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Medication use evaluation: The impact of introducing Nalbuphine on hospital management of Meperidine

I-Hsuan Tsai[1], Hsin-Yueh Hu[1], Chen-Chun Kuo[1], Kuang-I Cheng[2] and Ying-Hao Lu[1,3*]

[1]Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
[2]Department of Anesthesiology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
[3]School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan.

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ABSTRACT

Meperidine was often used for postoperative pain relief, but it has addictive and neurotoxic side effects. In order to reduce the use of Meperidine and meet the needs of clinical use, the hospital started using Nalbuphine in August 2018, and the effectiveness for about three years was analyzed with the expectations of reducing the risk of Meperidine use and improving the safety of analgesic treatment. The clinical departments in the hospital advocated that Nalbuphine can replace Meperidine, and the notification of short message service for those with large usages was enhanced. Finally, the data on the changes in the usage of Meperidine and Nalbuphine from August 2018 to December 2021 were collected. Overall, the usage of Nalbuphine increased month by month after it was introduced; in contrast, the average monthly usage of Meperidine decreased from 545 in 2018 to 47 in 2021. It was found that a key point of the golden cross appeared for the use of the two drugs one year after Nalbuphine was introduced. In conclusion, Nalbuphine can indeed replace Meperidine to meet the clinical needs for pain relief when it is used in hospitals. In addition, the annual drug purchase cost of Meperidine can be significantly saved to improve the effectiveness of hospital operations, so the non-controlled drug Nalbuphine has the added benefit of drug profit. Finally, it is hoped that other medical institutions can learn and apply these research findings to the management of controlled drugs in the hospital.

Keywords: Meperidine, Nalbuphine, patient safety, hospital management.

*Corresponding author. E-mail: yhlu@kmuh.org.tw. Tel: 886-7-3121101 ext. 7161.

INTRODUCTION

Meperidine (also called Pethidine or Demerol) has often been used for postoperative pain relief in the past, but its active metabolite Norpethidine (Normeperidine) can easily cause central nervous system side effects, such as tremor, epilepsy, delirium, and higher iatrogenic addiction risks (Latta et al., 2002). And its analgesic effect on biliary tract spasms is not as effective as other opioids, so Meperidine has almost no therapeutic advantage compared with other opioids (Latta et al., 2002). Institute for Safe Medication Practices Canada (ISMP Canada) issued a warning in 2004 that “It is recommended to avoid the use of Meperidine. If needed, it should be used in a limited dose (the total amount of IV or IM injections in adults should not exceed 600 mg within 24 hours) for a limited duration (no more than 48 hours)” (ISMP Canada, 2004). After the ISMP Canada issued the warning, the use of Meperidine in Manitoba, Canada from April 2001 to March 2014 was analyzed, and it was found that the number of users and prescriptions both decreased significantly(Friesen et al., 2015). The Meperidine use guidelines of other international medical institutions, such as the American Pain Society (APS) are also similar to the warning message of ISMP Canada (American Pain Society, 2016).

Referring to the relevant use guidelines of advanced foreign countries, Taiwan Food and Drug Administration

also convened a national consensus meeting and solicited trials from different levels of hospitals. In 2011, it formulated the “Pethidine Clinical Use Guidelines”, which clearly pointed out that “Pethidine should not be used as a first-line analgesic; for patients with normal renal function, Pethidine should not be used continuously for more than 48 hours or the cumulative dose should not exceed 600 mg per day (Chien et al., 2010; Food and Drug Administration, 2011). It was also mentioned in the recommendation for the use of opioid analgesics in the emergency clinic in “Guidelines for the Use of Addictive Narcotic Drugs for Patients with Acute Pain” that “prescribing Pethidine should be avoided in the emergency room (Food and Drug Administration, 2017). In addition, Meperidine belongs to the second-level controlled drugs under the Taiwanese regulations of controlled drugs. The damage, expiration and scrapping, loss or theft of Meperidine must be notified to the health authority within seven days of such occurrence and related administrative tasks shall be completed (Controlled Drugs Act, 2017), so its management is also more rigorous than general drugs.

