学 位 論 文 の 要 旨

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学 位 論 文 名　Low-dose Rectal Diclofenac Does not Prevent Post-ERCP Pancreatitis in Low- or High-risk Patients

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論 文 内 容 の 要 旨

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) findings are important for biliopancreatic diagnostic and therapeutic procedures. The most common adverse event following that procedure is post-ERCP pancreatitis (PEP) and rectal nonsteroidal anti-inflammatory drugs (NSAIDs) administration has shown promise to reduce the risk of PEP in high-risk patients. On the other hand, the role of NSAIDs administration in patients considered to be low risk remains controversial. In the present study, we examined the efficacy of rectal NSAIDs administration at a low dose (50 mg) for prevention of PEP in patients who underwent an ERCP procedure, including those considered to have a low or high risk of PEP development.

MATERIALS AND METHODS

This prospective, single-center, single-blinded, two-arm parallel-group, randomized controlled trial was performed to clarify the efficacy of low-dose (50 mg) rectal NSAID administration for preventing PEP in at-risk patients. Patients scheduled to undergo ERCP were randomized into 2 groups, without administration of diclofenac and with that administration, which included 50 mg of rectal diclofenac at 30 minutes before ERCP, with the amount reduced to 25 mg in those weighing less than 50 kg. The primary study endpoints were rate and severity

of PEP. The study protocol was approved by the institutional review-board of Hyogo Prefectural Awaji Medical Center.

Outcomes

Pancreatitis was defined based on criteria presented by Cotton, and diagnosed in patients with development of upper abdominal pain and increased serum amylase concentration greater than 3 times over the upper limit of normal within 24 hours after ERCP. The severity of PEP was graded as mild (2-3 days required for recovery), moderate (4-10 days required for recovery), and severe (more than 10 days required for recovery). In addition, we performed additional analysis after dividing into subgroups based on risk. The high-risk group was defined based on the presence of at least one patient- or procedure-related risk factor. Patient-related factors included sphincter of Oddi dysfunction, age less than 50 years, female gender, history of recurrent pancreatitis, and history of PEP, while procedure-related factors included difficult cannulation (cannulation duration ≥10 minutes), total procedure time ≥40 minutes, pancreatic sphincterotomy, pancreatic brush cytology, pancreatic injection ≥3 times, and pancreatic guidewire passage. Patients without any risk factors were classified into the non-high-risk group.

Statistical methods

For analysis, a chi-squared test, Fisher's exact test, and logistic regression analysis were used, as appropriate. In addition, statistical analysis of the effect of each risk factor on preventing adverse effects of NSAIDs treatment was also performed. All statistical analyses were done using R, version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS AND DISCUSSION

Results

A total of 303 patients were randomized into the study groups. Four patients declined participation following randomization and another 2 were later withdrawn. As a result, 147 patients were assigned to the diclofenac group and 150 to the control group. The baseline and procedural characteristics were similar in both. The primary endpoint of PEP occurrence was seen in 13 of 297 patients (4.4%), including 8 (5.4%) in the diclofenac group and 5 (3.3%) in the control group (P=0.286). The high-risk group was comprised of 171 (57.6%) patients (57.6%) and the non-high-risk group (low-risk) 126 (42.4%) patients, with PEP noted in 12 (7.0%) and 1 (0.8%), respectively. Those results were not significantly different between patients classified as non-high- and high-risk. Among the high-risk group, few (11.8%) had patient-related risk factors, while most (98.8%) showed procedure-related risk factors.

Discussion

Our results showed that NSAIDs administration did not prevent PEP regardless of level of risk, possibly because very few of the enrolled patients had patient-related risk factors for its occurrence. Nevertheless, a previous meta-analysis of mainly patients with low risk also found no beneficial effect of an NSAIDs for prevention of PEP. Another possible reason for lack of beneficial effect of NSAIDs treatment in our study is the lower dose of diclofenac given. In

nearly all related studies performed in western countries, the dose was 100 mg, higher than that used in the present cohort (25 or 50 mg). Although previous studies conducted in Japan have suggested a beneficial value of a 25- or 50- mg dose of diclofenac, those were retrospective in design, had a small number of participants, or were performed at a center with a low volume of ERCP cases. Therefore, the quality of the present prospective randomized large scale study performed at a high-volume center is considered to be superior.

We also examined PEP incidence after dividing the patients into high- and non-high-risk groups, and found that the incidence was not different between them, which might be related to the low incidence of PEP in these patients regardless of diclofenac usage. In univariate analysis, factors associated with the incidence of PEP were shown to be longer procedure time and longer cannulation time, while multivariate analysis revealed longer total procedure time as the only significant risk factor. Therefore, administration of low-dose diclofenac for prevention of PEP is considered to be inappropriate for high-risk patients with procedure-related risk factors, especially difficult cannulation, as well as extended procedure time, and also for non-high-risk patients.

This study has some limitations, including performance in a single center with a single blinded design. Furthermore, most of the enrolled patients were elderly, though that is a reflection of the recent aging trend in Japan. Also, the dose of diclofenac given was lower than that in western studies. Finally, we estimated that the occurrence of PEP in the control group would be 16% based on past trials of PEP prevention by NSAIDs treatment, whereas the actual incidence of PEP was much lower in our results. A future study with a larger population is necessary to confirm the present findings.

CONCLUSIONS

Prophylactic low-dose rectal diclofenac did not reduce the incidence of PEP following ERCP in patients classified as having either a low or high risk of its development.