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# Effect of Platelet-Activating Factor Receptor Antagonist, Etizolam, on Resolution of Chronic Subdural Hematoma

## —A Prospective Study to Investigate Use as Conservative Therapy—

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## Abstract

**Inflammatory reaction is very important for formation of the neomembrane of chronic subdural hematoma (CSDH). The present study evaluated medical treatment with the platelet-activating factor receptor antagonist, etizolam, for the resolution of CSDH, and the factors indicating surgery or conservative therapy. Alternate patients were assigned to the etizolam group or control group without medical treatment. Patients in the etizolam group received 3.0 mg etizolam per day for 14 days. A total of 53 patients were followed up for at least 6 months. Univariate analysis of differences in demographic characteristics, clinical findings, and initial computed tomography (CT) findings, and multiple logistic regression analysis of the relationship between etizolam treatment and requirement for surgery using age, sex, low density of hematoma on CT, and paresis as confounders were performed. Etizolam treatment (adjusted odds ratio [OR] 0.156, 95% confidence interval [CI] 0.024–0.999, p = 0.049) was negatively correlated with requirement for surgery. Low density of hematoma (adjusted OR 0.125, 95% CI 0.019–0.846, p = 0.033) was found to be an independent negative predictor, and paresis as an initial symptom (adjusted OR 6.35, 95% CI 1.04–38.7, p = 0.045) was an independent positive predictor of requirement for surgery. Etizolam administration can promote the resolution of CSDH, especially at the stage of hygroma appearing as low density on CT. Surgery is recommended if the patient presents with paresis.**

Key words: chronic subdural hematoma, computed tomography, etizolam, platelet-activating factor receptor antagonist

## Introduction

Chronic subdural hematoma (CSDH) is frequently encountered in daily neurosurgical practice, and can be successfully treated by relatively less invasive procedures such as one-burrhole evacuation and irrigation of the hematoma. Both the origin and mechanism of hematoma enlargement are still incompletely understood. The rebleeding hypothesis is widely accepted as the cause of enlargement of CSDH,[2] but the origin is still obscure.

The inflammatory reaction is an important stimulus for the formation and growth of CSDH.[10] Previously, we found that platelet-activating factor (PAF), a highly potent lipid mediator of inflammation, is involved in these processes.[7,8] Our recent prospective study showed that etizolam, a PAF receptor antagonist, attenuates the recurrence of CSDH after hematoma evacuation and irrigation.[9]

The present study examined whether oral administration of etizolam decreased the requirement for surgery and identified the predictive factors.

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## Materials and Methods

This study included 62 patients treated under initial diagnoses of CSDH based on brain computed tomography (CT) at the Toyama Medical and Pharmaceutical University between May 1994 and May 1999. Patients were excluded using the following criteria: massive hematoma; impending signs of

brain herniation; severe headache and vomiting; severe paresis; severe complications, such as cardiopulmonary, hepato-renal, or metabolic disease; and administration of corticosteroid or mannitol. All 62 patients could walk and eat without any help.

Informed consent was obtained from all patients. Alternate patients were assigned to the group treated with etizolam or the control group without medical treatment. Placebo was not given in the control group. Patients in the etizolam group were given 3.0 mg etizolam orally per day for 14 days.

Clinical data including age, sex, initial symptoms, presence of head trauma, and duration between head trauma and symptoms were obtained on the day of diagnosis. CT was performed in the 1st and 2nd weeks, and 1 month, 2 months, 3 months, and 6 months. If necessary, additional CT examination was performed. Symptoms were also carefully observed at these examinations. The primary team in the outpatient clinic decided whether surgery was required for removal of hematoma based on an increase in hematoma size and aggravation of symptoms. The site (unilateral or bilateral) and the density (low or other) of the hematoma, the presence or absence of layering of the hematoma, and multiplicity of hematoma cavities were evaluated independently on the first CT scan by three trained neurosurgeons, who were not the primary physicians for these patients and who were unaware of the medical record and other CT findings. If the densities of bilateral hematomas differed, the density of hematoma was judged to be other. Layering of the hematoma consisted of two components of different densities separated by a clear boundary.[24] Multiplicity of hematoma cavities was defined as hematoma with heterogenous content and a high-density septum running between the inner and outer membranes.[24] Agreement by at least two observers was required to establish the finding.

