学 位 論 文 の 要 旨

氏名　伊豆原　宗人

学 位 論 文 名	Real-World Preventive Effects of Suvorexant in Intensive Care Delirium: A Retrospective Cohort Study
発 表 雑 誌 名 （巻，初頁～終頁，年）	The Journal of Clinical Psychiatry (6;81(6):20m13362, 2020)
著 者 名	Muneto Izuhara, Hisae Kihara Izuhara, Keiko Tsuchie, Tomoko Araki, Tsukasa Ito, Kouhei Sato, Shoko Miura, Koji Otsuki, Michiharu Nagahama, Maiko Hayashida, Sadayuki Hashioka, Rei Wake, Tomohiro Kimura,Shusaku Tsumoto, Yoji Saito, Masatoshi Inagaki

論 文 内 容 の 要 旨

INTRODUCTION

Approximately 50% patients in the intensive care unit (ICU) suffer from delirium. Delirium is independently associated with worsening cognitive function and an increased risk of death. Therefore, strategies for delirium prevention are urgently needed. However, no medications have been approved for its prevention yet.

The relationship between delirium and sleep has recently gained global attention, and accumulating evidence suggests that sleep and/or circadian rhythm disruption contributes to delirium development. However, the pharmacological treatment of sleep disturbance in ICU is currently not recommended because typical hypnotics, including benzodiazepines and propofol, disrupt sleep architecture, such as the duration of rapid eye movement sleep, and eventually induce delirium.

Two randomized controlled trials (RCTs) have shown that suvorexant, which is prescribed for insomnia, is effective in preventing delirium. However, a network meta-analysis failed to show the preventive effect of suvorexant against delirium because of a lack of conclusive evidence. Furthermore, the effectiveness of suvorexant in delirium prevention in daily clinical settings remains unknown; therefore, a study examining the effectiveness of this drug in delirium prevention in real-world settings is needed. In this retrospective study, we examined whether suvorexant prevented delirium in a relatively large sample of ICU patients in a real-world

setting.

MATERIALS AND METHODS

We conducted a retrospective cohort study to compare delirium occurrence between suvorexant users and non-users. We further explored the association between delirium occurrence and use of other drugs prescribed for insomnia or delirium. This study protocol was approved by the Research Ethics Committee of Shimane University (approval number: 20171113-2). Data were collected anonymously; therefore, the ethics board waived the need for informed consent from individual patients. An opt-out option was provided through our website.

The study population included all patients admitted to ICU between January 2016 and December 2018. The exclusion criteria were as follows: duration of stay in ICU < 72 h, age ≤ 2 years (to exclude patients who could not be evaluated using the Confusion Assessment Method for the ICU [CAM-ICU]), and missing data.

Delirium was evaluated using CAM-ICU. This tool was applied by bedside nurses in a clinical setting from 8:00 a.m. to 9:00 a.m. and from 6:00 p.m. to 7:00 p.m. until the patient was discharged from ICU. The assessments were continuously performed at our hospital even before or after the study was conducted.

Baseline demographic information, including age, past history of delirium, and severity of illness, was collected to evaluate the influence of previously detected delirium-related covariates. Cox regression analyses were performed to explore the preventive effects of suvorexant and other medications against delirium.

RESULTS AND DISCUSSION

During the study period, a total of 2,807 patients were admitted to ICU. After a review of these patients' medical records, 2,108 patients were excluded. Among these patients, 1,801 patients had an ICU stay of <3 days, 94 patients were aged ≤2 years, and 74 patients did not have a detectable delirium-free day (to exclude patients with delirium at admission). Furthermore, 139 patients were excluded because of insufficient data. Thus, medical records of the remaining 699 patients were examined; these patients were then divided into two groups: suvorexant users (n = 84) and suvorexant non-users (n = 615). Delirium was diagnosed in 214 patients, whereas the remaining 485 patients were delirium-free during the observation period.

Suvorexant users were significantly more likely to be prescribed dexmedetomidine, trazodone, risperidone, haloperidol, or ramelteon; to have experienced coma; to have higher body weight; and to be male. Hemiplegia and functional disability were less prevalent among suvorexant users. Regarding medication, 727 different drugs were prescribed. There was no significant between-group difference in terms of the number of medications used. We included

22 predictor variables in the Cox model: 9 patient background covariates and 13 frequently prescribed, delirium-related drugs.

Delirium was significantly less prevalent in suvorexant users than in non-users (17.9% vs. 32.4%; P = 0.007). Cox regression analysis showed that suvorexant users had a low hazard ratio (HR) for delirium occurrence (HR 0.472, 95% CI 0.267–0.832; P = 0.009); similar findings were observed for patients using trazodone (HR 0.345, 95% CI 0.149–0.802; P = 0.013). However, other drugs, including dexmedetomidine, ramelteon, Z-drugs, haloperidol, inhaled anesthetics, benzodiazepines, propofol, and risperidone, did not have significant effects on delirium occurrence.

This retrospective cohort study showed that suvorexant had a preventive effect against delirium in critically ill patients. Our results expand the evidence from previous RCTs in experimental trial settings to real-world settings. In these RCTs, patients had to give informed consent and sedated or comatose patients were therefore excluded. To overcome this bias in RCTs, we examined consecutive patients and included those who were treated in routine clinical practice. A retrospective cohort study, similar to the present one, analyzed delirium prevalence in ICU. However, only eight covariates were examined in that study because of the limited number of patients. In contrast, we included 699 patients and investigated 22 covariates based on previously reported delirium-related factors. Consequently, the present study, with a larger sample size, may have overcome some of the previous limitations.

There are some limitations to our study. First, it was a retrospective study; therefore, unknown covariates may have affected the results. Second, in our study population, patients had a clinical need for suvorexant treatment. Physicians may have prescribed suvorexant for insomnia rather than for delirium prevention. Therefore, suvorexant users in this study may not completely coincide with patients at high risk for delirium and those in whom delirium prevention is actually required. Third, all data were collected from medical charts; therefore, some information may have been missing. For example, CAM-ICU data were missing for approximately 10% of person-days. Finally, several antipsychotics or hypnotics were prescribed for only a small number of patients; therefore, we could not examine the effects of these medications on delirium prevention.

CONCLUSION

The present study showed the preventive effect of suvorexant against delirium in a real-world setting.