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ORIGINAL ARTICLE

Impact of remifentanil introduction on practice patterns in general anesthesia

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Abstract
Purpose The introduction of new medicine can change clinical practice patterns and may affect patient outcomes. In the present study, we investigated whether introduction of remifentanil in Japan affected the practice patterns of anesthesia.
Methods Using the Japanese Diagnosis Procedure Combination database, we extracted records of 423,491 patients who underwent surgery with general anesthesia in 243 hospitals before (2006) and after (2007) the introduction of remifentanil, and identified anesthetic agents used for each patient. A hierarchical mixed-effects logistic regression analysis was performed to analyze the factors that affected selection of remifentanil. Further, we compared postoperative length of stay (LOS), in-hospital mortality, and total costs between 2006 and 2007.
Results In 2007, remifentanil was used for up to 41.4% of all general anesthesia, accompanied by a reduction in nitrous oxide use and an increase in total intravenous anesthesia. Female gender, increasing age, and preoperative comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with the use of remifentanil, whereas accompanying cardiac disease and co-application of epidural anesthesia were negatively associated. In 2007, a similar in-hospital death rate, similar or decreased total costs, slightly reduced duration of anesthesia, and substantially reduced postoperative LOS were seen compared to those in 2006.
Conclusions Our data revealed rapid changes in practice patterns in anesthesia after the introduction of remifentanil in Japan. Remifentanil was used more often in patients with comorbidities and without epidural anesthesia, and its introduction did not affect increase in total medical costs.

Keywords Remifentanil · Anesthetic practice · Postoperative outcome · In-patient medical cost

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Introduction

The introduction of new medical devices such as the drug-eluting stent for angina pectoris [1] or new drugs such as anti-tumor necrosis factor-α antibody for rheumatoid arthritis [2] had a major impact on medical practice patterns over a short time period, affecting not only patient outcomes but also total medical costs, although published reports gave variable results [3].

In anesthesiology, only a limited number of reports show changes in practice patterns in anesthesia [4]. It is

also not clear to what extent such changes affect medical costs and patient outcome [5].

Remifentanil, a mu-opioid receptor agonist, has a unique pharmacokinetic profile, characterized by rapid equilibration with the central compartment, and a short half-life, independent of infusion duration [6, 7]. Although its use is common in Western countries [8], it was finally approved in Japan in December 2006, and its use in clinical practice commenced in January 2007. The unique pharmacological properties of this novel drug facilitated its rapid assimilation into Japanese clinical procedures, making a considerable impact on anesthetic practice. However, accurate data have not been reported on the expansion of remifentanil use and the subsequent changes in practice patterns in general anesthesia. In addition, the effects of remifentanil introduction on patient outcomes remain unclear.

In the present study, we investigated the proportion of remifentanil use in the first year of its introduction and changes in the patterns of anesthetic drug use. Then, we analyzed factors affecting selection of remifentanil. We also compared duration of anesthesia and total costs as well as postoperative length of stay (LOS) and in-hospital mortality before and after introduction of remifentanil, using the nationwide Japanese administrative claims database, the Diagnosis Procedure Combination (DPC) database.

Materials and methods

DPC database and participants

The DPC is a mixed-case system, similar to the diagnosis-related groups (DRG) in the U.S. Medicare program. It was launched in 2002 by the Ministry of Health, Labor and Welfare of Japan and is linked with a lump-sum payment system. Key objectives of the DPC system are to implement a standardized electronic claims system and to provide transparency of hospital performance [9, 10]. All 82 university teaching hospitals must adopt the DPC system, and community hospitals can voluntarily adopt this system. Data are mainly used for profiling practice patterns, refining case-mix classification, and planning health policies such as resource allocation.

The DPC database comprises discharge abstracts and administrative claims, with data compiled between July 1 and December 31 each year by the DPC Research Group [10–13]. The database initially included 82 hospitals in 2003. The numbers of inpatients and participant hospitals are increasing each year, with around 3 million patients from 926 hospitals in 2007, which represented approximately 45% of all acute care inpatient hospitalizations in Japan [11]. The database includes the following data: unique identification number of each hospital; patient age and sex; diagnoses recorded in the Japanese language together with the *International Classification of Diseases, 10th Revision*; surgical procedures coded with original Japanese codes; drugs and devices used; LOS; in-hospital mortality; and total costs (including costs for hospitalization, surgery, anesthesia, drugs and devices used).