Univariate analysis was used to assess the relationships between each variable and the requirement for surgery to remove hematoma with the Mann-Whitney U-test and Fisher's exact test. Univariate and multivariate statistical analyses were also performed of variables related to the requirement for surgery using a logistic regression model. Variables in the final model of multiple logistic regression analysis were selected according to a stepwise method, and those considered to be of clinical importance were included. To determine the independent variables affecting requirement for surgery, odds ratios were evaluated after adjustment for other variables.

## Results

Ten of the 30 patients in the etizolam group suffered somnolence as a side effect of etizolam administration. Six patients in this group were dropped from the study because the duration of drug administration was less than 14 days. The somnolence disappeared after stopping etizolam administration, so was not caused by the increase of hematoma. Three patients in the control group could only be followed up for 18 days, 18 days, and 21 days, which were insufficiently long periods. All other patients were followed up for at least 6 months. Finally, the etizolam group consisted of 16 men and eight women aged 53 to 80 years (mean 67.9 years) whereas the control group consisted of 22 men and seven women aged 54 to 86 years (mean 68.3 years). Surgery for CSDH was required in 40 patients within 14 days of entry into the study, whereas surgery was not required for 13 patients during the follow-up period of 6 months. Irrigation of hematoma using one burrhole was performed with neuroleptanalgesia and local anesthesia in 39 patients, and craniotomy under general anesthesia in only one patient.

Demographic variables such as patient sex and age showed no difference between the etizolam and control groups (Table 1). There were no significant differences in the incidence of head trauma or initial symptoms including headache, nausea and/or vomiting, dementia, urinary incontinence, and aphasia between the two groups. Only paresis was significantly associated with the control group. Surgery was performed more frequently in the control group than in the etizolam group.

Interobserver agreement of the initial brain CT findings was estimated using the overall $\kappa$ coefficient between two observers. The indices of agreement for hematoma site, CT density of hematoma, layering of hematoma, and multiplicity of hematoma cavity were 0.913, 0.842, 0.741, and 0.551 between observers 1 and 2, 0.781, 0.740, 0.773, and 0.616 between observers 2 and 3, and 0.617, 0.694, 0.781, and 0.710 between observers 3 and 1, respectively. The incidence of low density of hematoma was significantly higher in the etizolam group than in the control group (Table 2). The other initial brain CT findings showed no significant difference between the two groups.

Univariate logistic regression analysis showed that etizolam administration, presence of paresis as an initial symptom, and low density of hematoma were related to the requirement for surgery (data not shown).

After eliminating variables that were closely relat-

**Table 1 Demographic characteristics and clinical findings in 53 patients with chronic subdural hematoma**

| Factor | No. of patients | | Total (n=53) | p Value |
|---|---|---|---|---|
| | Etizolam group (n=24) | Control group (n=29) | | |
| Sex | | | | |
| male | 16 | 22 | 38 | 0.547 |
| female | 8 | 7 | 15 | |
| Age (yrs)* | 67.9±8.63 | 68.3±8.65 | 68.1±8.56 | 0.865 |
| Head trauma | | | | |
| present | 20 | 25 | 45 | 0.771 |
| absent | 4 | 4 | 8 | |
| Initial symptom: | | | | |
| headache | | | | |
| present | 8 | 15 | 23 | 0.266 |
| absent | 16 | 14 | 30 | |
| nausea and/or vomiting | | | | |
| present | 3 | 4 | 7 | 0.890 |
| absent | 21 | 25 | 46 | |
| dementia | | | | |
| present | 8 | 8 | 16 | 0.767 |
| absent | 16 | 21 | 37 | |
| urinary incontinence | | | | |
| present | 1 | 4 | 5 | 0.362 |
| absent | 23 | 25 | 48 | |
| paresis | | | | |
| present | 10 | 22 | 32 | 0.023 |
| absent | 14 | 7 | 21 | |
| aphasia | | | | |
| present | 1 | 1 | 2 | 0.891 |
| absent | 23 | 28 | 51 | |
| Surgery | | | | |
| present | 13 | 27 | 40 | 0.001 |
| absent | 11 | 2 | 13 | |

*Values are expressed as mean±standard deviation.

ed to others, the following items were adopted as confounders of the main effect, i.e. etizolam administration, in the logistic regression model for multivariate analysis: age (1 year), sex (male), CT density of hematoma (low), and paresis (present). This analysis revealed that etizolam administration was negatively correlated with the requirement for surgery (Table 3, Fig. 1). Furthermore, non-low density of hematoma, and presence of hemiparesis as an initial symptom were significantly associated with the requirement for surgery after adjustment for other confounders (Table 3).