Due to the limitations of Meperidine in clinical use and administrative management, the hospital reduced its usage through hospital notifications, advocacy in each department, and electronic prescription system management. The usage had been reduced from 1,022 per month in 2013 to 545 per month in 2018. Although the usage has fallen sharply, there are still over 500 per month on average usage. The Controlled Drugs Management Committee of the hospital has proposed to discuss whether the use of Meperidine can be discontinued, but an investigation shows that nearly 90% of 19 medical centers in Taiwan (89.47 %) continue to use Meperidine (Table 1). It is obvious that there is still a clinical need for Meperidine, and alternatives must be found if its usage is to be reduced further.

The opioid analgesic Nalbuphine is a non-controlled drug that is easier to manage. It is transformed into a *kappa* receptor agonist and a partial *mu* receptor antagonist. The analgesic effect of Nalbuphine is mainly derived from the *kappa* receptor. Its analgesic effect is similar to Morphine and better than Meperidine (Zeng et al., 2015; Hew et al., 1987). In addition, due to the particularity of its mechanism, related side effects such as respiratory depression, pruritus and dependence are lower than those of other opioids (Table 2) (Zeng et al., 2015; Hew et al.,1987; Dinges et al., 2019).

Table 1. Use of Meperidine in Taiwan medical centers in 2021.

Area	Hospital	Usage
North	National Taiwan University Hospital	◎
	Taipei Veterans General Hospital	Currently, it is only used for 1~2 patients allergic to Morphine.
	Tri-Service General Hospital	◎
	Taipei Municipal Wanfang Hospital	No more purchases will be made after special patients use up the remaining medicine.
	MacKay Memorial Hospital	◎
	Linkou Chang Gung Memorial Hospital	◎
	Cathay General Hospital	◎
	Far Eastern Memorial Hospital	◎
	Shin Kong Wu Ho-Su Memorial Hospital	◎
Central	Taichung Veterans General Hospital	◎
	Changhua Christian Hospital	◎
	China Medical University Hospital	◎
	Chung Shan Medical University Hospital	◎
South	National Cheng Kung University Hospital	◎
	Kaohsiung Veterans General Hospital	◎
	Chi Mei Medical Center	◎
	Kaohsiung Medical University Chung-Ho Memorial Hospital	◎
	Kaohsiung Chang Gung Memorial Hospital	◎
East	Hualien Tzu Chi Hospital	◎

Table 2. Comparison of side effects of opioid analgesics.

Drug	Sedation	↓ Respiration	Pruritus	Constipation	Dependence
Nalbuphine	**	*	*	***	*
Morphine	**	**	**	***	**
Meperidine	**	**	*	***	***
Tramadol	**	*	**	**	*

Another indication of Meperidine is the treatment of postanesthetic shivering (PAS) (Food and Drug Administration, 2011; Lopez, 2018). PAS is a common complication of anesthesia, which may increase the risk of hypoxemia and postoperative complications. Shivering is also one of the main reasons for patients' postoperative discomfort. Meperidine is a common treatment drug for PAS, but it is more likely to induce nausea, vomiting, and respiratory depression (Lopez, 2018). A double-blind randomized controlled trial compared the therapeutic effect of IV Nalbuphine 0.08 mg/kg (30 people), IV Meperidine 0.4 mg/kg (30 people) and IV saline placebo (30 people) on PAS. For five minutes after administration, both Nalbuphine and Meperidine quickly relieved PAS with a response rate (RR) of 80% and 83%, respectively, and the RR of the saline group was 0% ($P < 0.01$); 30 minutes after administration, the RR of Nalbuphine and Meperidine was 90% and 93%, respectively, and RR of the saline group was 17% ($P < 0.01$). This study showed that Nalbuphine and Meperidine had similar effects in the treatment of PAS, and it also indicated that Nalbuphine can be used as an alternative drug for Meperidine to treat PAS (Wang et al., 1999). Taiwan Pain Society has once recommended in the "National Consensus Study on Use Guidelines and Quality Management Process of Narcotic Controlled Drug Pethidine" that health authorities should introduce more and better opioid analgesics to increase the diversification of drug use (Chien et al., 2010). In order to reduce the usage of highly addictive Meperidine and meet the needs of clinical use, this study explored the feasibility of introducing Nalbuphine to replace Meperidine. It is expected to reduce the amount of Meperidine used, reduce the risk of iatrogenic addiction and drug side effects, and thereby improve the safety of the analgesic medication and the benefits of hospital management.

