geriatric patients following PD.

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