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Analysis of trends in usage of analgesics and sedatives in intensive care units of South Korea

A retrospective nationwide population-based study

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Abstract

The use of analgesics and sedatives plays an important role in improving patient outcomes in the intensive care unit (ICU). Various drugs exist, each with associated differences in patient outcomes; therefore, critical and intensive care medicine societies have developed guidelines for usage of analgesics and sedatives for improved patient outcomes. However, studies investigating drug use in the ICU have been based on surveys administered to medical staff, without accurate insight into the drug use based on prescriptions and behaviors of ICU medical staff, thus failing to demonstrate the actual status of the implementation of these guidelines into clinical practice. Using data from the Health Insurance Review and Assessment Service in South Korea, we analyzed the current use of analgesics and sedatives in ICUs nationally. In addition, we compared the use of analgesics and sedatives in the ICU based on the latest guidelines.

We performed a nationwide retrospective study using data available in the Health Insurance Review and Assessment Service database. We included 779,985 patients who had been admitted to the ICU from January 1, 2010, to December 31, 2014. Descriptive statistics were calculated to analyze the type and frequency of analgesic and sedative use in the ICU, using drug codes for analgesics and sedatives commonly prescribed in the ICU.

The most commonly used analgesics and sedatives for all patients admitted to the ICU were pethidine (26.14%) and midazolam (32.18%), respectively. Sedatives and analgesics were more commonly used in mechanically ventilated patients. Among analgesics, the usage rate of pethidine and morphine decreased, whereas the usage rate of fentanyl and remifentanil increased. Among sedatives, the usage rate of benzodiazepine decreased, whereas the usage rate of propofol increased.

There was discordance between current usage of analgesics and sedatives and the recommended usage stipulated by ICU guidelines. However, the trend of drug usage is changing to match the guidelines, which recommend maintenance of light sedation using an analgesia-based regimen and usage of short-acting drugs for routine monitoring of pain, agitation, and delirium in ICU care.

Abbreviations: HIRA = Health Insurance Review and Assessment Service, ICU = intensive care unit.

Keywords: analgesics, intensive care units, sedatives

1. Introduction

Treatment with analgesics and sedatives promotes tolerance to pain, anxiety, and agitation during mechanical ventilation and other invasive procedures in patients admitted to the intensive care unit (ICU).[1]

However, it is difficult to balance the comforting and sedating effects of analgesics and sedatives.[2] Balanced sedation can result increased co-operation, and patients are more likely to mobilize and wean from mechanical ventilation earlier than over-sedated patients. However, inadequate sedation may lead to agitation, while over-sedation is associated with prolonged mechanical ventilation, longer ICU stay, and development of post-ICU psychological problems.[3–6]

To facilitate the appropriate clinical use of analgesics and sedatives for favorable clinical and functional long-term outcomes in ICU patients, at both a national and international level, societies associated with critical and intensive care medicine have supported the development of guidelines and offer simulations and online-training tools to improve analgesia, sedation, and delirium management.[7–9]

In the latest guidelines published by the Society of Critical Care Medicine in January 2013, proper pain management, through routine assessment and monitoring of pain scale, improves the prognosis of patients treated in the ICU, with intravenous opioids recommended as first-line analgesics.[9] Maintaining

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Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Ajou University Medical Center (IRB No. AJIRB-MED-MDB-17-346). The need for informed consent was waived by the Institutional Review Board because all data were deidentified.

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light levels of sedation, by monitoring the depth of sedation and brain function, in adult ICU patients has been associated with improved clinical outcomes, and nonbenzodiazepine sedatives may be preferred to improve clinical outcomes in ICU patients.[9]

However, at present, studies investigating the use of drugs in the ICU have been based on surveys administered to medical staff, without accurate insight into the use of these drugs in the ICU based on prescriptions and behaviors of ICU medical staff.[1,10–14] Therefore, previous national and international surveys have failed to demonstrate the actual status of the implementation of these guidelines into clinical practice.