MATERIALS AND METHODS

Besides continuing advocacy in accordance with the "Pethidine Use Guidelines" issued by Taiwan Food and Drug Administration, the Pharmacy and Therapeutic Committee of the hospital has conducted an overall assessment of opioid controlled drugs and decided to introduce Nalbuphine in the hospital in August 2018. Firstly, hospital-wide email notifications were made regarding the drug information related to Nalbuphine stating that it can replace Meperidine. Departments with a large amount of Meperidine usage were notified further by short message service (SMS), and the clinical education and training for the entire hospital were conducted by the pharmacy and the Department of Anesthesiology. The data on the monthly usage of Meperidine and Nalbuphine in the whole hospital from August 2018 to December 2021 were collected, the usage of each clinical department was analyzed, and group analysis was made according to the usage amount to evaluate the improvement effect after the introduction of Nalbuphine.

RESULTS

Before Nalbuphine was introduced to the hospital, the average monthly usage of Meperidine had been reduced from 1,022 in 2013 to 545 in 2018 through hospital notification, advocacy in each department, and electronic prescription system management (Figure 1). Nalbuphine was introduced in July 2018, when it was not a general medicine and its use was restricted to the Department of Anesthesiology and Department of General and Gastrointestinal Surgery. Although Nalbuphine is an alternative to Meperidine, the use of Meperidine cannot be completely prohibited. After the Pharmacy and Therapeutic Committee of the hospital decided to list Nalbuphine as general medicine in this hospital in December 2018, it can be seen from Figure 1 that the average monthly usage of Meperidine fell to 151 per month in 2019, there was an average of 47 per month remaining in 2021, and the decline reached 91.37% during the four-year period from 2018 to 2021.

According to the overall statistics of the hospital, the usage of Nalbuphine has increased month by month after the introduction. The average monthly usage from October to December 2021 reached about 165, while the average monthly usage of Meperidine was reduced to less than 50 per month (from October to December 2021) from more than 500 from August to October 2018. Figure 2 shows that the usage of two drugs has had a gold cross in April 2019 since Nalbuphine was introduced less than a year ago.

According to the results of the secondary analysis of the usage for each department, there was an obvious decrease in the usage of Meperidine by those

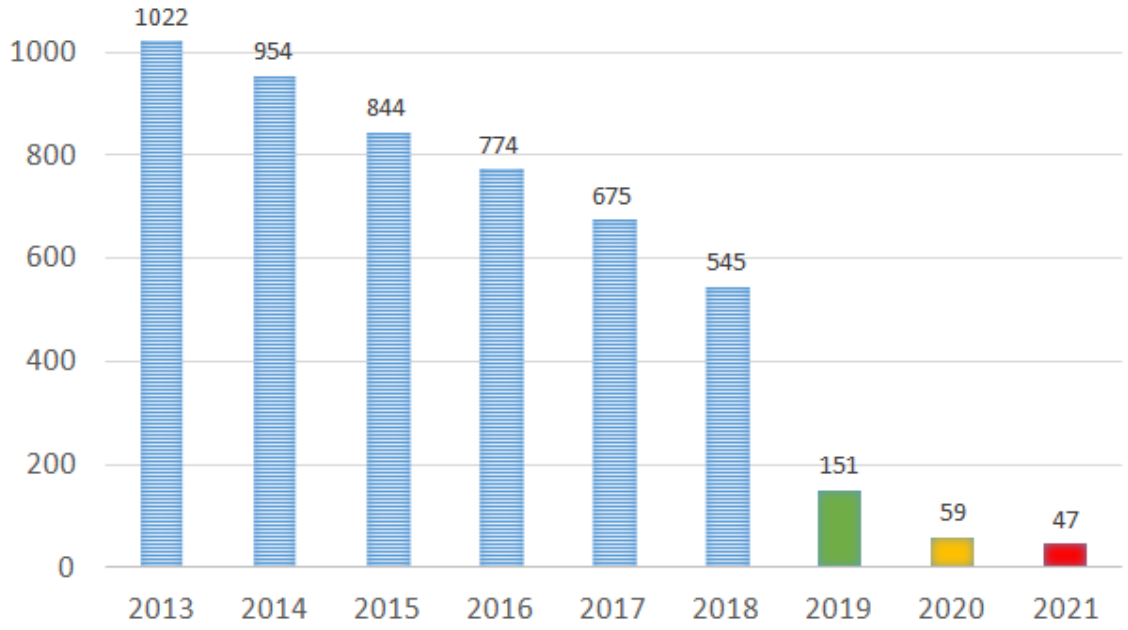

Figure 1. The annual average monthly usage of Meperidine.