The DPC database corresponds to the Nationwide Inpatient Sample in the United States [14] to some extent but has several advantages [10]. To optimize the validity of the recorded diagnoses, physicians in charge record the diagnoses in reference to the medical charts. Detailed data are available for the treatments administered on a daily basis (e.g., types of drugs administered, duration of anesthesia, volume of blood transfusion). Medical clerks and licensed medical information managers accurately record the dates of each surgery and other procedures and the dates of use of each drug and device. Physicians and hospitals consistently comply with data submission because it is mandatory to obtain DPC-based reimbursement of medical fees.

All patient identifiers have been removed from this database. Because of the anonymous nature of the data, obtaining informed consent from patients was unnecessary. The Institutional Review Board of the University of Occupational and Environmental Health approved this study design.

Data extraction

To compare the pre-remifentanil period (July–December 2006) with the remifentanil treatment period (July–December 2007), we included data from all 243 hospitals that participated in the DPC survey in both years. We extracted data on all surgical patients who underwent general anesthesia in these hospitals, including type of hospital, type of admission, patient age, sex, surgical procedures, duration of anesthesia (min), volume of blood transfusion, postoperative LOS (days), in-hospital mortality, and total costs. General anesthesia was defined as anesthesia for surgery for at least 20 min with volatile anesthetics and/or intravenous anesthetics supplemented with oxygen via a mask including laryngeal mask or endotracheal tube.

We also extracted data regarding medications used for general anesthesia, including barbiturates, nitrous oxide, volatile anesthetic agents, muscle relaxants, hypnotics, and narcotics.

Patients who underwent the following eight classes of surgery in 2007 were subdivided to evaluate differences in distribution of remifentanil among surgical subcategories: cardiac surgery, neurosurgery, thoracic surgery, vascular surgery, general surgery, gynecology, orthopedic surgery, and otolaryngology. When a patient underwent two or more surgeries during the hospitalization, the patient was

classified into one group according to the most recent surgery. If a patient underwent multiple surgeries at the same time, we selected the one surgery that required the most medical resources. Postoperative LOS was determined as the days between the day of the surgery and that of discharge.

Descriptive statistics

The proportions of patients who received each drug were compared between 2006 and 2007. Combinations of remifentanil and fentanyl, and of nitrous oxide and volatile agents, were also compared between the 2 years. Further, postoperative in-hospital mortality, duration of anesthesia, postoperative LOS, and total costs were compared between the 2 years for all populations and eight surgical subcategories.

Logistic regression to determine factors for selecting remifentanil

To determine possible contributing factors for selection of remifentanil, we extracted the data of patients who had general anesthesia with either fentanyl alone or remifentanil and fentanyl in 2007. In the logistic regression model, the dependent variable was set as "remifentanil use" (fentanyl alone = 0; both remifentanil and fentanyl = 1). A hierarchical mixed-effects logistic regression analysis was performed in which age, sex, intraoperative use of epidural anesthesia, comorbidities, and surgical subcategories were set as fixed effects, and sites (described by unique identifiers for all 243 hospitals) were used as random intercepts.

Statistical analysis

We performed univariate comparisons of variables for the two groups, using the Mann–Whitney *U* test for nonparametric data and the chi-square test for categorical data as appropriate. All statistical analyses were conducted using the SAS 9.1 (SAS Institute, Cary, NC, USA), and *P* values <0.05 were considered to be significant. The exchange rate was assumed to be 100 yen to 1 U.S. dollar (USD).

Results

Patient demographics

All 243 acute care hospitals that participated in DPC in both 2006 and 2007 were enrolled in this study. A total of 423,491 patients (206,102 in 2006 and 217,389 in 2007) were identified. Overall, 59.6% of patients were admitted to 53 teaching hospitals, while the remaining 40.4% were treated at 190 non-teaching hospitals (Supplemental Tables 1, 2).