**Table 2 Treatment with etizolam and summary of computed tomography (CT) findings for 53 patients with chronic subdural hematoma**

| Factor | No. of patients (%) | | p Value |
|---|---|---|---|
| | Etizolam group (n=24) | Control group (n=29) | |
| Hematoma site | | | |
| unilateral | 17 | 15 | 0.174 |
| bilateral | 7 | 14 | |
| CT density of hematoma | | | |
| low | 8 | 3 | 0.049 |
| other | 16 | 26 | |
| Layering of hematoma | | | |
| present | 6 | 7 | 0.942 |
| absent | 18 | 22 | |
| Multiplicity of hematoma cavity | | | |
| present | 3 | 5 | 0.391 |
| absent | 21 | 24 | |

## Discussion

Various hypotheses have been suggested to explain the origin, pathogenesis, and natural history of CSDH.[11] CSDH has dual origins, subdural hygroma and acute subdural hematoma. Certain pre-morbid

**Table 3 Results of multiple logistic regression analysis of variables related to requirement for surgery in patients with chronic subdural hematoma**

| Variables | Unit | Adjusted OR (95% CI) | p Value |
|---|---|---|---|
| Main effect: | | | |
| etizolam administration | present | 0.156 (0.024-0.999) | 0.049 |
| Confounders: | | | |
| age | 1 year | 0.939 (0.839-1.051) | 0.274 |
| sex | male | 1.36 (0.233-7.97) | 0.731 |
| CT density of hematoma | low | 0.125 (0.019-0.846) | 0.033 |
| paresis | present | 6.35 (1.04-38.7) | 0.045 |

CI: confidence interval, CT: computed tomography, OR: odds ratio.

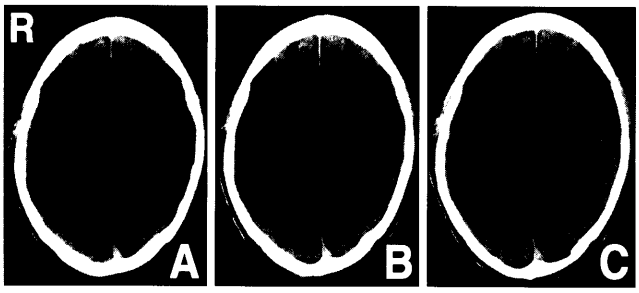


**Fig. 1 Computed tomography scans showing sequential changes in a 76-year-old man with chronic subdural hematoma manifesting as mild headache. (A) Chronic subdural hematoma appeared as near-low density in the left cerebral hemisphere on the day of diagnosis. (B) Etizolam (3.0 mg orally per day) was given for 14 days. (C) The volume of hematoma decreased gradually and disappeared after almost 3 months.**

conditions, i.e. sufficient potential subdural space such as arachnoid cyst, brain atrophy, or intracranial hypotension with or without head injury,[13,19,22] are prerequisites for the occurrence of CSDH. Unresolved subdural hygroma with or without blood induces proliferation of dural border cells by evoking inflammatory reaction and production of neomembranes.[6] Micro-hemorrhage occurs repeatedly from fragile new vessels in the neomembranes and is accompanied by local hyperfibrinolysis. The hematoma then enlarges and becomes symptomatic when rebleeding exceeds absorption. The density of the hematoma changes from low to isodensity or high density on CT. If the potential subdural space is sufficient, acute subdural hematoma may become develop into CSDH by exactly the same mechanism. The principal mechanism of resolution is maturation of the neomembrane.[11] Neovessels are no longer fragile in the mature neomembrane, and if absorption exceeds rebleeding, the hematoma will disappear.

