

Intravenous Patient-controlled Analgesia Has a Positive Effect on the Prognosis of Delirium in Patients Undergoing Orthopedic Surgery

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Background:

Postoperative delirium is relatively common. However, the relationship between intravenous patient-controlled analgesia (IV-PCA) and delirium has not been thoroughly investigated. The aim of this study was to evaluate the effects of IV-PCA on the prognosis of postoperative delirium in patients undergoing orthopedic surgery.

Methods:

Medical records of 129 patients with postoperative delirium were reviewed. Patients were divided into two groups according to whether they used IV-PCA with fentanyl and ketorolac. The IV-PCA group consisted of 73 patients who were managed with IV-PCA; the NO-PCA group consisted of 56 patients who were managed without PCA.

Results:

Incidences of multiple psychiatric consultations and prolonged delirium were significantly lower in patients using IV-PCA with fentanyl and ketorolac than in those without PCA.

Conclusions:

We recommend the use of IV-PCA for pain control and management of delirium in patients with postoperative delirium. (Korean J Pain 2014; 27: 271-277)

Key Words:

delirium, patient-controlled analgesia, postoperative, psychiatric.

Received March 18, 2014. Revised May 17, 2014. Accepted June 10, 2014.

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INTRODUCTION

Postoperative delirium is relatively common [1–3], and is often ignored because of spontaneous improvement or because of its relatively mild symptoms. However, some patients experience persistent and severe symptoms that do not respond to treatment. These patients arouse concern in guardians and doctors; moreover, the patients displaying a poor prognosis incur increased costs and have extended hospital stays [4–6].

Recently, the use of intravenous patient-controlled analgesia (IV-PCA) has been increasing in patients undergoing surgery. However, pain and opioid use are the main causes of postoperative delirium [7], and IV-PCA commonly employs opioids. Therefore, the use of IV-PCA may affect postoperative delirium. Surprisingly, the relationship between IV-PCA and delirium has not been thoroughly investigated.

In the present study, we aimed to evaluate the effects of IV-PCA using fentanyl and ketorolac on the prognosis of postoperative delirium in patients undergoing orthopedic surgery.

MATERIALS AND METHODS

The present study was a retrospective analysis of postoperative delirium in patients who underwent orthopedic surgery at a single university hospital from January through December of 2012. This study was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [8], approved by the local institutional review board, and conducted in accordance with the Declaration of Helsinki [9].

A total of 1625 patients underwent orthopedic surgery between January 1 and December 31, 2012. Patients were included in this study if they had undergone orthopedic surgery with regional or general anesthesia, if they had displayed postoperative delirium, and if they had received at least one psychiatric management consultation during the postoperative period. Patients with preoperative delirium or epidural PCA were not enrolled in the study. Of the 1625 patients, 912 patients used PCA through the intravenous route and 132 patients received psychiatric management for postoperative delirium. Of the 132 patients who satisfied the inclusion criteria, three were excluded because it was difficult to differentiate delirium from

dementia. The final 129 patients were divided into one of two groups according to whether they used IV-PCA. The IV-PCA group consisted of 73 patients, and the NO-PCA group consisted of 56 patients.

Before surgery was completed, the PCA pump (AutoMed3400[®], Ace Medical, Seoul, Korea) was initiated via intravenous infusion. The PCA solution contained fentanyl, ketorolac tromethamine, and Ondansetron mixed with 100 ml normal saline. The basal infusion rate was set at 2 ml/h, the bolus at 2 ml, and the lockout time at 12 minutes. The initial dose of fentanyl was 800–1200 μ g and that of ketorolac tromethamine was 90–150 mg, depending on the physical status and body weight of the patient as well as the surgical procedure the patient underwent. Mean duration of PCA use was 55.6 ± 10.9 h (between 48 and 96 h in each patient), with a mean fentanyl dose of 1018 ± 128 μ g, and a mean ketorolac dose of 116.0 ± 20.4 mg. In patients not using PCA, morphine sulfate, meperidine, fentanyl, oxycodone, and ketorolac tromethamine were used as rescue analgesics. All opioids administered to the patients were converted to their equivalent dose of 10 mg of IV morphine sulfate; 100 μ g of IV fentanyl, 30 mg of oral oxycodone, or 75 mg of IV meperidine [10,11].