In this study, we analyzed the current prevalence of analgesic and sedative use in ICUs nationally, based on claims data obtained from the Health Insurance Review and Assessment Service (HIRA) in South Korea. We also compared the use of analgesics and sedatives in the ICU based on the latest guidelines.[9]

2. Methods

This study was a nationwide, retrospective, observational study. The study protocol was reviewed and approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-EXP-17-346). The need for informed consent was waived by the Institutional Review Board because all data were deidentified.

2.1. Enrolled patients and study setting

The National Health Insurance system is the public insurance system of the Republic of Korea, covering >99% of the South Korean population. The data generated by the HIRA in South Korea are derived from payment claims made during patient visits or inpatient admissions to medical institutions. The data collected includes patient demographics (sex, age, and residential area) and clinical details (diagnosis, procedures, and prescriptions). This nationwide study based on the HIRA claims data included patients who were admitted to the ICU from January 1, 2010, to December 31, 2014. Patients diagnosed with major burns and pediatric cases aged below 18 years were excluded, as we focused on the general trends associated with the use of analgesics and sedatives in the ICU. To analyze the current prevalence of analgesic and sedative usage in the ICU according to the department of care, departments were classified into surgical and medical categories. General surgery, neurosurgery, and cardiovascular surgery were classified as surgical departments, whereas internal medicine and neurology were classified as medical departments.

2.2. Data collection

The study population consisted of patients with the following procedure codes on admission to the ICU: AJ100-AJ190, AJ200-AJ290, and AJ300-AJ390, or the procedure code of care AJ001 assigned by the intensivist in the ICU. To confirm the analgesics and sedatives prescribed during hospitalization periods, we used the related drug codes: 1972 and 1973 for morphine; 2115 for pethidine; 1582, 1583, and 6218 for fentanyl; 1047 for alfentanil; 4576 for remifentanil; 1952 for midazolam; 1429 for diazepam; 1855 for lorazepam; and 2198 for propofol. There was no lag time between the actual visit and filing of the claim.

2.3. Statistical analysis

Descriptive statistics were calculated to estimate the frequency and rate of analgesic and sedative use in all patients admitted to the ICU, including mechanically ventilated patients. We analyzed the use of analgesics and sedatives according to hospital categories (tertiary general hospital, general hospital, and hospital) and departments of care (medical or surgical). For statistical comparison between the frequency and rate of analgesics and sedatives used in different years, sex, age, hospital grade, and department of care, we performed the chi-square test. A P-value of $<.05$ was considered statistically significant. All statistical analysis was performed using R 3.0.2 (R Core Team [2016], Vienna, Austria).

3. Results

A total of 779,985 patients were admitted to an ICU between 2010 and 2014 in South Korea. The number of patients who required mechanical ventilation was 283,631 (30.59%). The frequency of analgesic and sedative usage is shown in Table 1. The mean age at admission to the ICU was 63.89 years, and 460,673 patients (59.06%) were men (Table 2). Overall, the most commonly used analgesics and sedatives in ICU patients were pethidine (26.14%) and midazolam (32.18%), respectively. Analgesics and sedatives were more frequently used in mechanically ventilated patients than in all patients admitted to the ICU, and the use of midazolam in mechanically ventilated patients was more than two-fold higher than that in all ICU patients (67.17% vs 32.18%).

Except for remifentanil among analgesics and propofol among sedatives, the overall rate of drug use was higher in male patients. The number and proportion of patients admitted to the ICU increased with age. Patients older than 60 years accounted for more than half of all patients admitted to the ICU (63.96%). The rate of drug use in patients older than 70 years was less than that in all other age groups. Among all age groups, pethidine and midazolam were the most commonly used analgesics and sedatives, respectively. The rate of pethidine use in all patients decreased with age (Table 2).

Among all patients admitted to the ICU, 61.20% were admitted to a tertiary general hospital. A higher grade of hospital was associated with a higher rate of analgesic usage, while the rates of diazepam use were the highest in the hospital category and those of lorazepam were the highest in general hospitals. The number of patients admitted to medical departments was higher than that admitted to surgical departments (60.55% vs 39.45%). Except for morphine among analgesics and lorazepam among sedatives, the use of the other drugs was generally higher in surgical departments than in medical departments. The rates of remifentanil usage among analgesics and propofol among sedatives were higher in surgical departments than in medical departments by more than 10-fold (Table 3).

