Perioperative plasma melatonin concentration in postoperative critically ill patients: its association with delirium

Authors

Shiho Yoshitaka, Moritoki Egi, Hiroshi Morimatsu, Tomoyuki Kanazawa, Yuichiro Toda, Kiyoshi Morita

Site of study

Department of Anesthesiology and Resuscitology, Okayama University Medical School.

Funding source

This study was supported by the grants-in-aid for scientific research from the Ministry of Education, Science, and Culture of Japan.

Address correspondence to

Moritoki Egi, MD

Department of Anesthesiology and Resuscitology, Okayama University Medical School.

2-5-1 Shikatachou, Okayama, Okayama 700-8525, Japan

Phone: +81-86-235-7778

Fax: +81-86-235-6985

E-mail: moriori@tg8.so-net.ne.jp

Conflict of interest: The author has declared no competing interests that might be perceived to influence the content of this manuscript. All remaining authors have declared that they have no proprietary, financial, professional, or any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered a potential conflict of interest that might have influenced the views expressed in this manuscript.

Trial registration: ClinicalTrials.gov (NCT01570881)

Abstract

Purpose: Delirium is a common complication in postoperative critically ill patients. Although abnormal melatonin metabolism is thought to be one of the mechanisms of delirium, there have been few studies in which the association between alteration of perioperative plasma melatonin concentration and postoperative delirium was assessed.

Materials: We conducted a prospective observational study to assess the association of perioperative alteration of plasma melatonin concentration with delirium in 40 postoperative patients who required intensive care for more than 48 hours. We diagnosed postoperative delirium using CAM-ICU and measured melatonin concentration 4 times (before the operation as the preoperative value, 1 hour after the operation, POD 1 and POD 2).

Results: Postoperative delirium occurred in 13 (33%) of the patients. Although there was no significant difference in preoperative melatonin concentration, delta melatonin concentration at 1 hour after the operation was significantly lower in patients with delirium than in those without delirium (-1.1 vs. 0 pg/ml, p=0.036). After adjustment of relevant confounders, delta melatonin concentration was independently associated with risk of delirium (odds ratio; 0.50, p=0.047).

Conclusions: Delta melatonin concentration at 1 hour after the operation has a significant independent association with risk of postoperative delirium.

Introduction

Delirium is a common complication in postoperative critically ill patients[1, 2]. Delirium appears to be correlated with increased rates of morbidity, mortality and long-term cognitive impairment[3]. Despite its importance, the etiology and pathophysiology of postoperative delirium are still not fully understood[4].

Melatonin is a hormone produced and secreted by the pineal gland. In postoperative patients, melatonin concentration may decrease[5-7] and lose its circadian variation[6, 8]. Such an abnormal melatonin metabolism or production is thought to be one of the mechanisms of postoperative delirium[9, 10]. However, there have been few studies in which the association of decrease in plasma melatonin concentration with delirium was assessed.

We therefore conducted a prospective observational study to assess the association of perioperative alteration of plasma melatonin concentration with delirium in postoperative patients. Our null hypothesis is that there is no significant association between delta plasma melatonin concentration from the preoperative value and delirium that develops within 48 hours after the operation.

Materials and Methods

Study design

This study was a prospective observational investigation conducted in a tertiary teaching hospital with 22 beds in the ICU. The study was approved by the Human Research Ethics Committee of Okayama University Hospital. Written informed consent was obtained from all patients.

Patients

Patients over 20 years of age who had undergone elective surgery with general anesthesia and were expected to require postoperative intensive care for more than 48 hours were included. This study was conducted from April 1, 2010 to January 31, 2011. Exclusion criteria were emergency surgery, cardiopulmonary bypass surgery and brain surgery, history of psychosis and dementia, history of or current substance drug/alcohol abuse and vision or hearing impairment.

The decision for discharge from the ICU was made by attending physicians, who were blinded to the results of CAM-ICUs and plasma melatonin concentrations, when a patient's physiologic status had stabilized and the patient was free from 1) requirement of mechanical ventilation or risk of re-intubation, 2) requirement of inotropic support or hemodynamic instability and 3) requirement of renal replacement therapy. Patients discharged from the ICU within 48

hours were excluded from this study.