For the comparison of response to psychiatric management in patients with or without IV-PCA, patients with postoperative delirium were divided into two groups according to the number of psychiatric consultations received and duration of delirium symptoms. Previous studies have reported a median delirium duration of 3–5 days [12,13]. In the present study, the re-consult of patients with postoperative delirium was performed after 1 week. Therefore, one group consisted of patients who had received one psychiatric consultation and displayed improved symptoms after 7 days, while the other group consisted of patients who had received multiple psychiatric consultations and displayed persistent symptoms for more than 7 days. Because previous studies have reported that most patients who have undergone orthopedic surgery and display delirium recover within 4 weeks [14,15], we defined "transient delirium" as postoperative delirium lasting 4 weeks or less and "prolonged delirium" as delirium lasting more than 4 weeks [15].

The following data were collected from each patient's medical records: age, gender, weight, height, total surgery time, total anesthesia time, American Society of Anesthesiologists physical status, type of anesthesia, use of

IV-PCA, total opioid dose, admission to the intensive care unit (ICU), emergency surgery, intraoperative hypotension, pre-existing cognitive impairment, blood transfusion, time from surgery to psychiatric management, type of surgery, and comorbidities. All patients were diagnosed with delirium by psychiatrists. Development and duration of delirium were evaluated using the Confusion Assessment Method [16].

1. Statistical analysis

Data are presented as means \pm standard deviations, or number of patients (%). Unpaired *t*-tests were used to compare differences between group means, and Chi-square tests were used to compare differences between group proportions. In all comparisons, $P < 0.05$ was considered significant. Statistical analyses were performed using SPSS, version 21.0 (IBM Corporation, USA).

RESULTS

Patient characteristics are presented in Table 1. There were no significant differences between groups in terms of age, gender, weight, height, total surgery time, total anes-

thesia time, American Society of Anesthesiologists physical status, total opioid dose, pre-existing cognitive impairment, type of anesthesia, admission to the ICU, emergency surgery, intraoperative hypotension, blood transfusion, and time from operation to psychiatric management.

Table 2 lists surgical procedures used in the patients. Internal fixation was the most commonly applied surgical procedure, followed in descending order of frequency by spine fusion, and arthroplasty. The number of patients that underwent internal fixation, spine fusion, and arthro-

Table 2. Surgical Procedures of Patients with Postoperative Delirium

Surgical procedure	Total (n = 129)	Group IV-PCA (n = 73)	Group NO-PCA (n = 56)
Internal fixation	49	20	29
Spinal fusion	36	26	10
Arthroplasty	34	25	9
Et cetera	10	2	8

Data are presented as number of patients. Group IV-PCA: patients with intravenous patient-controlled analgesia, Group NO-PCA: patients without patient-controlled analgesia, PCA: patient-controlled analgesia.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Total (n = 129)	Group IV-PCA (n = 73)	Group NO-PCA (n = 56)
Age (yr)	64 \pm 17.2	64 \pm 17.1	64 \pm 17.2
Gender (M/F)	68 / 61	38 / 35	30 / 26
Weight (kg)	63 \pm 11.5	63 \pm 11.2	63 \pm 11.7
Height (cm)	158 \pm 11	159 \pm 11	158 \pm 9
Surgery time (min)	166 \pm 70	155 \pm 66	180 \pm 74
Anesthetic time (min)	195 \pm 71	177 \pm 70	218 \pm 73
ASA physical status	2.4 \pm 0.7	2.4 \pm 0.7	2.5 \pm 0.7
Time until consult (days)	5.6 \pm 5.2	6.1 \pm 5.6	4.9 \pm 4.8
Total opioid dose, from surgery until delirium onset (morphine equivalents, mg)	99 \pm 15	102 \pm 13	96 \pm 18
Type of anesthesia			
General	82 (64%)	45 (62%)	37 (66%)
Regional	47 (36%)	28 (38%)	19 (34%)
Hypotension	61 (47%)	34 (46%)	27 (48%)
Transfusion	44 (34%)	26 (36%)	18 (32%)
ICU admission	80 (62%)	43 (59%)	37 (66%)
Emergency operation	13 (10%)	7 (10%)	6 (11%)
Pre-existing cognitive impairment	17 (13%)	8 (12%)	9 (16%)

Data are presented as mean \pm SD or number of patients (%). Group IV-PCA: patients with intravenous patient-controlled analgesia, Group NO-PCA: patients without patient controlled analgesia, Time until consult: time interval from surgery until postoperative psychiatric consultation, ICU: intensive care unit, PCA: patient-controlled analgesia, ASA: American Society of Anesthesiologists. There were no significant differences between groups.

