Prevalence of Postoperative Delirium According to the Intraoperative General Anesthetic Agents in Patients Undergoing Cardiac Surgery: a Retrospective and Propensity-Score Matched Study

Hyun-Jung Shin
Seoul National University Bundang Hospital
Soo Lyoen Choi
Seoul National University Bundang Hospital
Hyo-Seok Na (hsknana@gmail.com)
Seoul National University Bundang Hospital https://orcid.org/0000-0003-0986-3243

Research

Keywords: sevoflurane, propofol, dexmedetomidine, cardiac surgery, postoperative delirium

Posted Date: August 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-57423/v1

Abstract

Background: Cognitive alterations after cardiac surgery are a growing concern. We retrospectively evaluated the incidence of postoperative delirium (PD) in cardiac surgical patients according to the main anesthetic agent.

Methods: The medical records of 534 patients, who had undergone heart valve surgery or coronary artery bypass graft surgery with cardiopulmonary bypass (CPB) between January 2012 and August 2017, were investigated. They were divided into two groups according to the main anesthetic agent: inhalation with dexmedetomidine (InDex group, n = 340) and propofol (propofol group, n = 194). The incidence of PD was evaluated as the primary outcome. Patient-, surgery-, and anesthesia-related factors and postoperative complications were investigated as secondary outcomes. To reduce the risk of confounder effects between the two groups, 194 patients were selected from the InDex group after propensity-score matching.

Results: After propensity-score matching, the incidence of PD was not significantly different between the InDex (6.2%) and propofol (10.8%) groups (P = 0.136). In comparison of the incidence of each type of PD, only hyperactive PD occurred significantly less in the InDex group than in the propofol group (P = 0.021). Older age, lower preoperative albumin levels, and emergency surgery were significant risk factors for PD.

Conclusions: The overall incidence of PD after cardiac surgery with CPB is not associated with the main anesthetic agents, inhalation and dexmedetomidine-based *vs*. propofol-based anesthesia. Only hyperactive PD occurred less frequently after in patients receiving inhalation and dexmedetomidine-based anesthesia.

Introduction

With ongoing advancements in anesthetic and surgical techniques, cardiac surgeries in the elderly patients have increased and are safely performed. However, postoperative delirium (PD) is still an issue in post-cardiac surgery patients despite the constant efforts to reduce it.

Various risk factors for PD after cardiac surgery have been identified (Hollinger et al., 2015), such as advanced age, preexisting cognitive impairment, cerebrovascular disease, metabolic syndrome, and type and duration of surgery (Hollinger et al., 2015; Lin et al., 2012). However, clinical data regarding the effect of intraoperative anesthetic agents on the PD are rare.

Generally, sevoflurane or desflurane is used for inhalational anesthesia, while propofol is the primary drug for intravenous anesthesia. Data are conflicting regarding the neurocognitive function-sparing effect between inhalation agents and propofol. Inhalation anesthetics are associated with better postoperative cognitive function than propofol after coronary artery bypass graft (CABG) surgery (Royse et al., 2011; Schoen et al., 2011). In contrast, Oh et al. (Oh et al., 2017) described that PD was observed with similar incidence between sevoflurane and propofol anesthesia in off-pump CABG surgery. In addition, recent studies have reported that dexmedetomidine could reduce PD in cardiac (Cheng et al., 2016; Djaiani et al., 2016; Maldonado et al., 2009) or non-cardiac surgery (Duan et al., 2018; Xie and Xie 2018); however, the optimal timing or dose of dexmedetomidine has not been fully confirmed.

The aim of this study was to investigate if PD is reduced when dexmedetomidine is added as an intraoperative adjuvant agent during inhalation anesthesia compared to total intravenous anesthesia. Patients were divided into

groups of inhalation agent with dexmedetomidine and propofol, and the incidence of PD was evaluated in patients who underwent cardiac surgery with cardiopulmonary bypass (CPB).

Methods

Study population and data collection

After obtaining approval from the Institutional Review Board at Seoul National University Bundang Hospital (B-1510/318-04), electronic medical records from January 2012 to July 2017 were reviewed. The requirement for informed consent was waived.