Anesthetic drug used

Table 1 shows the use of each anesthetic drug in 2006 and 2007. Remifentanil accounted for 41.4% of all general anesthesia usage in 2007. The proportion of cases in which either fentanyl or remifentanil was used increased from 76.5% in 2006 to 83.3% in 2007. The proportion including remifentanil in 2007 was higher in teaching hospitals than

Table 1 Anesthetic drugs used

Drug	2006 (n = 206,102) (%)	2007 (n = 217,389) (%)	P*
Narcotics			
Remifentanil	0.0	41.4	<0.001
Fentanyl	76.5	71.2	<0.001
Morphine	13.7	13.4	<0.001
Hypnotics			
Barbiturates	18.4	14.9	<0.001
Propofol	72.8	76.9	<0.001
Midazolam	9.4	12.6	<0.001
Nitrous oxide	25.8	14.0	<0.001
Volatile anesthetic agents			
Sevoflurane	79.5	74.2	<0.001
Isoflurane	4.6	3.3	<0.001
Halothane	0.1	0.1	0.732
Muscle relaxants			
Suxamethonium	0.5	1.3	<0.001
Vecuronium	84.2	81.9	<0.001
Rocuronium	0.0	2.6	<0.001
Pancuronium	1.0	0.9	0.158
Others			
Droperidol	12.2	13.9	<0.001
Ketamine	5.1	3.8	<0.001
Diazepam	1.3	1.2	0.023
Combination of fentanyl and remifentanil			
Neither	23.5	16.7	<0.001
Fentanyl alone	76.5	41.9	<0.001
Remifentanil alone	0.0	12.1	<0.001
Both	0.0	29.3	<0.001
Combination of nitrous oxide and volatile agents			
Neither	14.0	21.0	<0.001
Nitrous oxide alone	2.1	1.6	<0.001
Volatile agents alone	60.1	65.0	<0.001
Both	23.8	12.4	<0.001

* P value for the comparison between 2006 and 2007 evaluated with the chi-square test