All results of the chi-square test for comparing differences in the frequency and rate of analgesic and sedative use between the 2010 and 2012 group and the 2013 and 2014 group were statistically significant. The rates of morphine and pethidine usage decreased from 2010 to 2012 compared with the reported usage from 2013 to 2014, while there was a relative increase in fentanyl and remifentanil use among analgesics in all patients admitted to the ICU. Among sedatives, the use of all benzodiazepine drugs decreased, while that of propofol increased. The patterns of drug use were similar in mechanically ventilated patients in the ICU (Fig. 1).

Table 1

The frequency of prescription of analgesics and sedatives in intensive care unit (n, %).

	All patient						Mechanically ventilated patients					
	Year						Year					
Drugs	2010	2011	2012	2013	2014	*P*-value	2010	2011	2012	2013	2014	*P*-value
Analgesics												
Morphine	24,554 (16.47%)	23,460 (15.31%)	23,628 (14.68%)	21,319 (13.55%)	21,312 (13.36%)	<.001	11,072 (24.04%)	10,823 (23.40%)	10,412 (20.98%)	9106 (18.93%)	8796 (18.10%)	<.001
Pethidine	40,188 (26.96%)	39,523 (25.80%)	41,808 (25.98%)	41,961 (26.68%)	40,397 (25.33%)	<.001	14,653 (31.82%)	14,220 (30.74%)	14,653 (29.52%)	14,535 (30.22%)	13,920 (28.64%)	<.001
Fentanyl	30,070 (20.17%)	31,839 (20.78%)	34,564 (21.48%)	33,250 (21.14%)	34,530 (21.46%)	<.001	12,915 (28.05%)	13,746 (29.72%)	14,319 (28.85%)	14,002 (29.11%)	14,787 (30.42%)	<.001
Alfentanil	2826 (1.90%)	1550 (1.01%)	1618 (1.01%)	1790 (1.14%)	1705 (1.07%)	<.001	1532 (3.33%)	644 (1.39%)	742 (1.49%)	760 (1.58%)	668 (1.37%)	<.001
Remifentanil	22,492 (15.09%)	24,826 (16.21%)	30,857 (19.17%)	32,589 (20.72%)	32,771 (20.55%)	<.001	8143 (17.68%)	9232 (19.96%)	11,195 (22.56%)	11,721 (24.37%)	11,979 (24.65%)	<.001
Sedatives												
Midazolam	48,980 (32.86%)	48,938 (31.95%)	52,376 (32.54%)	49,818 (31.67%)	50,891 (31.91%)	<.001	30,935 (67.18%)	31,104 (67.25%)	33,841 (68.18%)	31,771 (66.06%)	32,634 (67.14%)	<.001
Diazepam	15,589 (10.46%)	12,293 (8.02%)	11,440 (7.11%)	9947 (6.32%)	8171 (5.12%)	<.001	4870 (10.58%)	3817 (8.25%)	3405 (6.86%)	2805 (5.83%)	2179 (4.48%)	<.001
Lorazepam	20,786 (13.94%)	21,030 (13.73%)	22,952 (14.26%)	21,651 (13.77%)	21,007 (13.17%)	<.001	11,288 (24.51%)	11,349 (24.54%)	12,343 (24.87%)	11,204 (23.30%)	10,520 (21.64%)	<.001
Propofol	16,516 (11.08%)	17,803 (11.62%)	20,580 (12.79%)	21,341 (13.57%)	21,321 (13.37%)	<.001	6545 (14.21%)	6817 (14.74%)	8031 (16.18%)	8059 (16.76%)	7993 (16.45%)	<.001
Ketamine	1750 (1.17%)	2093 (1.37%)	2452 (1.52%)	2215 (1.41%)	1858 (1.16%)	<.001	1499 (3.26%)	1865 (4.03%)	2186 (4.40%)	1966 (4.09%)	1664 (3.42%)	<.001
Total patients	149,068	153,193	160,938	157,288	159,488		46,048	46,252	49,634	48,093	48,604	

Table 2

The frequency and rate of prescription of analgesics and sedatives according to sex and ages (n, %).