Diagnosis of postoperative delirium

One trained physician (S.Y.) performed five assessments of delirium using CAM-ICU at 1 hour after the operation and at 8 AM and 5 PM on postoperative day (POD) 1 and POD 2 (Appendix 1). We defined patients with delirium as those with positive CAM-ICU in at least one of the 5 assessments.

Measurements of plasma melatonin concentration

We collected blood samples for measurements of plasma melatonin concentrations at 1) 8 AM before the operation as the preoperative value, 2) 1 hour after the operation, 3) 8 AM on POD 1 and 4) 8 AM on POD 2 (Appendix 1). Plasma was separated by centrifugation and stored at -30 ^{o}C in a polypropylene tube until the time of assay. Plasma melatonin concentrations were measured with a melatonin radioimmunoassay kit (Buhlmann Laboratories AG, Allschwil, Switzerland) (referential standard value in the morning: 2.8-5.6 pg/ml).

Then delta plasma melatonin concentration from the preoperative value in each measurement was calculated (Δ melatonin 1 hour, Δ melatonin POD 1, and Δ melatonin POD 2).

Light exposure in the ICU

Between 6 AM and 9 PM, all patients remained in standard artificial light from 300 lx to 750 lx. Between 9 PM and 6 AM, the patients remained quiet in bed with the television off and lights off unless it was necessary for assessment of vital signs and treatment (Appendix 1).

Sedation during mechanical ventilation

Patients who required postoperative mechanical ventilation were sedated using continuous propofol infusion of 1 to 3 mg/kg/h as long as necessary by the treating physician. None of the patients were given any benzodiazepines during mechanical ventilation.

Standard anesthesia

No premedication was given to any of the patients. Anesthesia was induced with propofol at 1-2 mg/kg, rocuronium at 0.6 mg/kg and fentanyl at 1-2 μg/kg or remifentanil at 0.3-0.5 μg/kg/minutes to facilitate tracheal intubation. Anesthesia was maintained by sevoflurane inhalation or propofol infusion with fentanyl and/or remifentanil. When epidural anesthesia was used, the epidural catheter was inserted preoperatively and a preemptive dose of local anesthetic was given before the surgical incision. Patients without epidural anesthesia received intravenous patient-controlled morphine infusion programmed to deliver morphine boluses of 1 mg with a lockout time of 10 min.

Patients' demographics

We obtained data for patients' demographics including age, sex, acute physiology and chronic health evaluation (APACHE) II score[11], Charlson comorbidity index[12], use of postoperative epidural analgesia, requirement of postoperative mechanical ventilation, operation categories, intraoperative blood loss and length of ICU stay.

Statistical analysis

The primary outcome was postoperative delirium. We separated patients with and without delirium. Demographic variables and delta melatonin concentrations were summarized using proportions or medians (interquartile ranges) as appropriate and compared using the chi square test and Wilcoxon rank-sum test.

Since a 100% increase of melatonin concentrations from the morning values is seen in the natural circadian rhythm in preoperative patients [5] and since the average preoperative melatonin concentration was 2.0 pg/ml in our pilot observations, we considered a difference of 2.0 pg/ml in delta melatonin concentration to be meaningful. To calculate the sample size for the current study, assuming a standard deviation of 2.0 pg/ml, an incidence of delirium of 30%, a power of 0.80, and an α level of 0.05, 40 participants were required.

To determine independent contribution of delta melatonin concentration to the prediction of postoperative delirium, we constructed multivariate models using potential predictors of delirium (criteria for inclusion at p=0.1). Results from the multivariate models were

shown using odds ratios with 95% confidence intervals. We determined model calibration using the Hosmer-Lemeshow test for goodness of fit. We tested for multicollinearity using the variance inflation factor. All variance inflation factors were less than 5, indicating absence of severe multicollinearity.

P values of less than 0.05 were considered statistically significant. All statistical analyses were performed using commercially available statistical software (SPSS 19.0, SPSS Inc., Chicago, IL). Data were reported in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines[13].