Resolution of CSDH may occur spontaneously without treatment.[14,16] The hematoma membrane might proceed from the proliferative stage to the degenerative stage during its natural history, so CSDH could resolve without surgery if intracranial pressure is controlled at the expanding stage of CSDH by medical treatment such as mannitol administration.[18] Decreased fibrinolytic activity of the hematoma capsule and fluid might also result in spontaneous resolution.[15] Medical treatment using mannitol or steroid has also been proposed as a mechanism.[1,6,20] Hematoma resolution may be due to enhanced vascular permeability changes and absorption of the hematoma. However, treatment with osmotic agents often fails to induce resolution of CSDH due to its effect on intracranial pressure.[5] Inflammatory processes are important for neovascularization within the neomembrane. Therefore, the anti-inflammatory activity of steroids might contribute to inhibition of the development of neomembrane.[6]

PAF is a highly potent lipid mediator of inflammation. We previously demonstrated that PAF is confined to the endothelial cells of new vessels in the neomembrane at the expanding stage of CSDH, and that the concentration of the hematoma decreased due to increased activity of PAF-acetylhydrolase at the late stage of CSDH. PAF may be involved in the formation of neomembrane with fragile neovascularization from subdural hygroma. PAF may also contribute to the development of CSDH with completion of the neomembrane. Whether there is a close relationship between neomembrane formation and increased fibrinolytic activity in the membrane and hematoma remains unknown. Infiltration of eosinophils and subsequent degranulation often occurs in the neomembrane of CSDH.[25] Eosinophils secrete plasminogen-rich granules.[25] The locations of PAF and tissue plasminogen activator are exactly the same, i.e. in the endothelial cells.[8] PAF is released from various cells[3,4,12,17] and can induce chemotaxis of inflammatory cells including eosinophils.[21,23] By increasing local fibrinolysis, PAF might strongly enhance repeated bleeding from neomembrane in addition to formation of fragile vessel formation.

Etizolam, an anti-anxiety agent, is an antagonist of PAF receptors. Our previous preliminary study revealed that administration of etizolam attenuated recurrence after surgery for CSDH, and that the remaining volume of hematoma 1 month after sur-

gery was significantly smaller in the etizolam group than in the control group.[9] In the present study, etizolam administration and low density of hematoma on CT were found to be independent predictors for resolution without surgery, whereas hemiparesis as an initial symptom was an independent predictor for requirement for surgery. The initial symptoms of spontaneous resolution of CSDH are usually described as mild, such as headache and decrease in cognitive level.[14,16] Hemiparesis may indicate the need for reduction of intracranial pressure by medical or surgical procedures. Low density on CT might be observed at two stages in the natural history of CSDH, the stage of hygroma, i.e. subdural cerebrospinal fluid accumulation with or without blood, and the stage of membrane maturation. Theoretically, anti-inflammatory agents might be effective in either stage. However, almost all patients with low CT density of hematoma in this study were thought to be in the former stage, based on their history.

Surgery is recommended for patients with severe initial symptoms such as hemiparesis and elevated intracranial pressure, to maximize the efficacy and cost-effectiveness of surgery. The present study indicates that etizolam administration can promote the resolution of CSDH, especially at the stage of hygroma appearing as low density or near-low density on CT. Medical treatment with etizolam based on the specific indications and careful follow up may have clinical and economic benefits in patients with CSDH. Further studies to determine the dose needed to prevent side effects such as somnolence and a multicentric randomized controlled trial are needed.

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## Commentary

*The authors have prospectively studied the potential efficacy of etizolam, a platelet-activating factor receptor antagonist, in the nonsurgical treatment of chronic subdural hematomas. The precise cause for enlargement of chronic subdural hematomas is controversial, but previous studies have suggested that the inflammatory process may play a major role. In this study, the authors have followed up on previous reports from their own experience on the presence of platelet-activating factor (PAF), which is a potent mediator of inflammation. In the current study, the authors randomized 62 patients with chronic subdural hematomas to a group given three milligrams of etizolam per day for 14 days and a control group in which no specific treatment was provided. Using a univariate analysis, the authors determined that the use of etizolam was associated with a decreased necessity for surgical intervention.*

*Despite the result of this univariate analysis, there are some important differences between the etizolam and control groups that could potentially influence the outcome. Six patients in the etizolam group were unable to continue their therapy because of side effects attributed to the study drug. More patients in the control group appeared to have symptomatic chronic subdural hematomas manifested by headache and paresis. On the other hand, the etizolam group had a higher incidence of low-density hematomas, which was subsequently found to be associated with a lower incidence of surgical intervention.*

*Despite these potential detractors, the article is quite provocative and suggests that the use of a PAF inhibitor may provide an option in the nonsurgical management of selected chronic subdural hematomas.*

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