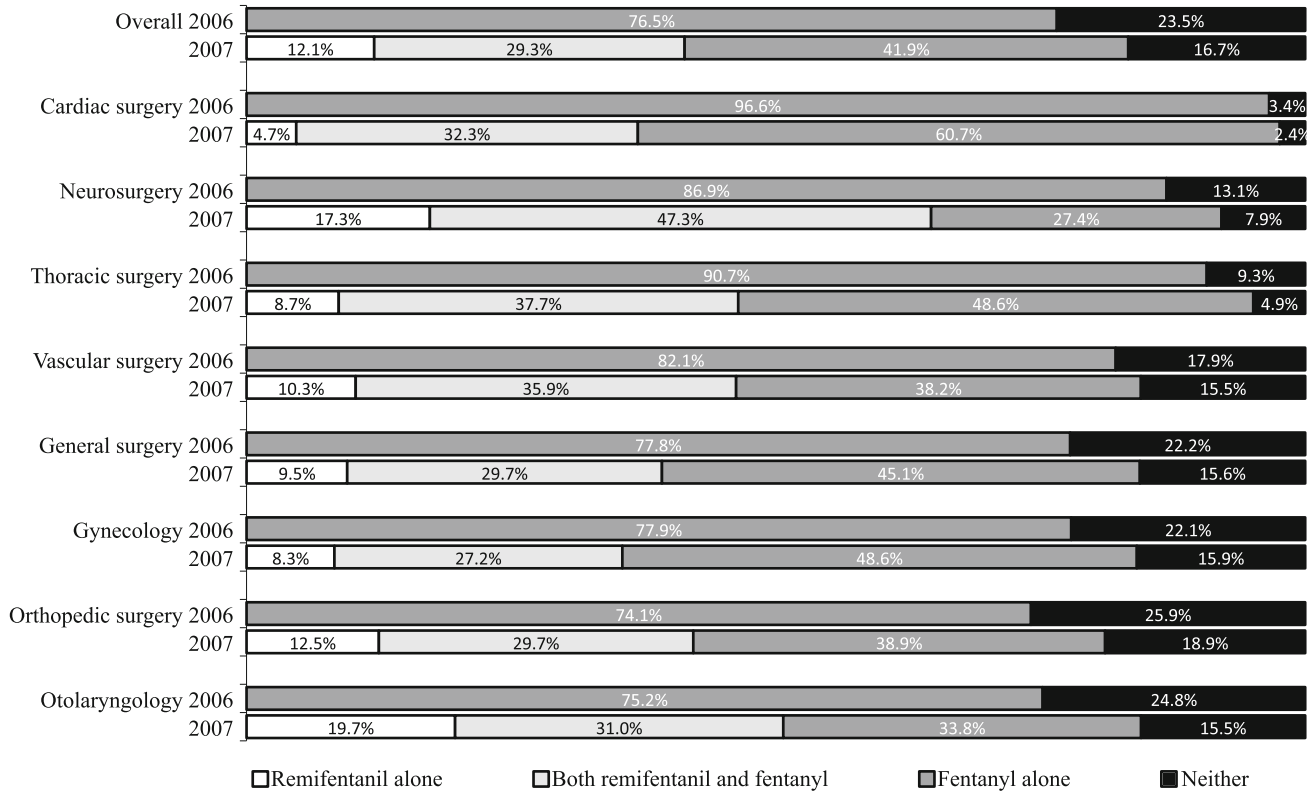

Fig. 1 Combination of remifentanil and fentanyl in each surgical field: percentage of surgeries using fentanyl and/or remifentanil in 2006 and 2007. *Open bars* cases in which remifentanil alone was used; *light gray bars* both remifentanil and fentanyl; *dark gray bars* fentanyl alone; *closed bars* neither remifentanil nor fentanyl

in non-teaching hospitals (48.1% vs. 36.9%, $P < 0.01$). The use of remifentanil in 2007 was exceptionally high in neurosurgery (64.6%) and otolaryngology (50.7%) (Fig. 1). The use of nitrous oxide decreased from 25.9% in 2006 to 14.0% in 2007. The proportion of patients who received neither nitrous oxide nor volatile agents, i.e., those undergoing total intravenous anesthesia (TIVA), increased from 14.0% in 2006 to 21.0% in 2007.

Barbiturate use was lower in 2007 (14.9%) than in 2006 (18.4%), whereas use of propofol was higher in 2007 (76.9%) than in 2006 (72.8%). Vecuronium was used in more than 80% of general anesthesias in both years, whereas rocuronium, which was introduced in September 2007, was utilized in 2.6% of surgeries in that year.

Factors associated with selection of remifentanil

Among 217,389 patients in 2007, 91,097 received fentanyl alone, and 63,739 received both remifentanil and fentanyl. Both patient factors and surgical factors affecting use of remifentanil were analyzed with adjustment for site effects by incorporating hospital identification numbers into the hierarchical mixed-effects logistic regression model. Female sex, increasing age, and comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with selection of remifentanil. In contrast, cardiac diseases and intraoperative epidural anesthesia were negatively associated with selection of remifentanil. Neurosurgical patients were more than fivefold more likely to receive remifentanil compared with cardiac surgery patients (Table 2).

Postoperative outcomes

Table 3 shows in-hospital mortality, mean duration of anesthesia, mean postoperative LOS, and mean total cost in each surgical field. All outcomes were compared between 2006 and 2007. No significant difference in in-hospital mortality was seen in any surgical subcategory showed between the 2 years. The mean duration of anesthesia was slightly shorter in 2007 than in 2006, and the differences were statistically significant in general surgery, gynecology, and orthopedic surgery. Mean postoperative LOS was shorter in 2007 in all surgical subcategories, and most of these findings were statistically significant, except for otolaryngology cases. Total cost was comparable between the 2 years, except for general surgery and gynecology, which were significantly less in 2007 compared with 2006.

Table 2 A hierarchical mixed-effects logistic regression analysis for selecting remifentanil (fentanyl alone = 0; both remifentanil and fentanyl = 1)

	Odds ratio	95% confidence interval	*P* value
Sex (female)	1.09	1.06–1.12	<0.001
Age	1.02	1.02–1.02	<0.001
Epidural anesthesia	0.36	0.35–0.37	<0.001
Diabetes mellitus	1.07	1.02–1.11	0.006
Hypertension	1.08	1.04–1.13	<0.001
Cardiac diseases	0.91	0.86–0.95	<0.001
Cerebrovascular diseases	1.07	1.00–1.15	0.068
Chronic lung diseases	1.01	0.93–1.08	0.888
Liver cirrhosis	1.19	1.00–1.41	0.049
Chronic renal failure	1.17	1.08–1.27	<0.001
Surgical category			
Cardiac surgery	Reference		<0.001
Neurosurgery	5.49	5.05–5.98	
Thoracic surgery	3.20	2.94–3.47	
Vascular surgery	2.36	2.17–2.58	
General surgery	2.00	1.87–2.13	
Gynecology	2.01	1.86–2.17	
Orthopedic surgery	1.89	1.76–2.02	
Otolaryngology	2.48	2.31–2.76	

Discussion

Population representation

According to the Survey of Medical Institutions 2008 in Japan, the average number of surgeries under general anesthesia throughout the country was 187,097 per month. [Survey of Medical Institutions 2008 (in Japanese). Vital and Health Statistics Division, Ministry of Health, Labour and Welfare, Japan. Available at: http://www.mhlw.go.jp/toukei/saikin/hw/iryosd/08/index.html. Accessed June 14, 2011.] Our data included 423,491 cases in 12 months, representing about 19% of all patients who underwent general anesthesia during the data extraction period in Japan. The age distribution was similar to that in another large database of anesthesia maintained by the Japanese Society of Anesthesiologists [15, 16].