Results

We screened 66 candidates for enrollment. Among those 66 patients, there were 4 patients who declined to participate. We obtained written informed consent for participation from the remaining 62 patients. We excluded 22 patients, including one patient who canceled operation and 21 patients who did not require postoperative intensive care for more than 48 hours. Finally, 40 patients were included in this study, and all of them completed the study to follow-up (Fig. 1).

Postoperative delirium occurred in 13 (33%) of the patients. In those 13 patients, CAM-ICU was positive 2.6 per 5 assessments on average. Table 1 shows demographics of the patients with and without delirium. APACHE II score was significantly higher in patients with delirium ($p<0.001$). Patients with delirium tended to be older ($p=0.083$), have less frequent use of epidural analgesia ($p=0.059$) and more frequently require postoperative mechanical ventilation ($p=0.059$), and have a longer operation ($p=0.07$) than patients without delirium. The times of the start and end of the operation were not significantly different between the two groups ($p=0.21$ and 0.22, respectively).

The duration of mechanical ventilation was not significantly different between patients with and those without delirium ($p=0.35$). In patients with delirium, 5 of 9 patients (55.6%) were extubated from ventilation during a period of 48 hours after the operation, and this percentage

was not significantly different from that (70%, 7 of 10 patients) in patients without delirium (p=0.81). There was no patient who required re-intubation during the study period. Among patients who required mechanical ventilation, 17.8% of assessments could not be performed in patients with delirium because of deep sedation. This was not significantly different from the percentage (12.0%) in patients without delirium (p=0.56).

In patients with delirium, 30.8% (n=4) were administered anti-delirium drugs postoperatively (2: intravenous haloperidol in the ICU, 1: enteral quetiapine in the ICU and 1: oral lorazepam in the ward) and this percentage was significantly higher than that (0%) in patients without delirium. These drugs were administered after the study period.

The median preoperative plasma melatonin concentration in patients with delirium was 1.7 pg/ml, which was not significantly different from the median concentration of 1.2 pg/ml in patients without delirium (p=0.46). Table 2 shows a comparison of delta melatonin concentrations in patients with delirium and patients without delirium. The Δ melatonin 1 hour was significantly lower in patients with delirium than in patients without delirium (-1.1 vs. 0 pg/ml, p=0.037). There was no significant difference in Δ melatonin POD 1 or Δ melatonin POD 2 (Δ melatonin POD 1: -0.3 vs. 0.9 pg/ml, p=0.08; Δ melatonin POD 2: 0.6vs. 0 pg/ml, p=0.21). There was no significant difference in blood sampling time at 1 hour after the operation between the two groups (p=0.23).

Since age, APACHE II score, postoperative epidural analgesia, postoperative mechanical ventilation and operative duration may confound the association of Δ melatonin 1 hour with delirium, we performed multivariate analysis to assess their independent associations with risk of delirium. Even after adjustment for these relevant variables, Δ melatonin 1 hour was independently associated with postoperative delirium (Table 3). This model was a good fit for data (Hosmer- Lemeshow: p=0.90). There was no independent association of Δ melatonin POD 1 or Δ melatonin POD 2 with delirium (Δ melatonin POD 1: adjusted odds ratio=0.79 (95%CI: 0.55-1.14), p=0.21; Δ melatonin POD 2: adjusted odds ratio=1.05 (95%CI: 0.96-1.15), p=0.29).

Discussion

Main findings

This study was a prospective observational study to assess the association of perioperative alteration of plasma melatonin concentration with delirium in postoperative patients who required intensive care for more than 48 hours. Postoperative delirium diagnosed using CAM-ICU occurred in thirty-three percent of the patients. Although preoperative melatonin concentration was not significantly different, delta melatonin concentration at 1 hour after the operation was significantly lower in patients with delirium than in patients without delirium. Even after adjustment for relevant confounders, delta melatonin concentration at 1 hour after the operation was independently associated with risk of postoperative delirium.

Limitations of the study

This study has several limitations. First, this was an observational study in nature, and thus our findings showed an association but not a causality link. Our study, however, might have a potential to generate a hypothesis for establishing methods to prevent and/or treat postoperative delirium.

Second, this was a small single-center study with a chance of a type I error and weak generalizability. Although the study was conducted according to power analysis, our findings

should be confirmed or refuted by future studies.