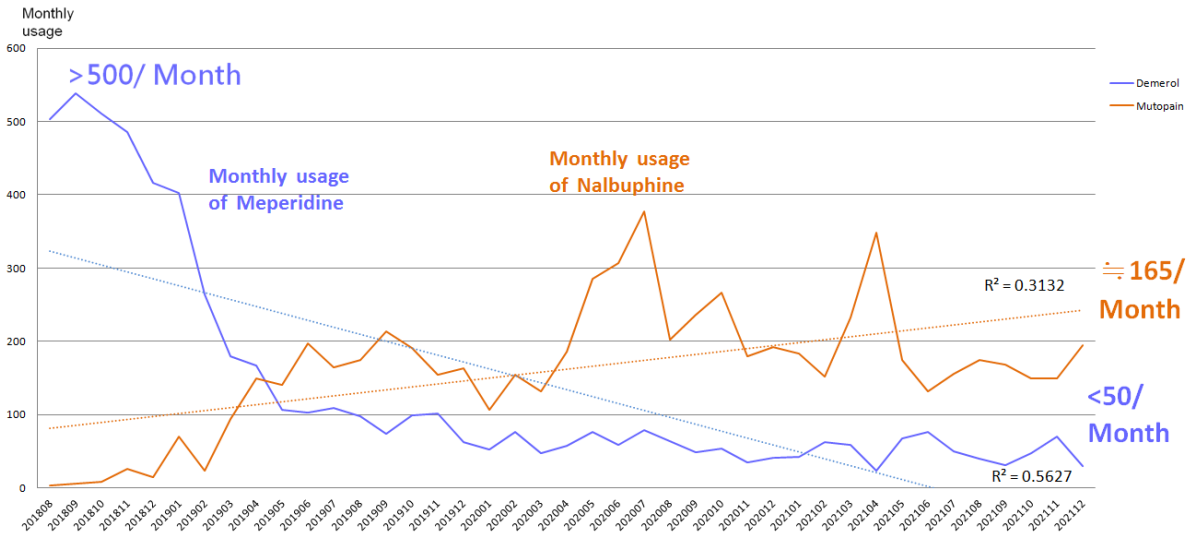

Figure 2. The trend of average monthly usage for Nalbuphine and Meperidine (Duration: August 2018 to December 2021).

departments with original high monthly usage of Meperidine (>50 pcs/month), such as departments of General and Gastrointestinal Surgery, Orthopedics, Hepatobiliary and Pancreatic Internal Medicine and Emergency Department (Figure 3). Most of the departments with the original medium monthly usage of Meperidine (25~50 pcs/month) and the original low monthly usage (<15 pcs/month) also showed a gradual decrease in its usage after the introduction of Nalbuphine. However, only the Department of Obstetrics and Gynecology (26 pcs/month) and the Department of Neurosurgery (4 pcs/month) showed no steady decline, and sometimes there was an abnormal increase in usage.

The change in the number of drugs used in clinical practice also affected the cost of drugs and their profits. Before the introduction of Nalbuphine, through the hospital notification, the advocacy in each department and electronic prescription system management, it is learned from Figure 4 that the annual drug purchase cost of Meperidine dropped from NTD 324,970 in 2013 to NTD 173,390 in 2018, which is a decrease of 46.64%. After