	Sex			Ages						
Drugs	Male	Female	*P*-value	18–29	30–39	40–49	50–59	60–69	≥70	*P*-value
Analgesics										
Morphine	72,743 (15.79%)	41,530 (13.01%)	<.001	2593 (12.47%)	5005 (14.12%)	12,222 (15.35%)	23,475 (16.17%)	28,547 (16.50%)	42,421 (13.02%)	<.001
Pethidine	121,309 (26.33%)	82,568 (25.86%)	<.001	7126 (34.26%)	11,755 (33.15%)	23,951 (30.08%)	42,279 (29.13%)	48,458 (28.01%)	70,289 (21.57%)	<.001
Fentanyl	98,176 (21.31%)	65,775 (20.60%)	<.001	5019 (24.13%)	8153 (23.00%)	18,089 (22.72%)	34,875 (24.03%)	41,792 (24.16%)	56,015 (17.19%)	<.001
Alfentanil	5692 (1.24%)	37,97 (1.19%)	.07	365 (1.75%)	593 (1.67%)	1231 (1.55%)	2058 (1.42%)	2207 (1.28%)	3034 (0.93%)	<.001
Remifentanil	80,661 (17.51%)	62,874 (19.69%)	<.001	5235 (25.17%)	9019 (25.44%)	18,736 (23.53%)	33,010 (22.74%)	35,680 (20.63%)	41,839 (12.84%)	<.001
Sedatives										
Midazolam	154,305 (33.50%)	96,698 (30.28%)	<.001	8121 (39.04%)	13,167 (37.14%)	26,866 (33.74%)	47,841 (32.96%)	57,708 (33.36%)	97,265 (29.85%)	<.001
Diazepam	34,807 (7.56%)	22,633 (7.09%)	<.001	1520 (7.31%)	2859 (8.06%)	6771 (8.50%)	11,730 (8.08%)	13,573 (7.85%)	20,978 (6.44%)	<.001
Lorazepam	69,522 (15.09%)	37,904 (11.87%)	<.001	3997 (19.22%)	6143 (17.33%)	12,520 (15.72%)	19,741 (13.60%)	21,332 (12.33%)	43,682 (13.40%)	<.001
Propofol	54,698 (11.87%)	42,863 (13.42%)	<.001	3761 (18.08%)	6242 (17.61%)	13,406 (16.83%)	23,077 (15.90%)	24,334 (14.07%)	26,730 (8.20%)	<.001
Ketamine	6608 (1.43%)	3760 (1.18%)	<.001	389 (1.87%)	534 (1.51%)	894 (1.12%)	1810 (1.25%)	2483 (1.44%)	4254 (1.31%)	<.001
Total patients	460,673 (59.06%)	319,312 (40.94%)		20,801 (2.67%)	35,455 (4.55%)	79,633 (10.21%)	145,159 (18.61%)	172,977 (22.18%)	325,880 (41.78%)	

Table 3

The frequency and rate of prescription of analgesics and sedatives according to hospitals and departments (n, %).

Drugs	Hospital categories				Department of care		
	Tertiary general hospital	General hospital	Hospital	*P*-value	Surgical department	Medical department	*P*-value
Analgesics							
Morphine	81,330 (17.04%)	32,599 (11.05%)	344 (4.52%)	<.001	40,014 (13.00%)	74,259 (15.72%)	<.001
Pethidine	144,651 (30.30%)	58,740 (19.91%)	486 (6.38%)	<.001	135,833 (44.15%)	68,044 (14.41%)	<.001
Fentanyl	122,775 (25.72%)	40,840 (13.84%)	339 (4.45%)	<.001	121,430 (39.46%)	42,523 (9.00%)	<.001
Alfentanil	7224 (1.51%)	2265 (0.77%)	0 (0.00%)	<.001	8480 (2.76%)	1009 (0.21%)	<.001
Remifentanil	111,106 (23.28%)	32,269 (10.94%)	160 (2.10%)	<.001	126,350 (41.06%)	17,185 (3.64%)	<.001
Sedatives							
Midazolam	176,983 (37.08%)	73,218 (24.82%)	802 (10.53%)	<.001	120,414 (39.13%)	130,589 (27.65%)	<.001
Diazepam	30,541 (6.40%)	25,688 (8.71%)	1211 (15.90%)	<.001	25,365 (8.24%)	32,075 (6.79%)	<.001
Lorazepam	61,006 (12.78%)	45,356 (15.37%)	1064 (13.97%)	<.001	31,621 (10.28%)	75,805 (16.05%)	<.001
Propofol	79,873 (16.73%)	17,462 (5.92%)	226 (2.97%)	<.001	78,171 (25.41%)	11,290 (2.39%)	<.001
Ketamine	7245 (1.52%)	3108 (1.05%)	15 (0.20%)	<.001	3498 (1.14%)	5870 (1.24%)	<.001
Total patients	477,328 (61.20%)	295,043 (37.83%)	7614 (0.98%)		307,692 (39.45%)	472,293 (60.55%)	