Third, our study was conducted for only 48 hours, which might be too short to observe the development of postoperative delirium[14, 15]. Thus, observation for a longer period should be conducted in a future study. However, it should be noted that a significant association of alteration of melatonin concentration was found at 1 hour after the operation but not on POD 1 or POD 2. In this regard, a postoperative period of 48 hours may have been sufficient for the current study.

Fourth, we included a heterogeneous population of subjects who underwent a variety of surgical procedures, which may have resulted in different modifications of melatonin concentrations by stress response[7]. However, we found no significant difference in the type of operation between patients with delirium and those without delirium. Thus, the variety of operation may not have biased our findings.

Fifth, we used delta plasma melatonin concentrations from the preoperative value, not raw plasma melatonin concentrations. We decided to use delta since we assumed that preoperative melatonin values (8 AM before the operation) might vary among patients. We performed sensitive analysis to confirm whether our results using delta could be seen in raw values as well (appendix 2). Even using raw values, melatonin concentration at 1 hour after the operation was significantly lower in patients with delirium than in patients without delirium

(p=0.011).

Sixth, we included both patients with postoperative mechanical ventilation and those without postoperative mechanical ventilation, which might have affected the accuracy of diagnosis of delirium and confounded our findings. However, we used CAM-ICU for diagnosis of delirium in all study patients because it has been recommended for use in not only verbal patients[16] but also nonverbal mechanically ventilated patients[17]. Among patients who required mechanical ventilation, there was no significant difference in duration of mechanical ventilation or rate of extubation during the study period between patients with and those without delirium. Then, we reported an independent association of Δ melatonin 1 hour with delirium even after adjusting its effect. Nonetheless, our findings should be confirmed in a larger study in which subgroup analysis between patients with mechanical ventilation and those without mechanical ventilation can be performed.

Seventh, we excluded 22 patients who stayed in the ICU for less than 48 hours. Although this pre-planned exclusion criterion was for excluding patients who were admitted to the ICU but were not critically ill, this might have let to selection bias and skewed our results. However, our policy of ICU discharge is based on the patients' condition, and physicians who decided discharge from the ICU were blinded to the results of CAM-ICUs and plasma melatonin concentrations. In this regard, our exclusion criterion is unlikely to lead selection bias.

Finally, the timing of melatonin measurements might have affected our findings, since melatonin concentration has a circadian rhythm and nocturnal peak[18, 19]. However, there were no significant differences in blood sampling time at 1 hour after the operation, start and end time of operation between patients with delirium and those without delirium. Thus, the timing of measurements was unlikely to have biased our findings.

Prior findings related on the association of plasma melatonin concentration with postoperative delirium

So far, there have been two studies in which the relationship between plasma melatonin concentration and postoperative delirium was investigated. Miyazaki et al. studied 41 post-thoracic esophagectomy patients[20]. They defined delirium using their original criteria. The plasma melatonin concentration in patients with ICU-psychosis tended to be low on POD 1 but did not reach significance (p=0.27). Shigeta et al. studied 29 patients after major abdominal surgery[21]. They diagnosed delirium using CAM-ICU. They found no significant association between plasma melatonin concentration on POD 2 and incidence of postoperative delirium.

In our study, a significant association of delta melatonin concentration with delirium was observed at 1 hour after the operation. This association was weakened on POD 1(p=0.08) and disappeared on POD 2. Thus, our findings and the results of the two previous studies suggest

that the predictability of plasma melatonin concentration for postoperative delirium depends on the timing of monitoring and is stronger in the period immediately after the operation.

Interpretation of our findings

Melatonin is a hormone produced and secreted by the pineal gland. In the postoperative period, melatonin concentration has been reported to decrease [5-7] and lose its circadian variation[6, 8]. There are several possible explanations for the association of decrease in melatonin concentration with risk of later delirium.

First, decrease in melatonin concentration might be a sign of the severity of illness. Severity of illness score has been reported to correlate negatively with nocturnal melatonin concentration in patients with severe sepsis[22] and it has also been reported to be a significant precipitating risk factor for postoperative delirium[23].

Second, decrease in melatonin concentration might be a sign of the aging process. In the course of aging, the nocturnal peak usually decreases with considerable interindividual variability[24], and it is notable that age is one of the most frequently cited predisposing factors for postoperative delirium[23].