Adult patients aged 20 years or over, who had undergone heart valve or CABG surgery with CPB were included in this study. Patients who had been preoperatively diagnosed with neuropsychological diseases, such as dementia or Parkinson's disease, were excluded. Patients with visual disturbances, hearing loss, postoperative sedation, or reoperation due to postoperative complications were excluded.

Routine general anesthesia practice

On arrival in the operating room, standard monitoring (pulse oximetry, electrocardiogram, and noninvasive arterial pressure) and invasive arterial monitoring were established. Central vein catheterization was performed after induction of general anesthesia.

During the investigation period, different general anesthetic agents were administered to patients. Based on these different anesthetic agents, patients were divided into two groups: InDex and propofol groups. In the InDex group, anesthesia was induced with intravenous propofol, remifentanil, and sevoflurane. During the intraoperative period, anesthesia was maintained with sevoflurane and dexmedetomidine. In the propofol group, total intravenous anesthesia was performed using propofol and remifentanil via a target-controlled infusion device (Orchestra®, Fresenius Vial, France) from the induction to the end of the surgery. Dexmedetomidine was not used in the propofol group. Rocuronium was administered as a neuromuscular blocking agent in both groups.

Assessment of postoperative delirium

PD was defined as the positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) during the ICU stay. According to the standard ICU practice of our institution, CAM-ICU was examined and recorded twice a day by directed bedside nurses, who had been extensively trained. After patients were transferred to the floor, PD was assessed until postoperative day 5 by nurses who had also been trained to evaluate the patient's cognitive status. The duration of delirium was defined as the total number of days with positive CAM-ICU.

The type of PD was determined according to the Richmond Agitation and Sedation Scale (RASS) score. When the RASS level was positive or negative, PD was classified as hyperactive or hypoactive, respectively. When a patient presented with mixed positive and negative RASS scores, they were diagnosed with mixed-type PD.

Other outcome variables

Data were collected and categorized into the following three variable sets: (1) preoperative factors, including age, sex, weight, height, body mass index, American Society of Anesthesiologist (ASA) physical status classification, and preoperative laboratory findings; (2) intraoperative factors, including the urgency of surgery, surgery time, CPB

time, volume of estimated blood loss, and amount of red blood cell (RBC) transfusion; and (3) postoperative factors, including the duration of ICU stay, extubation time, postoperative admission period, postoperative complications, amount of RBC transfusion, and postoperative laboratory findings. Pre- and postoperative laboratory tests including hematocrit, platelet counts, electrolytes, creatinine, and albumin, were performed within 1 month before surgery and within 24 h after surgery, respectively. We investigated whether or not patients developed postoperative complications related to the renal and neurological systems.

Statistical analysis

Data are expressed as median (interquartile range) or number (proportion). All continuous data were assessed for normality using the Shapiro-Wilk test. Incidence was analyzed using the chi-square test or Fisher's exact test. The Mann-Whitney U test or Wilcoxon signed rank test was performed to compare the numerical data, as appropriate. A binary logistic regression model was used to evaluate the predisposing factors of PD. The independent variables were the main anesthetic drug, age, sex, BMI, surgery type, ASA class, anesthesia time, CPB time, estimated blood loss, intraoperative and postoperative RBC transfusion amount, and preoperative and postoperative hematocrit, electrolytes, creatinine levels, and albumin level.

Propensity-score matching was performed to reduce the risk of confounder effects between the InDex and propofol groups. Propensity scores were calculated using a logistic regression model. Covariate included the sex, age, height, weight, BMI, ASA class, urgency of surgery, operation time, preoperative laboratory findings, estimated blood loss, duration of CPB, intra- and postoperative RBC transfused, extubation time, and type of surgery. The dependent variable was the main general anesthetic agent: inhalation with dexmedetomidine or propofol. We performed nearest-neighbor matching. After propensity-score matching, the paired *t*-test or Wilcoxon signed-rank test for continuous variables and McNemar or McNemar-Bowker test for categorical variables were performed, as appropriate.

All analyses were carried out using IBM® SPSS® Statistics, version 22.0 (IBM Corporation, NY, USA). $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 1,283 patients were evaluated for eligibility, 534 of whom were finally analyzed. According to the main general anesthetic agent, 340 and 194 patients were assigned to the InDex and propofol groups, respectively. After propensity-score matching, 194 patients were selected from the InDex group (Fig. 1).