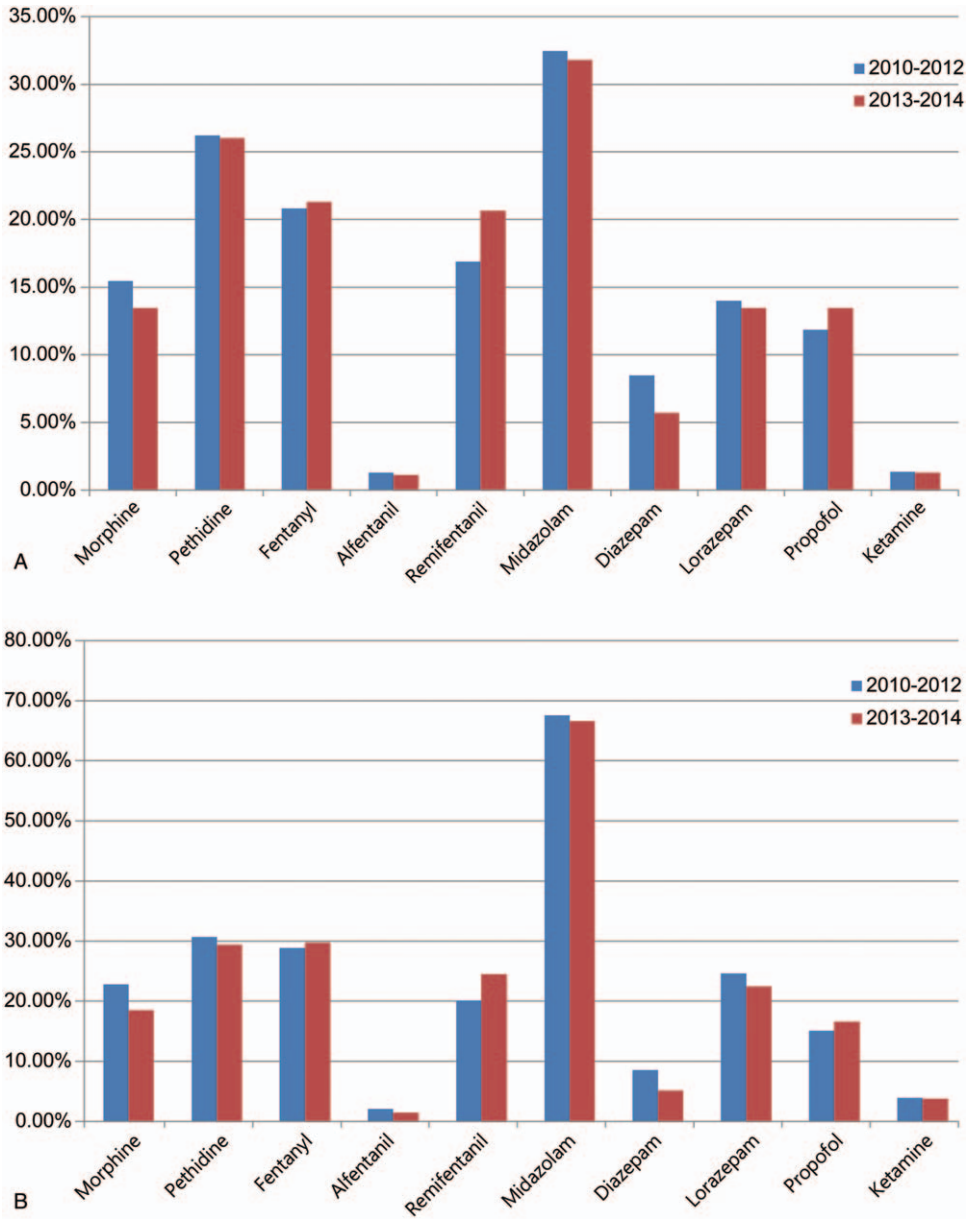
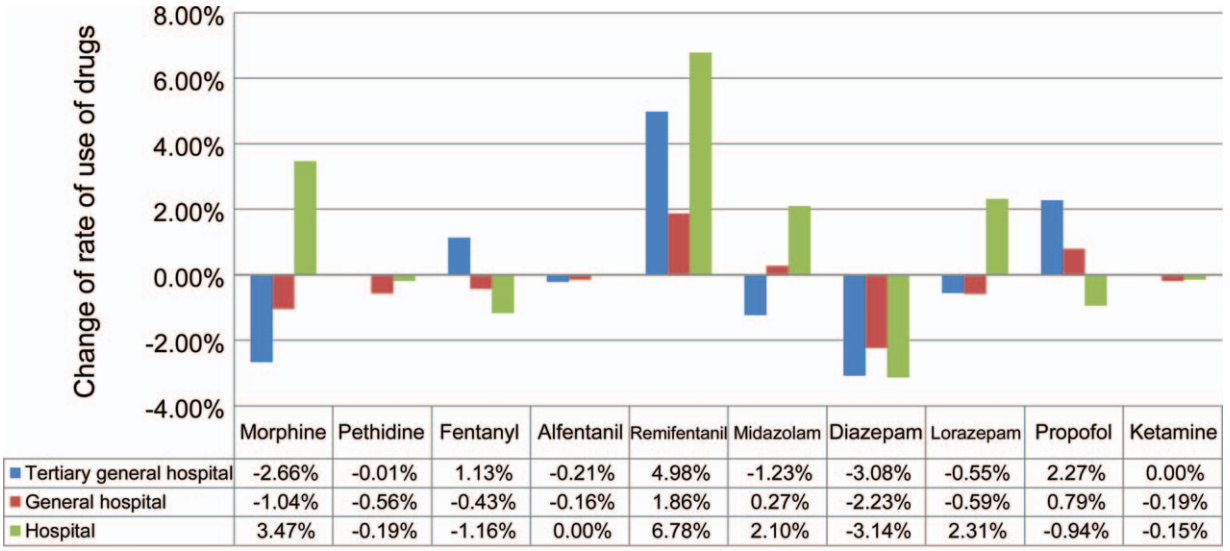