Third, administration of propofol for patients receiving postoperative mechanical ventilation might lower melatonin concentration and contribute to an increase in the risk of

delirium. Propofol has been shown to positively modulate gamma-aminobutyric acid (GABA) type A receptor function, which had interplay with the melatonergic system[25].

Fourth, decreased melatonin secretion in the postoperative period might trigger sleep disturbances and subsequent postoperative disruption of the sleep-wake cycle, which in turn may contribute to the development of delirium[26]. It should be noted that decrease in melatonin concentration was independently related to the risk of delirium even after adjustment for severity of illness, age and requirement of mechanical ventilation. Nonetheless, it should be noted that our results did not suggest any causality link between melatonin concentration and delirium.

Finally, there might be another unknown mechanism or any combination of the above mechanisms.

Conclusions

In the current study conducted in postoperative patients who required intensive care for 48 hours, the reduction of plasma melatonin concentration at 1 hour after the operation from the preoperative value was significantly larger in patients with delirium than in those without delirium. Further study is needed to confirm or refute our findings.

Acknowledgement: The current trial was registered at ClinicalTrials.gov (NCT01570881).

References

1Guenther U, Radtke FM: Delirium in the postanaesthesia period. Curr Opin Anaesthesiol 24:670-675, 2011

2Deiner S, Silverstein JH: Postoperative delirium and cognitive dysfunction. Br J Anaesth 103 Suppl 1:i41-46, 2009

3van den Boogaard M, Schoonhoven L, Evers AW, et al.: Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Crit Care Med 40:112-118, 2012

4Flacker JM, Lipsitz LA: Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci 54:B239-246, 1999

5Gogenur I, Ocak U, Altunpinar O, et al.: Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. World J Surg 31:290-298, 2007

6Guo X, Kuzumi E, Charman SC, et al.: Perioperative melatonin secretion in patients undergoing coronary artery bypass grafting. Anesth Analg 94:1085-1091, table of contents, 2002

7Cronin AJ, Keifer JC, Davies MF, et al.: Melatonin secretion after surgery. Lancet 356:1244-1245, 2000

8Ram E, Vishne TH, Weinstein T, et al.: General anesthesia for surgery influences melatonin and cortisol levels. World J Surg 29:826-829, 2005

9Lewis MC, Barnett SR: Postoperative delirium: the tryptophan dyregulation model. Med Hypotheses 63:402-406, 2004

10van der Mast RC, Fekkes D: Serotonin and amino acids: partners in delirium pathophysiology? Semin Clin Neuropsychiatry 5:125-131, 2000

11Knaus WA, Draper EA, Wagner DP, et al.: APACHE II: a severity of disease classification system. Crit Care Med 13:818-829, 1985

12Charlson ME, Pompei P, Ales KL, et al.: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373-383, 1987

13von Elm E, Altman DG, Egger M, et al.: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453-1457, 2007

14Fricchione GL, Nejad SH, Esses JA, et al.: Postoperative delirium. Am J Psychiatry 165:803-812, 2008

15O'Keeffe ST, Ni Chonchubhair A: Postoperative delirium in the elderly. Br J Anaesth 73:673-687, 1994

16Ely EW, Inouye SK, Bernard GR, et al.: Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 286:2703-2710, 2001
17Wei LA, Fearing MA, Sternberg EJ, et al.: The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc 56:823-830, 2008
18Claustrat B, Brun J, Chazot G: The basic physiology and pathophysiology of melatonin. Sleep Med Rev 9:11-24, 2005
19Brzezinski A: Melatonin in humans. N Engl J Med 336:186-195, 1997
20Miyazaki T, Kuwano H, Kato H, et al.: Correlation between serum melatonin circadian rhythm and intensive care unit psychosis after thoracic esophagectomy. Surgery 133:662-668, 2003
21Shigeta H, Yasui A, Nimura Y, et al.: Postoperative delirium and melatonin levels in elderly patients. Am J Surg 182:449-454, 2001
22Perras B, Kurowski V, Dodt C: Nocturnal melatonin concentration is correlated with illness severity in patients with septic disease. Intensive Care Med 32:624-625, 2006
23Steiner LA: Postoperative delirium. Part 1: pathophysiology and risk factors. Eur J Anaesthesiol 28:628-636, 2011
24Hardeland R: Melatonin in aging and disease -multiple consequences of reduced secretion, options and limits of treatment. Aging Dis 3:194-225, 2012
25Naguib M, Gottumukkala V, Goldstein PA: Melatonin and anesthesia: a clinical perspective. J Pineal Res 42:12-21, 2007
26Tabet N, Howard R: Pharmacological treatment for the prevention of delirium: review of current evidence. Int J Geriatr Psychiatry 24:1037-1044, 2009