Spread of remifentanil use and factors associated with its selection

Remifentanil was administered in more than 40% of all general anesthesias in the first year of its introduction, an extremely rapid increase in the proportion of its use [17].

Remifentanil was more frequently selected for patients with comorbidities, including hypertension, diabetes mellitus, and liver and kidney disease, presumably because it has advantages over other opioids such as a controllable, strong antinociceptive effect and rapid extrahepatic metabolism and elimination.

Epidural anesthesia was negatively associated with selection of remifentanil. Multiple publications suggest better patient intra- and postoperative condition with epidural anesthesia [18, 19]. It is anticipated that anesthesiologists did not believe it necessary to use remifentanil when they applied epidural anesthesia intraoperatively. The proportion of remifentanil use was higher in the nonepidural group than in the epidural group (45.2% vs. 30.6%). It was also higher in neurosurgery (64.6%) and otolaryngology (50.7%) cases. These results suggest that the pharmacological properties of remifentanil are highly

Table 3 Comparison of in-hospital mortality, average duration of anesthesia, postoperative length of stay, and total cost between 2006 and 2007 in each surgical subcategory

	In-hospital mortality (%)			Duration of anesthesia (min)			Postoperative length of stay (days)			Total costs (USD)		
	2006	2007	*P**	2006	2007	*P*†	2006	2007	*P*†	2006	2007	*P*†
Overall	1.41	1.36	0.242	211	208	<0.001	16.4	15.7	<0.001	12,733	12,648	0.051
Cardiac surgery	4.78	4.53	0.403	407	403	0.111	24.7	24.1	0.039	43,797	43,427	0.327
Neurosurgery	5.46	5.47	0.985	316	314	0.352	28.7	27.6	0.004	23,255	23,193	0.784
Thoracic surgery	1.73	1.69	0.862	259	255	0.296	14.5	14.0	0.046	15,926	15,820	0.669
Vascular surgery	3.59	3.50	0.761	267	262	0.074	24.0	22.6	0.002	18,489	18,458	0.927
General surgery	2.02	2.02	0.952	220	216	<0.001	16.9	16.1	<0.001	12,096	11,935	0.019
Gynecology	0.15	0.12	0.381	163	161	0.043	10.1	9.2	<0.001	7,046	6,951	0.042
Orthopedic surgery	0.66	0.56	0.092	191	188	<0.001	23.0	22.3	<0.001	14,108	14,112	0.957
Otolaryngology	1.33	1.43	0.314	177	174	0.429	12.3	12.1	0.222	8,448	8,555	0.330

LOS length of stay

* *P* value for the comparison between 2006 and 2007 evaluated with the chi-square test. Continuous variables, indicated with †, were evaluated using the Mann–Whitney *U* test

appreciated in those surgeries in which a neuraxial blockade cannot be applied.

Cardiac surgery had the smallest impact on the choice of remifentanil, presumably because of the greater surgical insult to patients, who frequently require postoperative mechanical ventilation; therefore, anesthetists can apply a large dose of fentanyl intraoperatively without considering early postoperative emergence and extubation in the operating theater. Coexisting cardiac disease was negatively associated with selection of remifentanil (Table 2). The well-known circulatory suppressive effect of remifentanil [20] may be another reason for the anesthetists to refrain from applying it in cardiac surgery.

Bramhall pointed out three prerequisites for an anesthetic drug to obtain a major share in the market. (Bramhall J. Remifentanil: Clinical use of an evanescent opioid. Available at: http://faculty.washington.edu/bramhall/lectures/opioids/remife~1.htm. Accessed June 14, 2011.) First, the drug must fit a "niche," allowing techniques to be used that were previously impractical; second, the drug must be cost effective; and third, it must have a safer profile than currently available agents. The safety of novel agents is generally extensively evaluated before clinical application, but it is usually difficult to show that the drug is "safer" than other drugs before substantial use. Similarly, the cost-effectiveness of anesthetic drugs cannot be clearly determined before substantial use, because various parameters can affect postoperative medical costs [21]. In contrast, intraoperative clinical advantages of remifentanil are evident even before substantial use. Its unique property as an ultra-short-acting opioid allowed application of new techniques that were previously impractical. For example, it enabled extensive opioid use as primary treatment for intraoperative pain that did not affect early postoperative emergence [22]. Bramhall also stated that the superiority of a drug over others should be assessed quite accurately, even if subjectively, by individual anesthetists in their daily practice. Because other short-acting opioids, i.e., sufentanil and alfentanil, had not been introduced into clinical use in Japan, the effect of remifentanil was likely to have a greater impression on Japanese anesthesiologists, and this may have boosted its penetration into the market.