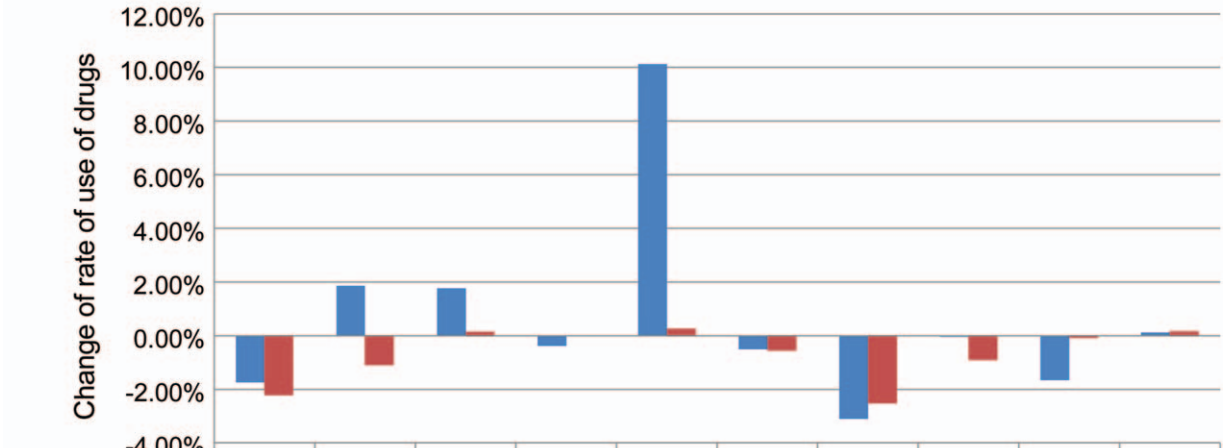