Table 1. Comparison of demographics of patients with and without delirium.

Characteristic	Patients with delirium (n=13)	Patients without delirium (n=27)	p-value	Total (n=40)
Age (y)	73 (63, 77)	64 (57, 73)	0.083	65 (60, 74)
Sex (Male)	11 (85%)	22 (81%)	0.81	33 (83%)
APACHE II score	18 (16, 21)	13 (12, 16)	<0.001	15 (13, 17)
Charlson comorbidity index	2 (1, 2)	2 (1, 3)	0.58	2 (1, 2)
Postoperative epidural analgesia	4 (31%)	17 (63%)	0.059	21 (53%)
Operation categories				
Gastrostomy	1 (7.7%)	2 (7.4%)	0.54	3 (7.5%)
Esophageal reconstruction	2 (15.4%)	4 (14.8%)	0.67	6 (15%)
Esophagectomy	4 (30.8%)	4 (14.8%)	0.45	8 (20%)
Pancreaticoduodenectomy	0 (0%)	5 (18.5%)	0.25	5 (12.5%)
Liver resection	1 (7.7%)	1 (3.1%)	0.82	2 (5%)
Lung resection	0 (0%)	4 (14.8%)	0.39	4 (10%)
Laryngectomy	5 (38.5%)	6 (22.2%)	0.48	11 (27.5%)
Spinal surgery	0 (0%)	1 (3.1%)	0.71	1 (2.5%)
Operation time (min)	530 (412, 643)	401 (303, 537)	0.07	416 (331, 611)
Intraoperative blood loss (ml)	430 (300, 575)	420 (230, 825)	1.00	425 (276, 814)
Postoperative mechanical ventilation	9 (69%)	10 (37%)	0.059	19 (48%)
Duration of mechanical ventilation (hours)	38.8 (17.7, 62.4)	16.3 (13.7, 118.5)	0.37	35.1 (14.9, 62.7)
Length of ICU stay (days)	3 (3, 7)	3 (2, 6)	0.38	3 (2, 6)

Results are shown as median, 25% and 75% quartiles, or number and proportion. Statistical analysis was performed for comparison of patients with delirium and patients without delirium.

ASA: American Society of Anesthesiologists, APACHE: acute physiology and chronic health evaluation, ICU: intensive care unit

Table 2. Comparison of delta melatonin concentrations in patients with and without delirium.

delta melatonin concentration (pg/ml)	Patients with delirium (n=13)	Patients without delirium (n=27)	p-value
Δ melatonin 1 hour	-1.1 (-1.7, 0.2)	0 (-0.8, 3.1)	0.036
Δ melatonin POD 1	-0.3 (-1.7, 0.5)	0.9 (-0.1, 3.1)	0.08
Δ melatonin POD 2	0.6 (0, 2.6)	0 (-0.9, 1.5)	0.21

Results are shown as median, 25% and 75% quartiles. Statistical analysis was performed for comparison of patients with delirium and patients without delirium.

POD: postoperative day

Table 3. Multivariate logistic regression analysis for postoperative delirium.

Variables	odds ratio (95% CI)	p-value
Age	1.18 (1.02, 1.36)	0.03
APACHE II score	1.76 (1.09, 2.85)	0.022
Postoperative epidural analgesia	0.27 (0.02, 3.55)	0.32
Postoperative mechanical ventilation	14.1 (0.38, 519.2)	0.15
Operative duration	1.00 (0.99, 1.01)	0.83
Δ melatonin 1 hour	0.50 (0.26, 0.99)	0.047

95%CI: 95% confidence interval

Figure 1.