The characteristics of patient, surgery, and anesthesia were comparable between the two groups, except for the estimated blood loss volume, intra- and postoperative RBC transfusion amount, and ICU stay period, which became comparable after propensity-score matching (Table 1).

Table 1
Characteristics of patients, surgery, and anesthesia

	Before matching			After matching		
	InDex	Propofol	*P* value	InDex	Propofol	*P* value
	(N = 340)	(N = 194)		(N = 194)	(N = 194)	
Age (year)	70 (58–76)	68 (56–76)	0.240	65 (56–74)	68 (56–76)	0.483
Gender			0.368			0.845
Male	169 (50%)	105 (54%)		108 (56%)	105 (54%)	
Female	171 (50%)	89 (46%)		86 (44%)	89 (46%)	
Weight (kg)	64 (57–71)	65 (58–71)	0.445	66 (57–73)	65 (58–71)	0.940
Height (cm)	160 (153–168)	163 (155–169)	0.053	162 (154–170)	163 (155–169)	0.977
BMI (kg/m^2)	25 (22–27)	24 (23–27)	0.805	24 (23–27)	24 (23–27)	0.781
ASA classification (1/2/3)			0.318			0.903
1	7	1		1	1	
2	64	38		43	38	
3	253	141		140	141	
4	16	14		10	14	
Surgery time (min)	260 (216–305)	245 (215–300)	0.364	255 (215–300)	245 (215–300)	0.867
Anesthesia time (min)	305 (265–355)	300 (265–345)	0.398	300 (264–340)	300 (265–345)	0.571
Estimated blood loss (mL)	900 (600–1275)	800 (500–1000)	0.002	800 (500–1000)	800 (500–1000)	0.866
RBCs (mL, during surgery)	750 (400–1200)	600 (200–1000)	0.008	500 (0–954)	600 (200–1000)	0.354
RBCs (mL, after surgery)	0 (0–250)	0 (0–500)	< 0.001	0 (0–250)	0 (0–500)	0.321
CPB (min)	125 (93–155)	124 (98–146)	0.344	123 (90–148)	124 (98–146)	0.454
Elective/emergency	322 (95%)/18 (5%)	190 (98%)/4 (2%)	0.075	189 (97%)/5 (3%)	190 (98%)/4 (2%)	1.000

Data are expressed as the median (interquartile range) or the number of the patients (proportion).

InDex, inhalation + dexmedetomidine; BMI, body mass index; ASA, American Society of Anesthesiologist classification; RBC, red blood cell; CPB, cardiopulmonary bypass; ICU, intensive care unit

	Before matching			After matching		
Extubation (days)	0 (0–1)	0 (0–1)	0.286	0 (0–1)	0 (0–1)	0.962
ICU stay (days)	2 (1–2)	1 (1–2)	0.024	1 (1–2)	1 (1–2)	0.265
Postoperative hospital stay (days)	9 (7–14)	9 (7–13)	0.473	8 (7–12)	9 (7–13)	0.331
Data are expressed as the median (interquartile range) or the number of the patients (proportion).						
InDex, inhalation + dexmedetomidine; BMI, body mass index; ASA, American Society of Anesthesiologist classification; RBC, red blood cell; CPB, cardiopulmonary bypass; ICU, intensive care unit						

The overall incidence, onset, and duration of PD were not significantly different between the InDex and propofol groups, even after propensity-score matching (Table 2). In comparison of the incidence of each type of PD, only hyperactive PD occurred significantly less in the InDex group than in the propofol group (P = 0.021). Incidences of other postoperative complications (seizure and acute kidney injury) were comparable between the two groups (Table 2).