Figure 1. Changes in the pattern of analgesic and sedative prescriptions in intensive care units. (A) Total patients admitted to intensive care units, (B) Patients who were mechanically ventilated. All differences between the two groups were statistically significant (*P*-value < .05).



	Morphine	Pethidine	Fentanyl	Alfentanil	Remifentanil	Midazolam	Diazepam	Lorazepam	Propofol	Ketamine
Tertiary general hospital	-2.66%	-0.01%	1.13%	-0.21%	4.98%	-1.23%	-3.08%	-0.55%	2.27%	0.00%
General hospital	-1.04%	-0.56%	-0.43%	-0.16%	1.86%	0.27%	-2.23%	-0.59%	0.79%	-0.19%
Hospital	3.47%	-0.19%	-1.16%	0.00%	6.78%	2.10%	-3.14%	2.31%	-0.94%	-0.15%

A



	Morphine	Pethidine	Fentanyl	Alfentanil	Remifentanil	Midazolam	Diazepam	Lorazepam	Propofol	Ketamine
Surgical departments	-1.74%	1.87%	1.77%	-0.38%	10.13%	-0.51%	-3.10%	-0.05%	-1.66%	0.11%
Medical departments	-2.23%	-1.10%	0.14%	-0.03%	0.26%	-0.56%	-2.53%	-0.92%	-0.09%	0.16%

B

Figure 2. Changes in the rate of analgesic and sedative usage in intensive care units. (A) Changes according to hospital categories, (B) Changes according to department of care.

Analysis of the trend associated with analgesic and sedative usage from 2010 to 2012 with the trend from 2013 to 2014, based on hospital category, suggested that pethidine usage had decreased, while that of remifentanil had increased among analgesics used in all categories of hospitals. Among sedatives, the use of diazepam was reduced in hospitals of all categories. Changes in the use of other analgesics and sedatives varied in all hospitals. Among analgesics, the rate of remifentanil use increased significantly in surgical departments, and the use of all benzodiazepines decreased in both surgical and medical departments among sedatives (Fig. 2).

4. Discussion

In this study, we analyzed the frequency of analgesics and sedatives used in the ICU based on claims data from the HIRA in South Korea. Additionally, we analyzed the changes in the use of analgesics and sedatives based on latest guidelines published by the Society of Critical Care Medicine in January 2013.[9] Our findings indicate that there is discordance between current usage of analgesics and sedatives and the recommended usage stipulated by ICU guidelines; however, the trend of drug usage is changing to match these guidelines.

Usage of analgesics and sedatives in patients admitted to the ICU is associated with clinical outcomes and post-ICU-care sequelae.[15–17] Guidelines including the usage of analgesics and sedatives proposed by societies of critical and intensive care medicine promote effective management of patients in the ICU,[7–9] and national and international studies have analyzed the implementation of such guidelines.[10–14] However, these studies have used survey data, which fails to capture the actual trends in usage. Therefore, we addressed these limitations and reported the current trends in the use of analgesics and sedatives in the ICU. We found that morphine and pethidine, both relatively long-acting opioids, were used as the main analgesics in the ICU, and the frequency of their use reduced throughout the study period.

We also found that the frequency of remifentanil use, a relatively short-acting opioid, has recently increased. Benzodiazepines, especially midazolam, are still the primary sedatives used in the ICU. These findings indicate that there are discordances in analgesic and sedative usage between ICUs, and the latest guidelines could be existent in South Korea. Furthermore, efforts to elucidate and reduce underlying factors responsible for such differences are needed to ensure favorable patient outcomes in the ICU.