Table 3. Psychiatric Management of Patients with Postoperative Delirium

Psychiatric management	Total (n = 129)	Group IV-PCA (n = 73)	Group NO-PCA (n = 56)
One consultation	89 (69%)	57 (78%)	28 (50%)
Multiple consultations	40 (31%)	16 (22%)	28 (50%)*

Data are presented as number of patients (%). Group IV-PCA: patients with intravenous patient-controlled analgesia, Group NO-PCA: patients without patient-controlled analgesia, PCA: patient-controlled analgesia. * $P < 0.05$, versus Group PCA.

Table 4. Prognosis of Patients with Postoperative Delirium

Prognosis	Total (n = 129)	Group IV-PCA (n = 73)	Group NO-PCA (n = 56)
Transient	103 (80%)	63 (86%)	40 (71%)
Prolonged	26 (20%)	10 (14%)	16 (29%)*

Data are presented as number of patients (%). Group IV-PCA: patients with intravenous patient-controlled analgesia, Group NO-PCA: patients without patient-controlled analgesia, PCA: patient-controlled analgesia. * $P < 0.05$, versus Group PCA.

plasty was 49, 36, and 34, respectively (Table 2).

All 129 patients received postoperative psychiatric management. Of the 129 patients, 89 received one psychiatric consultation, and 40 received multiple psychiatric consultations. The number of patients who received multiple psychiatric consultations in the IV-PCA group versus the NO-PCA group was 16 (22%) and 28 (50%), respectively (Table 3, $P < 0.05$). Of the 129 patients, 103 had transient delirium while 26 had prolonged delirium. The number of patients with prolonged delirium was 10 (14%) and 16 (29%) in IV-PCA and NO-PCA groups, respectively (Table 4, $P < 0.05$).

DISCUSSION

The present study showed that incidences of multiple psychiatric consultations and prolonged delirium were significantly lower in patients using IV-PCA than in patients without PCA.

The American Psychiatric Association defines delirium as an acute fluctuating disturbance of consciousness with signs of inattention, accompanied by a change in cognition and perception [17]. The main symptoms include changes in the level of consciousness, disorganized thinking, dis-

orientation, and disturbed memory [18,19]. Delirium usually develops within a week after surgery [1,18]. Postoperative delirium is the most common mental disorder of the psycho-neuronal system [20]. Thus, it is not surprising that surgery and anesthesia are powerful predisposing factors for delirium [21]. The average incidence of delirium in postoperative patients has been reported as 36.8% (range 9–87%) [18,19]. However, in the present study the incidence of delirium in the patients who underwent orthopedic surgery was 8%. The low incidence of delirium in this study could be due to the fact that a diagnosis of delirium was not made in patients that exhibited mild symptoms where psychiatric management was deemed unnecessary. Moreover, we found no significant difference in the prevalence of delirium between patients using intravenous PCA and those without PCA.

Along with surgery and anesthesia, older age and postoperative ICU stays are major risk factors for delirium [1,7]. Sieber et al. [22] reported that the incidence of ICU admission in patients with delirium was 36.7%. In the present study, the incidence of ICU admission in patients with delirium was 62%. This relatively high frequency could be due to factors related to delirium, such as older age, preexisting medical comorbidities, cognitive and functional impairment, stress, pain, and fluid and electrolyte disturbances [1,23]. Interestingly, the abovementioned causes are also factors that will determine whether or not a postoperative patient will be transferred to the ICU. In the present study, the average age of patients with postoperative delirium was 64 years. As previously mentioned, postoperative delirium and cognitive dysfunction have been reported to occur more frequently and more severely in elderly patients [24,25]. Therefore, medical personnel, including anesthesiologists, should closely monitor the condition of elderly patients. Patients who experience delirium after surgery also have higher risks of developing postoperative cognitive dysfunction and long-term cognitive impairment [21,24]. Moreover, patients with preoperative diseases that are accompanied by cognitive impairment, such as dementia or Alzheimer's disease, have a higher incidence of postoperative delirium [24,26]. Thus, it should be noted that cognitive decline can be exacerbated in these patients [21,24]. Along with a greater risk of experiencing delirium, it has been reported that patients with pre-existing cognitive impairment also endure prolonged delirium [27]. Lee et al. [15] reported that the incidence of prolonged

delirium in elderly patients after hip surgery was 20%. In the current study, the rate of prolonged delirium in patients using IV-PCA and without PCA was 14% and 29%, respectively. However, the number of patients with preoperative cognitive impairment was not significant between IV-PCA and NO-PCA groups. Recently, the management of patients with dementia and the aging population have become important social issues. Furthermore, patients with postoperative delirium have increased morbidity, mortality, and prolonged hospital stays [6]. Therefore, there is an increase need for the prevention and management of postoperative delirium.