Table 2
Characteristics of postoperative delirium and complications

	Before matching			After matching		
	InDex	Propofol	*P* value	InDex	Propofol	*P* value
	(N = 340)	(N = 194)		(N = 194)	(N = 194)	
PD (overall)	41 (12.1%)	21 (10.8%)	0.779	12 (6%)	21 (10.8%)	0.136
Hyperactive PD	26 (7.6%)	14 (7.2%)	1.000	4 (2.1%)	14 (7.2%)	0.021
Hypoactive PD	12 (3.5%)	5 (2.6%)	0.618	5 (2.6%)	5 (2.6%)	1.000
Mixed PD	3 (0.9%)	2 (1.0%)	1.000	3 (1.5%)	2 (1.0%)	1.000
Onset delirium (postoperative day)	0 (0–4)	0 (0–4)	0.710	0 (0–4)	0 (0–4)	0.194
Duration of delirium (day)	0 (0–7)	0 (0–4)	0.154	0 (0–7)	0 (0–4)	0.153
Seizure	11 (3.2%)	2 (1.0%)	0.148	7 (3.6%)	2 (1.0%)	0.180
Acute kidney injury	2 (0.6%)	1 (0.5%)	1.000	1 (0.5%)	1 (0.5%)	1.000
Data are expressed as the median (range) or number of the patients (proportion)						
InDex, inhalation + dexmedetomidine; PD, postoperative delirium						

Preoperative hemoglobin, sodium, potassium, creatinine, and albumin levels were comparable between the two groups. However, in the propofol group, lower potassium and higher albumin levels were observed postoperatively compared to the InDex group (P = 0.026 and P = 0.040, respectively). These different laboratory findings became comparable after propensity-score matching (Table 3).

Table 3
Preoperative and postoperative laboratory results

	Before matching					
	InDex (N = 340)		Propofol (N = 194)			
	Preoperative	Postoperative	Preoperative	Postoperative	P_1	P_2
Hematocrit (%)	12.8 (11.2–14.2)	11.1 (10.1–12.1)	13.0 (11.5–14.3)	10.6 (9.5–12.0)	0.269	0.028
Sodium (mmol/L)	139 (136–141)	139 (137–141)	139 (137–141)	139 (137–141)	0.367	0.171
Potassium (mmol/L)	4.2 (3.9–4.4)	3.9 (3.6–4.2)	4.1 (3.9–4.4)	3.8 (3.4–4.1)	0.438	0.026
Creatinine (mg/dL)	0.86 (0.70–1.05)	0.88 (0.74–1.09)	0.84 (0.66–0.99)	0.93 (0.77–1.15)	0.117	0.117
Albumin (g/dL)	4.1 (3.6–4.4)	3.3 (3.0–3.7)	4.1 (3.8–4.4)	3.4 (3.1–3.7)	0.336	0.040
	After matching					
	InDex (N = 194)		Propofol (N = 194)			
	Preoperative	Postoperative	Preoperative	Postoperative	P_1	P_2
Hematocrit (%)	13.1 (11.8–14.5)	10.9 (9.7–11.8)	13.0 (11.5–14.3)	10.6 (9.5–12.0)	0.573	0.692
Sodium (mmol/L)	139 (137–141)	139 (137–141)	139 (137–141)	139 (137–141)	0.598	0.982
Potassium (mmol/L)	4.2 (3.9–4.4)	3.8 (3.5–4.1)	4.1 (3.9–4.4)	3.8 (3.4–4.1)	0.894	0.899
Creatinine (mg/dL)	0.84 (0.70–0.99)	0.88 (0.76–1.07)	0.84 (0.66–0.99)	0.93 (0.77–1.15)	0.776	0.093
Albumin (g/dL)	4.2 (3.8–4.5)	3.4 (3.1–3.8)	4.1 (3.8–4.4)	3.4 (3.1–3.7)	0.383	0.645
Data are expressed as the mean ± SD.						
P1: compared the preoperative values between the two groups, P2: compared the postoperative values between the two groups						

The following parameters were confirmed as significant determinants for the occurrence of PD by the binary logistic regression analysis (Table 4):–patients were 1.06 (95% CI: 1.03–1.10, P < 0.001) times more likely to experience PD for every 1-year increase in age; patients with emergency surgery were 5.76 (95% CI: 1.66–19.98; P = 0.006) times more likely to experience PD than patients with elective surgery; and patients s were 0.46 (95% CI :0.22–0.98; P = 0.043) times less likely to experience PD for every 1 g/dl increase in albumin value.

