

## 学位論文の要旨

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学位論文名 Effects of Omeprazole on Sleep Disturbance: Randomized Multicenter Double-Blind Placebo-Controlled Trial

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## 論文内容の要旨

### INTRODUCTION

Sleep disturbance is an important extraesophageal complication in patients with gastroesophageal reflux disease (GERD) and a close association between them has recently been reported. Several clinical investigations have indicated that proton pump inhibitor (PPI) administration can improve sleep disorders associated with GERD, though the presented evidence is inadequate because of small sample sizes or inappropriate study design.

GERD without typical reflux symptoms may have some role in sleep disturbance, as affected individuals often have endoscopy-proven asymptomatic reflux esophagitis. Silent GERD patients also frequently develop sleep disturbance, thus PPIs may improve that in those with and without reflux symptoms. We examined whether PPI administration has a therapeutic effect for improving insomnia in patients without reflux symptoms in the same manner as those with reflux symptoms.

## **MATERIALS AND METHODS**

This multicenter randomized double-blind placebo-controlled prospective study of patients with sleep disturbance was conducted from 2010 to 2012 at Shimane University Hospital, and 13 affiliated hospitals and clinics. Patients who visited outpatient clinics for management of primary insomnia were enrolled. Those who took hypnotics, PPIs, and/or histamine H<sub>2</sub> receptor antagonists within 2 weeks before enrollment, with a history of treatment for mental disorders or with serious underlying diseases that may influence sleep quality were excluded. Women who were pregnant or had a high possibility of pregnancy, and patients allergic to omeprazole were also excluded. Background and clinical factors such as age, gender, height, body weight, body mass index, drinking, smoking, presence of typical GERD symptoms (heartburn, acid regurgitation), throat discomfort, cough, chest pain, otalgia, and asthma were recorded at the time of enrollment. The subjects were randomly assigned to 2 groups according to a prefixed order; with 1 receiving omeprazole (20 mg) and the other an indistinguishable placebo 30 minutes before dinner daily for 2 weeks. Four self-reporting questionnaires, QOLRAD-J (Japanese translation of Quality of Life in Reflux and Dyspepsia), Pittsburg Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and a sleep diary, were used to evaluate GERD-related quality of life (QOL) and sleep disturbance. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

## **RESULTS AND DISCUSSION**

A total of 176 patients were initially enrolled, with 171 analyzed after withdrawals for enrollment criteria violations and dropout during treatment. We investigated the prevalence of reflux symptoms in these subjects with insomnia and found that as many as 40% (69/171) had typical reflux symptoms, indicating an important role for GERD as a possible pathogenetic factor in sleep disturbance.

In patients with reflux symptoms, omeprazole significantly improved GERD-related





(QOLRAD-J, total) and sleep-related (QOLRAD-J, sleep-related) QOL from  $30.8 \pm 0.7$  to  $33.0 \pm 0.5$  and  $6.0 \pm 0.2$  to  $6.6 \pm 0.1$ , respectively (both  $P < 0.01$ ). Omeprazole also statistically significantly improved sleep quality (PSQI 15.1%, ESS 15.9%, diary record 14.3% improvement), whereas administration of the placebo had no significant therapeutic effect (3.4%, 7.7%, and 0% respectively). Several double-blind randomized studies have investigated the effectiveness of PPIs for treatment of sleep disturbance in patients with symptomatic GERD and all concluded that they improved sleep quality for such patients. The results of our study confirmed that PPI administration is effective for insomnia in patients with reflux symptoms.

In contrast, in patients without reflux symptoms, there was no difference between omeprazole and the placebo for improvement in sleep quality (PSQI 19.8% vs. 22.4%, ESS 7.7% vs. 17.3%, diary record 13.6% vs. 9.5%). The effect of the placebo on sleep quality was especially large in this group, and both that and omeprazole significantly improved sleep quality in subjects without reflux symptoms. We consider that the lack of effect from PPI administration for improving sleep disturbance in cases without typical reflux symptoms is an interesting finding of the present study. Based on this result, we concluded that silent gastroesophageal reflux is not a major factor causing sleep disturbance, in contrast to reflux symptoms. Furthermore, the presence of reflux symptoms may be a good indicator for predicting a good therapeutic effect from PPI administration for sleep disturbance.