In general, the type of anesthetic and analgesic methods employed have no bearing on postoperative delirium [1,18]. A meta-analysis found no difference between epidural and intravenous analgesia in preventing postoperative delirium [18]. IV-PCA is often used for pain control in patients undergoing orthopedic surgery [28]. While pain and opioids are both contributing factors to the occurrence of postoperative delirium [1,29,30], we found no significant effect of opioid dose on incidence of delirium or between PCA groups. However, incidences of multiple psychiatric management consultations and prolonged delirium were significantly lower in patients using IV-PCA than in those without PCA. These results indicate that the use of IV-PCA has positive effects on the management of delirium. Pre-existing cognitive impairment is strongly associated with prognosis of delirium [31]. However, in the present study, incidence of patients with preoperative cognitive impairment was no significant difference between groups.

As we have previously mentioned, pain has been shown to be associated with delirium development [7,32]. Moreover, undertreated pain and inadequate analgesia can either cause or exacerbate delirium [29]. The IV-PCA can provide improved analgesia compared with conventional opioid treatment [33]. Therefore, the poor prognosis of patients without PCA may be due to insufficient pain control. While many patients need opioids for postoperative pain control, there is controversy as to whether opioid administration may itself be a risk factor for postoperative delirium [22,32]. Therefore, short-acting drugs such as remifentanyl should be used instead of long-acting drugs like meperidine. In addition, replacing opioids with other medications such as pregabalin and gabapentin can help prevent psychiatric symptoms including delirium [1,18]. In the

present study, the opioid used in the IV-PCA was the intermediate-acting drug, fentanyl. When the above results were considered, adequate pain control through the use of IV-PCA with fentanyl had a positive effect on the prognosis of delirium without the negative side effects of opioids.

The first and most important step in the management of postoperative delirium is to remove reversible precipitating factors. The cause of delirium is usually complex, involving various elements [18,34], which include advanced age, dementia, depression, malnutrition, inflammation, alcohol, stress, surgery, and neurotransmitters such as acetylcholine and dopamine [18,34]. However, certain factors can be prevented by pre recognition, such as pain, anxiety, sleep disturbances, hypoxia, hypoglycemia, electrolyte imbalances, shock, ICU admission, prolonged hospital stays, and drugs such as sedatives [18,35]. In hospital patients, 30 to 40% of delirium cases are thought to be preventable [36]. Zhang et al. [18] reported that dexmedetomidine sedation, multicomponent interventions, and antipsychotics were useful in preventing postoperative delirium. It is important to note that prevention is more effective than management of postoperative delirium. Therefore, medical practitioners should attempt to prevent postoperative delirium. If prevention is not possible, it has been reported that the administration of antipsychotic drugs can be effective if postoperative psychiatric symptoms have already occurred [37,38]. In fact, in the present study, most patients received antipsychotic agents such as risperidone and quetiapine for the management of postoperative psychiatric disorders.

There were some limitations to this study. First, this study was retrospective; however, a prospective study is difficult to perform because the occurrence of delirium cannot be predicted. The retrospective study design was also selected because the study was performed in patients who received psychiatric management. Second, the present study did not collect data from patients undergoing a single type of surgical procedure. However, a single surgical procedure is unlikely to have similar proportions of patients with and without PCA. Therefore, our study was performed in patients undergoing various types of orthopedic surgery. In spite of the above limitations, this study is valuable as it is the first to evaluate the relationship between IV-PCA and the prognosis of postoperative delirium.

In conclusion, the incidences of multiple psychiatric

managements and prolonged delirium were significantly lower in patients with IV-PCA using fentanyl and ketorolac than in patients without PCA. Therefore, we recommend the use of IV-PCA for pain control and management of delirium in patients with postoperative delirium.

ACKNOWLEDGEMENTS

This study was supported by 2013 Research Grant (No. 120131405) from Kangwon National University.

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