Critical and intensive care medicine societies have recommended analgesia-based, light levels of sedation in care patients in the ICU unless clinically contraindicated.[9] The use of short-acting drugs without bioaccumulation, rather than those that are long-acting, is also recommended for the prevention of delayed emergence from sedation and for the routine monitoring of pain and delirium in patients.[18–21] However, morphine, pethidine, and fentanyl, which are relatively long-acting drugs that accumulative in the body, were commonly used analgesics, and benzodiazepines, which induce deep sedation, were the main sedatives used in our study.[22] These practices may cause unfavorable outcomes in ICU care. However, the increased frequency and ratio of remifentanil and propofol usage, as well as the decreased use of benzodiazepines, could also suggest favorable trends for patient outcomes in the ICU.

Even though opioids are generally recommended as the first choice for pain control in patients admitted to the ICU and the evidence for short-acting opioids compared with morphine is not conclusive, there is concern regarding the accumulation of morphine, a long-acting opioid.[23] A previous study reported that long-acting opioids such as morphine were associated with poor outcomes compared with short-acting opioids, such as remifentanil.[24] It is generally recommended to avoid the use of pethidine, a long-acting opioid, because of its potential for neurologic toxicity.[25] However, the main analgesics used in South Korean ICUs were morphine and pethidine, and these were used in approximately half of all patients admitted to the ICU. This frequent use of these long-acting opioids may interfere with the routine monitoring of pain, agitation, and delirium in patients, by prolonging the effects of long-acting opioids or their accumulation. Therefore, when intensivists in the ICU prescribe analgesics for pain control, they should consider the effects of duration and possibility of bioaccumulation in patients.

International trends suggest the transition from deep sedation based on hypnotics to light sedation based on analgesics. However, there is still frequent use of midazolam in the ICU, especially in mechanically ventilated patients.[9] The frequent use of benzodiazepines may result in poor patient outcomes, such as longer duration of mechanical ventilation and a longer length of ICU stay. Therefore, a decrease in the use of benzodiazepines and increased use of other sedatives, such as dexmedetomidine or propofol, is desirable and associated with better outcomes.

The frequency and rate of the usage of morphine, a long-acting opioid, and midazolam, a potent benzodiazepine, were increased in hospitals compared to tertiary or general hospitals (Fig. 2). This phenomenon could be explained by characteristics of the Korean medical society, which is led and changed by tertiary general hospitals. Novel guidelines in medical fields are generally first incorporated in tertiary general hospitals and later in smaller hospitals. Furthermore, the tertiary or general hospitals are also catching up with the latest guidelines, which recommend using short acting, rather than long acting, drugs and refraining from using benzodiazepines. Hospitals may still continue to use long-acting opioids as the main analgesics and benzodiazepines as sedatives in the care of ICU patients.

There were few limitations associated with this study. First, we analyzed cases admitted to the ICU based on claims data obtained from the HIRA, which provides only code and demographic details. Clinical data related to the severity of patients admitted to ICU, such as laboratory results, severity score, and concomitant disease history were not available from the HIRA. Therefore, without stratifying patients based on severity, especially those on mechanical ventilation, it may be difficult to determine whether any changes in the frequency and rate of analgesic and sedative use are due to a shift in clinicians' knowledge and recognition in critical care. Second, the HIRA only contains registered data claimed by medical staff supported by the health insurance service. The HIRA dataset does not include data of patients not reimbursed by this insurance service. Therefore, we could not analyze the current prevalence of dexmedetomidine use, which has been mainly used in the ICU as a short-acting sedative agent. Third, whether drugs were used continuously or intermittently is unknown because of limited data. Additionally, we could not confirm the total dose used in each patient within the admission period. Therefore, future studies need to combine the HIRA claims data with clinical datasets and whole drug datasets, such as national health insurance service data.

In conclusion, although the societies associated with critical and intensive care provide guidance on the usage of drugs based on sufficient evidence and suggest proper usage of drugs in ICUs, there was discordance between the current status of analgesic and sedative usage and the usage of analgesics and sedatives recommended in the ICU guidelines. Additionally, there were differences depending on patient sex and age, use of mechanical ventilation, and hospital category and department of care. However, the trend of drug usage is changing to match the guidelines, which recommend the maintenance of light sedation using an analgesia-based regimen and the usage of short-acting drugs for routine monitoring of pain, agitation, and delirium in ICU care.

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