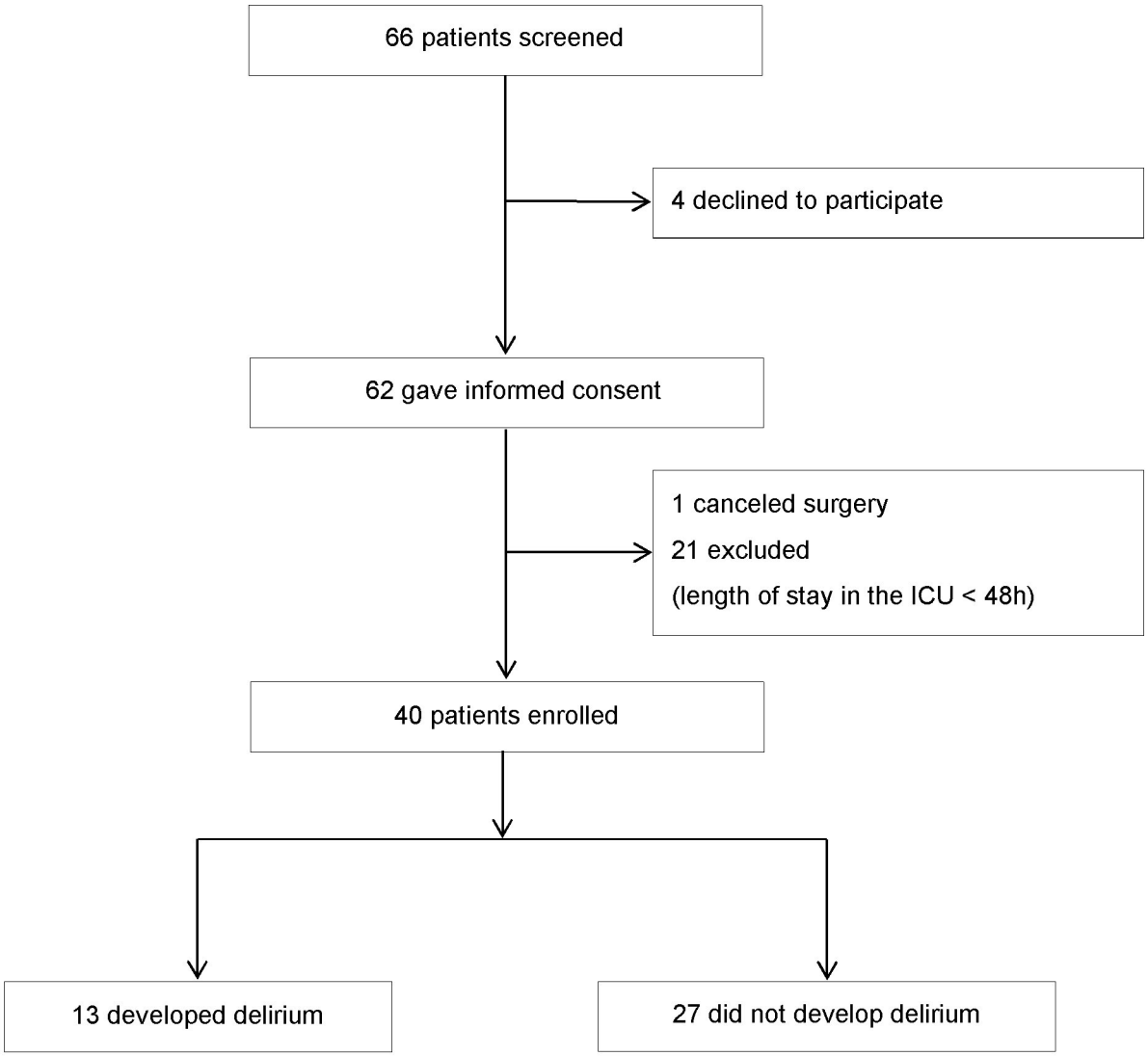
66 patients screened
4 declined to participate
62 gave informed consent
1 canceled surgery
21 excluded
(length of stay in the ICU < 48h)
40 patients enrolled
13 developed delirium
27 did not develop delirium

Figure legends

Figure 1. Study flow chart.