学 位 論 文 の 要 旨

氏名　　森田　祐介

学 位 論 文 名　Clinical Effectiveness and Adverse Events Associated With Tolvaptan in Patients Above 90 Years of Age With Acute Decompensated Heart Failure

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著 者 名　Yusuke Morita, Akihiro Endo, Yuzo Kagawa, Kazuto Yamaguchi, Hirotomo Sato, Takeshi Ouchi, Nobuhide Watanabe and Kazuaki Tanabe

論 文 内 容 の 要 旨

INTRODUCTION

In recent years, the number of elderly patients with heart failure (HF) has increased. Moreover, in-hospital cardiac mortality has increased with advancing age, especially in patients aged ≥85 years, even during their first episode of acute decompensated HF (ADHF). Elderly patients may have a higher mortality rate due to their increased frailty and higher prevalence of comorbidities, such as renal dysfunction, anemia, and chronic lung disease.

Tolvaptan is an oral vasopressin type 2 receptor antagonist that increases the excretion of free water, which decreases the body weight and improves symptomatic congestion, without resulting in hypokalemia or worsening renal function (WRF). However, the clinical effectiveness and adverse events associated with tolvaptan in very-elderly (VE) patients (≥90 years) with ADHF are yet to be clarified. Therefore, the aim of this study was to evaluate the clinical effectiveness and adverse events associated with tolvaptan administration in VE patients (≥90 years) with ADHF compared to those in patients with ADHF <90 years.

MATERIAL AND METHODS

In this study, we retrospectively analyzed data from our database. Patients with ADHF admitted to Shimane Medical University and initiated on tolvaptan treatment were enrolled.

From January 2011 to December 2018, 180 patients with ADHF were included. Patients were divided into two groups: VE patients ≥90 years of age (VE group, n = 32) and not-VE patients <90 years of age (NVE group, n = 148). Tolvaptan administration and initial dose were determined based on the attending physician's judgment, and the dose was increased when the diuretic effect was insufficient. Tolvaptan continuation or discontinuation after improvement of HF was also at the discretion of the attending physician. Urine volume; body weight; and blood test results, including serum sodium and creatinine levels, were evaluated daily during intensive treatment and at discharge. The exclusion criteria were as follows: tracheal intubation, hemodialysis, poor general condition, hypernatremia (≥145 mEq/mL) at the time of tolvaptan administration, and acute coronary syndrome occurring within 30 days prior to admission.

The primary efficacy endpoints for this study were the total urine volume and change in body weight. The total urine volume was assessed at 24 and 48 hours after tolvaptan administration. Body weight was evaluated at the time of initiating tolvaptan and 7 days later. The secondary efficacy endpoint was the duration of hospitalization.

The safety endpoints evaluated were the incidence of hypernatremia (≥150 mEq/L) and WRF at any time during hospitalization. WRF was defined as an absolute increase in serum creatinine level of >0.3 mg/dL in combination with a >50% relative increase from its level at admission.

The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

The median patient age was 93 [91–94] years and 80 [69–85] years in the VE and NVE groups, respectively ($p < 0.001$). Body weight was lower in the VE group than in the NVE group, while there were no significant differences between the groups in terms of hemoglobin, albumin, brain natriuretic peptide, medical history, and medication including diuretics at admission. In addition, serum creatinine and sodium levels were similar in both groups.

The treatments for HF during the acute phase were no significant differences in the usage rates of noninvasive positive pressure ventilation, carperitide, vasodilator, inotropic agents, and furosemide infusion between the groups.

The mean initial dose, mean dose for the first week after initiation, mean administration period, and the total dose of tolvaptan were not significantly different between the groups. Tolvaptan was initiated at 5.7 ± 5.0 days in the VE group and at 7.4 ± 3.8 days in the NVE group ($p = 0.42$). Furthermore, all patients received furosemide infusion or oral loop diuretics, the dose of which at the initiation of tolvaptan was similar in both groups.

The total urine volume at 24 and 48 hours after initiating tolvaptan increased in the VE and

NVE groups, but without a significant difference (1901 ± 666 mL vs. 2101 ± 1167 mL, p = 0.33 and 3707 ± 1274 mL vs. 4195 ± 1990 mL, p = 0.19, respectively). The body weight decreased equally in both groups 7 days after tolvaptan administration (-2.5 ± 2.0 kg, VE group; -2.7 ± 2.4 kg, NVE group; p = 0.70), and the rate of body weight change was also reduced (-5.6 ± 4.0%, VE group; -5.3 ± 4.9%, NVE group; p = 0.78). The median duration of hospitalization was similar in both groups (24 [20-49] days, VE group; vs. 31 [20-42] days, NVE group; p = 0.67).

Hypernatremia (≥150 mEq/L) occurred in 2 (6.3%) and 5 (3.4%) patients in the VE and NVE groups, respectively (p = 0.61). WRF occurred in 8 (25.0%) and 29 (19.6%) patients in the VE and NVE groups, respectively (p = 0.31). The incidence of hypernatremia and WRF was not significantly different between the groups.

The treatment goals for ADHF include decreasing congestion, reducing afterload, and avoiding neurohormonal activation. Loop diuretics such as furosemide are most commonly used to reduce fluid retention in patients with ADHF. However, they frequently result in electrolyte abnormalities and WRF are associated with a greater risk of death and renal dysfunction.

Tolvaptan, an oral selective vasopressin type 2 receptor antagonist, improved congestive symptoms without increasing WRF. Several studies have shown that the efficacy and safety of tolvaptan in VE patients with ADHF, but these studies did not evaluate these factors in patients ≥90 years of age.

This study has several limitations. First, this study was a single-arm, retrospective, observational study with a relatively small sample size, which may have led to selection bias. Second, this study included only HF patients on tolvaptan. Third, this study did not show the usefulness of long-term administration of tolvaptan. Finally, the initial dose of tolvaptan was chosen according to the physician's judgment. Therefore, we could not evaluate the direct effects of tolvaptan in patients with ADHF.

CONCLUSION

In this study, the frequency of adverse events was similar between the groups, and the clinical effectiveness was also the same. This study revealed that even patients above 90 years of age can use the same clinical effectiveness without being overly concerned about the risk of adverse events.