### **CONCLUSION**

Approximately 40% of our clinical patients with insomnia had typical reflux symptoms. Their condition was effectively improved by omeprazole, whereas patients without reflux symptoms were not improved by PPI administration.

論文審査及び最終試験又は学力の確認の結果の要旨

①・乙	氏名	宇野 吾一	
学位論文名	Simplified Classification of Capillary Pattern in Barrett Esophagus Using Magnifying Endoscopy With Narrow Band Imaging: Implications for Malignant Potential and Interobserver Agreement		
学位論文審査委員	主査	京 哲	   
	副査	並河 徹	
	副査	磯部 威	

論文審査の結果の要旨

Barrett腺癌は食道癌の中で最も増加率の高い癌として近年注目されている。申請者らはNarrow band imaging (NBI) という特殊光を用いた拡大内視鏡観察を行い、簡便で汎用性の高いBarrett食道粘膜の分類法の構築を目的に研究を行った。Barrett食道を有する患者を対象としてNBI拡大内視鏡観察を行い、粘膜血管の密度と形態に基づいたCapillary pattern (CP) 新分類を提唱し、粘膜をType IとType IIに分類した。この新分類法と従来からの色素内視鏡検査で判定される粘膜表層構造に基づいたPit pattern分類との相関性、さらに発癌に関連するとされる各種因子の発現との関係、血管密度、CP分類の検者間一致率を検討した。従来法との比較ではCP Type IIにおいてBarrett腺癌やBarrett異形上皮で認められるpatternが多くみられ、また生検組織の免疫染色において、腸上皮化生、炎症、血管新生、細胞増殖のマーカー（それぞれCDX2、COX-2、CD34、PCNA）の染色性が高値であった。さらに異型病変は全てCP Type IIに分類された。多変量解析ではCP Type IIが異型病変の検出、CD34高値、PCNA高値を予測しうる因子として同定された。CP分類の検者間一致率もこれまで報告されている粘膜表層構造に重点をおいた分類法よりもκ値が高く、優れているものと考えられた。これらの結果はBarrett食道において悪性度の高い粘膜を検出するのに新たに作成された内視鏡分類であるCP分類が有用であることを示しており、またその簡便性、汎用性を考慮すれば実地臨床への応用性が高く、十分に学位論文に値すると考えられた。

最終試験又は学力の確認の結果の要旨

申請者は、Narrow band imaging (NBI) という特殊光を用いた拡大内視鏡観察におけるBarrett食道粘膜の新分類法を提唱した。この分類法の特徴は従来の粘膜表層構造による分類とは異なり、血管密度とその形態に基づいた分類である。新分類法として血管構造に視点をあてた本論文はユニークであるが、本分類法の提唱により異型病変または悪性ポテンシャルを有する病変の選別能が向上し、また血管構造による分類は簡便で検者間一致率が高く、汎用性が高いこともアピールされた。したがって実地臨床への応用性に優れ、学位論文としての価値は高い。また申請者は審査員からの多岐にわたる質問にも全ての確に答え、十分に学位授与に値すると判断した。 (主査 京哲)

申請者は、narrow band imaging を用いた内視鏡観察技術を応用し、バレット癌につながる病変をより効率よく簡便に同定するための手法として血管パターンを観察が有用であることを示した。このことは今後のバレット癌診断技術の進展に資する臨床的に優れた成果である。背景の知識も豊富であり質疑応答も適確であったことから、学位授与に値すると判断した。 (副査 並河徹)

申請者は、日本でも増加傾向にあるバレット食道内に存在する癌化が予想される悪性度の高い粘膜を効率よく発見するために、narrow band imaging を用いた新しい内視鏡的血管パターン分類を構築した。この研究はバレット癌の早期診断に有用と考えられ、臨床的に優れた成果である。背景の知識も豊富であり質疑応答も適確であったことから、学位授与に値すると判断した。 (副査 磯部威)

(備考) 要旨は、それぞれ400字程度とする。