The Japanese health insurance system does not offer economic incentives to anesthesiologists, and the reimbursement of costs for surgery and anesthesia is based on a fee-for-service system [23]. Therefore, anesthesiologists in Japan choose drugs according to their clinical applicability and convenience, with little economic consideration. Indeed, the present study revealed that sevoflurane was used in an exceptionally large population of general anesthesia cases despite its relatively high costs compared with other volatile agents (Table 1) [24]. Because there was more than a 10-year delay in the clinical application of remifentanil in Japan from Western countries, anesthesiologists should already have been familiar with its pharmacological properties and practical clinical application, thus making it easy for them to bring it into their clinical practice.

Change in patterns of drugs used for general anesthesia

Along with the rapid escalation of remifentanil use, an increase in TIVA and a reciprocal decrease in nitrous oxide use were obvious. Increase in propofol users by 4.1% in contrast to the reduction in barbiturates users by 3.5% may be the consequence of the increase in TIVA population, because propofol, which is the most popular hypnotic for maintenance of TIVA, can also substitute for barbiturates as an induction agent. Remifentanil may be superior to nitrous oxide for pain control with less environmental effect (i.e., contamination of the atmosphere in the operating room) and fewer adverse effects on patients, such as postoperative nausea and vomiting [25]. Other volatile anesthetic agents, specifically sevoflurane and isoflurane, were significantly reduced in use in 2007, but the magnitudes are less than that of nitrous oxide (Table 1). These observations may possibly be the result of their known organ-protective effects [26], recognized by most of the anesthesiologists in Japan, as well as their easy and titratable properties in regular clinical practice.

Impact on patient postoperative outcome and cost

Postoperative LOS was significantly reduced in all the surgeries except for otolaryngology, although the magnitude of surgical insult indicated by duration of anesthesia were relatively similar in both years. However, whether application of remifentanil led to better postoperative recovery is not clear. Currently few publications have reported association between use of remifentanil and better postoperative recovery [27]. Other factors, such as less-invasive surgical techniques and improved perioperative care, which affects enhanced recovery after surgery [28], may have contributed to the reduction in postoperative LOS in surgical patients.

Remifentanil is relatively expensive, a 2-mg vial costing 25.34 USD, about 10 times that of fentanyl (0.1 mg ampule for 2.45 USD) in Japan. Rapid increase in the proportion of remifentanil use was anticipated to cause increase in total costs. However, all surgical subcategories showed similar or less total cost in 2007 compared with 2006. Although multiple factors affect patient postoperative outcome and total costs, we can at least say from the present results that application of remifentanil did not affect increase in total costs. To disclose the possible contribution of remifentanil to better postoperative recovery, further evaluation using a wider dataset or a randomized controlled trial is necessary.

Limitations

Several limitations to this study should be acknowledged. The first is the use of an administrative claims database. Generally, the recorded diagnoses in such databases are less well validated than those in planned prospective surveys. However, several advantages of the data submission processes in the DPC database, such as physician-dependent diagnosis reporting, requirement of data entry via a strict data format, and mandatory submission linked with reimbursement, maximize the accuracy and consistency of reporting. Second, the database does not include actual doses of each anesthetic that might affect patient outcome. Detailed information about patients' signs and symptoms or laboratory data are also missing; thus, it is impractical with the present data to determine whether introduction of remifentanil affected postoperative LOS and in-hospital mortality.

In conclusion, our data revealed a rapid increase in the proportion of surgeries using remifentanil following its introduction in 2007. Comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated and epidural anesthesia and coexisting cardiac diseases were negatively associated with the use of remifentanil. Postoperative LOS was reduced in 2007, and total cost was comparable in the 2 years, indicating higher drug acquisition costs for remifentanil could be offset by reduced postoperative hospital LOS.

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