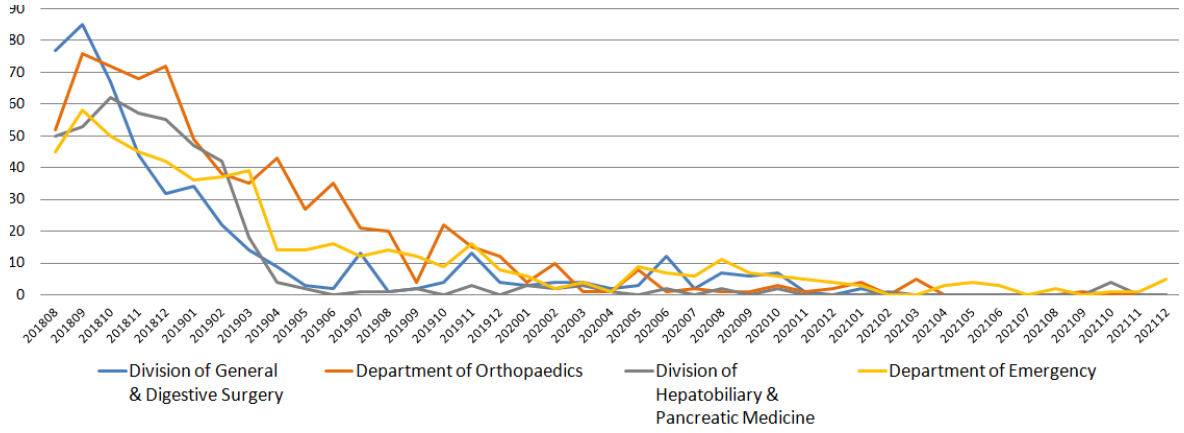

Figure 3. The trend of departments with original high monthly usage of Meperidine after the introduction of Nalbuphine.

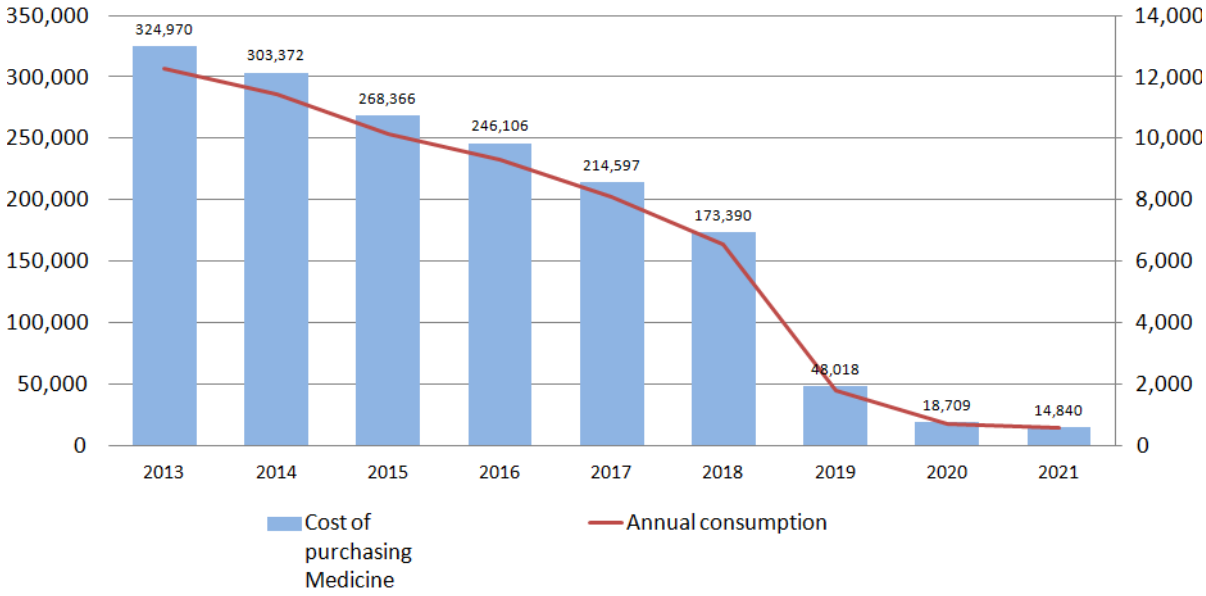

Figure 4. The annual purchase cost of Meperidine from 2013 to 2021.

the introduction of Nalbuphine, the use of Meperidine fell sharply, and the cost of Meperidine drug purchase decreased from NTD 173,390 per year in 2018 to NTD 14,840 in 2021. During the four-year period from 2018 to 2021, the decline was as high as 91.44% (Figure 4). In addition, the non-controlled drug Nalbuphine has the additional benefit of drug profits.