Table 4
Binary logistic regression for the occurrence of postoperative delirium

Independent variables	OR (95% CI)	*P*
Drug for anesthesia		0.340
Propofol	1	
Sevoflurane + dexmedetomidine	0.71 (0.35–1.44)	
Age (year)	1.06 (1.03–1.10)	< 0.001
Gender		0.839
Male	1	
Female	1.11 (0.40–3.12)	
BMI (kg/m^2)	0.83 (0.59–1.18)	0.295
Elective/emergency		0.006
Elective	1	
Emergency	5.76 (1.66–19.98)	
ASA		0.673
1	0.26 (0.02–4.08)	0.341
2	0.17 (0.01–2.42)	0.190
3	0.19 (0.01–3.18)	0.247
4	0.00	1.000
Anesthesia time (min)	1.01 (0.99–1.02)	0.081
CPB time (min)	1.01 (0.99–1.02)	0.145
Estimated blood loss (ml)	1.00 (1.00–1.00)	0.521
RBCs (mL, during surgery)	1.00 (1.00–1.00)	0.154
RBCs (mL, after surgery)	1.00 (1.00–1.00)	0.076
Preoperative laboratory findings		
Hematocrit (%)	1.12 (0.90–1.39)	0.314
Sodium (mmol/L)	0.99 (0.89–1.10)	0.827
Potassium (mmol/L)	0.89 (0.42–1.90)	0.761
Creatinine (mg/dL)	1.78 (0.82–3.97)	0.146
Albumin (g/dL)	0.46 (0.22–0.98)	0.043
Postoperative laboratory findings		

OR, odds ratio; CI, confidence interval; BMI, Body mass index; ASA, American Society of Anesthesiologist; CPB, cardiopulmonary bypass

Independent variables	OR (95% CI)	*P*
Hematocrit (%)	0.94 (0.76–1.17)	0.604
Sodium (mmol/L)	0.90 (0.79–1.03)	0.123
Potassium (mmol/L)	0.84 (0.39–1.78)	0.644
Creatinine (mg/dL)	0.53 (0.20–1.40)	0.199
Albumin (g/dL)	0.96 (0.48–1.93)	0.910

OR, odds ratio; CI, confidence interval; BMI, Body mass index; ASA, American Society of Anesthesiologist; CPB, cardiopulmonary bypass

Discussion

This study showed that the overall incidence of PD in cardiac surgery with CPB was not affected by the intraoperative anesthetic agent (sevoflurane with dexmedetomidine or propofol). However, hyperactive PD occurred less frequently when patients were anesthetized with sevoflurane and dexmedetomidine compared to propofol. Older age, emergency surgery, and preoperative lower albumin levels were factors contributing to PD occurrence in this study.

Neuroinflammation and ischemic insult of the brain are major concerns in cardiac surgery with CPB because these conditions may increase the risk of PD (O'Neal et al., 2017). Various attempts have been made to reduce brain injury, and the neuroprotective role of anesthetics has been suggested (Ishida et al., 2014; Kitano et al., 2007). Several previous studies have compared the effects of anesthetic agents on the development of PD. In experimental studies, pre- and postconditioning effects of inhalation agents on the neuronal tissue were suggested as a possible mechanism attenuating cerebral injury following CPB (Kapinya et al., 2002; Kitano et al., 2007). The application of volatile anesthetics before and immediately after an ischemic period attenuated ischemia-reperfusion injury in several organs, including the brain (Kapinya et al., 2002; Kitano et al., 2007; Zhu et al., 2009). Propofol has an anti-inflammatory effect, and it had improved the neurologic outcome by decreasing neuronal damage after cerebral ischemia in an experimental model (Kochs et al., 1992; Ye et al., 2013). Recently, Archer et al. (Archer et al., 2017) reported the impact of anesthetic treatment on the neurological outcome in an experimental stroke model. They surprisingly found that exposure to anesthetics, regardless of the type of anesthetic or time of administration, reduced neurological damage in experimental focal cerebral ischemia.

Contrary to experimental studies, results of clinical studies are few and inconsistent. In cardiac surgery, inhalation anesthetic agents are reportedly more beneficial than propofol in reducing PD; however, no relationship between anesthetic agents and PD has also been reported (Oh et al., 2017; Royse et al., 2011; Schoen et al., 2011). Similarly, these inconsistent results are observed in non-cardiac surgery (Ishii et al., 2016; Tanaka et al., 2017).

Recently, the role of dexmedetomidine in reducing PD has been highlighted. Dexmedetomidine has neuroprotective effects (Wang et al., 2018). However, the exact mechanism through which dexmedetomidine reduces the incidence of PD remains poorly understood. At present, the suggested mechanisms based on the pharmacological

characteristics of dexmedetomidine are as follows (Maldonado 2008; Nemoto et al., 2013; Wang et al., 2018): (1) suppression of sustained increase of 5 -aminobutyric acid type A receptor expression by anesthesia; (2) maintenance of anticholinergic level; and (3) minimization of multiple neurotransmitter pathways disruption.

In this study, although dexmedetomidine was administered as an adjuvant to inhalation anesthesia, an additional significant effect for the reduction of PD was not observed. After propensity-score matching, the overall incidence of PD was lower in the InDex group than in the propofol group (6% vs. 10.8%); however, the difference was not statistically significant. The small cohort in each group might not have been sufficient for generalizability of results. To obtain statistical significance, more than 563 patients are required under 80% power and 0.05 type I error.

In our previous study performed in the elderly patients who had undergone orthopedic surgery under regional anesthesia (Shin et al., 2017), the postoperative agitated behavior decreased more after intraoperative dexmedetomidine sedation compared to propofol sedation. Interestingly, the present study also showed that hyperactive PD occurred significantly less in the InDex group than in the propofol group. Therefore, we should consider that dexmedetomidine might play a specific role in reducing postoperative abnormal hyperactive behavior, such as agitation, confusion, and aggression. These behaviors are injurious to patients themselves and medical personnel; therefore, proper management is required, and dexmedetomidine can be a potential preventive medication.

Risk factors for PD after cardiac surgery include advanced age, dementia, electrolyte derangement, prolonged CPB time, high perioperative transfusion requirement, preoperative low albumin levels, postoperative high C-reactive protein concentration, and longer ICU stay (Cereghetti et al., 2017; Norkiene et al., 2013). Similar contributing factors were found in the present study, which included older age, emergency surgery, and preoperative lower albumin levels.

The present study had several limitations. First, we could not confirm which anesthetic drug caused the decrease in the incidence of hyperactive PD, although dexmedetomidine was strongly suspected. Since there is no conclusion regarding the superior anesthetic drug for the prevention of PD, further research is required. Second, PD was evaluated by well-trained nurses and the attending physician using CAM-ICU. Because the pure hypoactive form of PD is usually more difficult to detect than the hyperactive form, although precisely evaluated, the hypoactive form of PD might have been missed. Finally, this study was performed using data from a single center; therefore, the generalizability may be compromised.

In conclusion, the overall incidence of PD after cardiac surgery with CPB is not associated with the main anesthetic agent, inhalation and dexmedetomidine-based *vs.* propofol-based anesthesia. Only hyperactive PD occurred less frequently in patients receiving inhalation and dexmedetomidine-based anesthesia. Further large randomized controlled trials are required to confirm the impact of the anesthetic on the postoperative cognitive function.

Abbreviations

ASA
American Society of Anesthesiologist; CABG:coronary artery bypass graft; CAM-ICU:confusion Assessment Method for the Intensive Care Unit; CPB:cardiopulmonary bypass; PD:postoperative delirium; RASS:Richmond Agitation and Sedation Scale; RBC:red blood cell.

Declarations

Financial disclosures

None.

Authors' contribution

Hyun-Jung Shin: concept/design, data collection, drafting article, approval of article. Soo Lyoen Choi: data collection, approval of article. Hyo-Seok Na: concept/design, critical revision of article, approval of article. All authors read and approved the final manuscript.

Funding

None

Conflicts of Interest: None

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the regulation of Institutional Review Board, but are available from the corresponding author after getting permission from IRB for sharing the dataset on reasonable request.

Ethics approval and consent to participate

After obtaining approval from the Institutional Review Board at Seoul National University Bundang Hospital (B-1510/318-04), electronic medical records from January 2012 to July 2017 were reviewed. The requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

Author details

Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang, Seongnam 13620, South Korea.