DISCUSSION

Based on the results of this study, the introduction of Nalbuphine for hospital management of the highly addictive drug Meperidine had a significant impact on clinical use and drug cost management. However, there were still a few departments that need to be improved. In the statistics as of December 2021, the Department of Obstetrics and Gynecology had the worst improvement effect for unstable usage. In July 2020, the amount of use has raised to 29 per month. There were two main reasons which are prescribing habits and the insufficient knowledge of Nalbuphine. According to the literature review, because of the prolonged half-life of Normeperidine, the active metabolite of Meperidine in mothers and newborns, the American College of Obstetricians and Gynecologists (ACOG) has strongly discouraged the use of Meperidine in peripartum analgesia (ACOG,2019), while Nalbuphine is currently commonly used in the United States for obstetrical analgesia, and it is also approved for labor analgesia based on its safety. Nalbuphine can also be used for the itching caused by analgesic analgesia of nerve axis

anesthesia during caesarean section (ACOG, 2019). Therefore, the above latest drug information of Nalbuphine was provided to the supervisor of the Department of Obstetrics and Gynecology for doctor education and training, and then the Meperidine usage in this department has significantly decreased from 26 pcs/month to 9 pcs/month. In addition, the results showed no steady decrease in the Department of Neurosurgery, and it was found from further exploration that there was abnormal use from March to July 2020, with the main usage concentrated in 2 patients for non-cancer cases. The pharmacist in charge had specifically reminded their doctor to prescribe other analgesics (such as Nalbuphine or Morphine) or adjuvant analgesics (such as Oxcarbazepine) after evaluation, and the subsequent use of Meperidine in this department significantly decreased. The role of the pharmacist in the hospital is to provide constant knowledge updates on available pain drugs and their side effects for clinicians.

This study is a successful example of medication use evaluation with new drugs that have better efficacy, higher safety and additional management cost benefits. Here, we will further explore the main motivations for the introduction of new drugs by medical institutions, which can be summarized into the following four types:

(1) Better clinical efficacy: For example, Neuraminidase inhibitor (Oseltamivir, Peramivir, and Zanamivir) is a commonly used influenza antiviral drug. A systematic literature review of 7 trials from 2011 to 2015 covering 1,676 patients found that compared with taking Oseltamivir twice a day, the intravenous injection once a day of the new drug Peramivir can shorten the patient's fever relief time by 7.17 hours (Lee et al., 2017).
(2) Higher safety: For example, direct-acting antiviral agent (DAA) of an oral new drug for hepatitis C has replaced traditional interferon therapy (Piecha et al, 2020); compared with Warfarin, novel oral anticoagulants (NOAC) do not require frequent monitoring, has a more stable effect, and lower risk of bleeding.
(3) Better compliance: For example, long-acting sustained-release dosage forms of oral drugs and patches. World Health Organization (WHO) and National Comprehensive Cancer Network (NCCN) both recommend switching to a long-acting or sustained-release dosage form after stable pain control for patients with chronic cancer pain so that the administration time can be simplified to improve medication compliance (World Health Organization,1996; National Comprehensive Cancer Network, 2021).
(4) Enhancing the cost benefits of drug management: For example, biologics are expensive, and the clinical efficacy and safety of biosimilars are equivalent to the original biologics, but the price is lower than that of the original biologics. Therefore, biosimilars offer another alternative to make medicines more extensively used, reduce the hospitals' cost of purchasing medicines and relieve the burden on patients (McCamish et al., 2016).

CONCLUSION

This study mainly explored the possibility of using the non-controlled drug Nalbuphine to replace the highly addictive second-level controlled drug Meperidine in real hospitals. According to the research results, the introduction of Nalbuphine can indeed replace Meperidine to achieve clinical pain relief and reduce the risk of drug addiction and side effects. In addition, the cost must be considered in hospital operations. This study introduced Nalbuphine to successfully replace Meperidine clinically and effectively reduce the cost of drug purchase in hospital operations to improve the cost benefits of drug management. Finally, it is hoped that other medical institutions can learn from and apply this research to the relevant management operations of their controlled drugs.

Ethics approval and consent to participate

Because this study did not involve the data of human subjects, the need for ethics approval and consent was waived by the IRB of Kaohsiung Medical University Hospital.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the HIS of Kaohsiung Medical University Hospital.

Competing interests

The authors declare that they have no competing interests.

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