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Figures

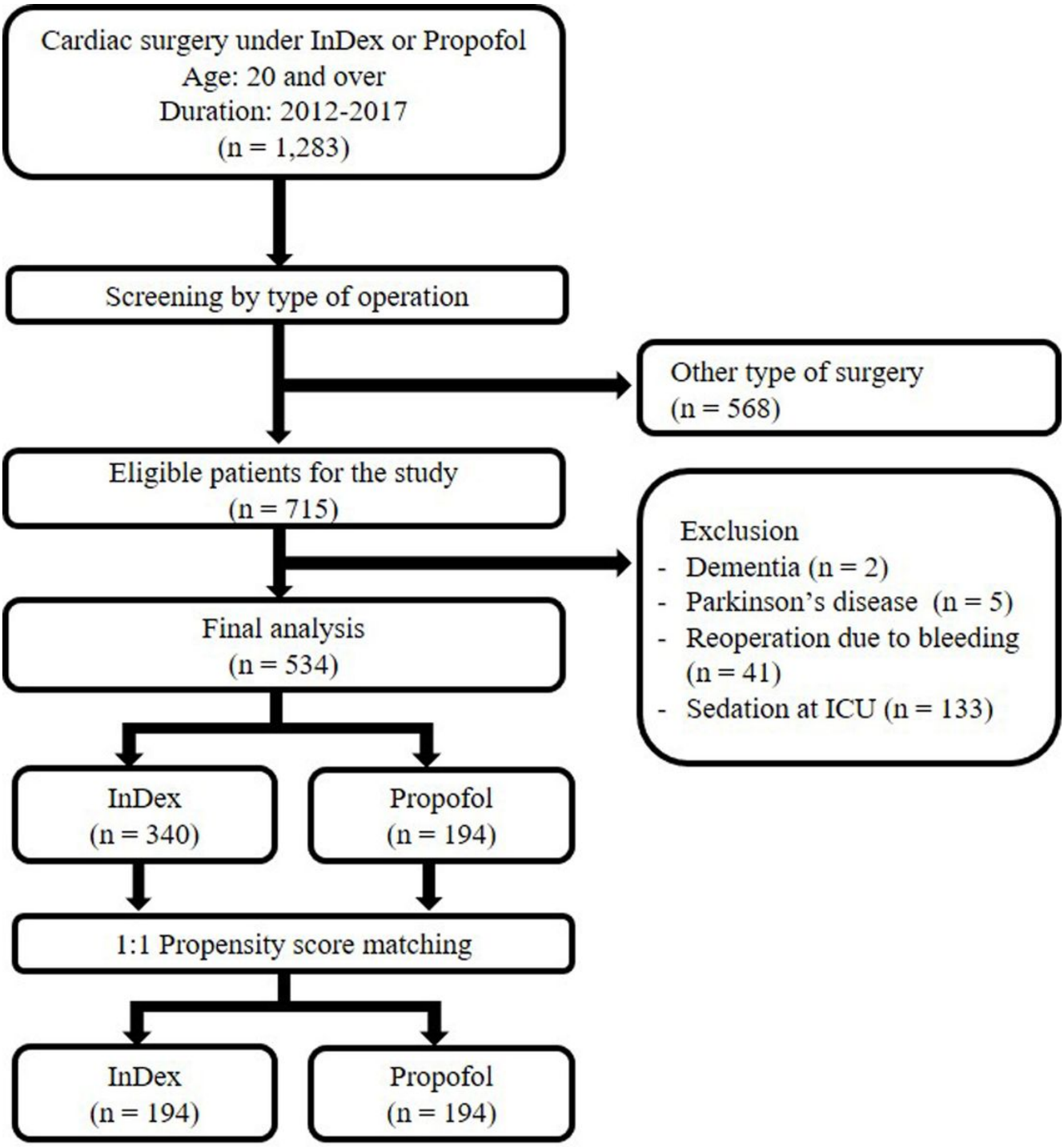

Figure 1

Flow chart InDex, inhalation + dexmedetomidine; ICU, intensive care unit