Original Contribution

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Effect of Preoperative Immunonutrition in Patients Undergoing Hepatectomy; A Randomized Controlled Trial

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Summary: No consensus has been reached concerning the effects of preoperative immunonutrition in patients undergoing hepatectomy. We evaluated the effects of immunonutrition before hepatectomy on perioperative management. This study was performed as a randomized controlled trial. Patients expected to undergo segmentectomy or more extensive hepatectomy for liver tumors were randomized to immunonutrition (IM) and control (C) groups each consisting of 13 patients. The IM group was given 750 ml of IMPACT in addition to half-size hospital meals orally from 5 days before to the day before surgery, and the C group was given conventional hospital meals. The blood level of eicosapentaenoic acid was elevated preoperatively in all patients of the IM group. The white blood cell count and interleukin 6 levels, which are indices of postoperative inflammation, were significantly lower in the IM group. As regards liver function, postoperative increases in the aspartate aminotransferase and alanine aminotransaminase levels were slightly suppressed in the IM group. No significant difference was noted in postoperative complications or duration of postoperative hospital stay. In patients undergoing hepatectomy, preoperative immunonutrition reduced inflammation and protected against liver dysfunction.

Key words immunonutrition, hepatectomy, ω-3 fatty acid, eicosapentaenoic, arginine, postoperative complications

INTRODUCTION

Nutritional management in the perioperative period affects postoperative complications [1]. Recently, there have been reports that postoperative infectious complications were reduced by the intake of oral preparations containing nutrients that enhance immune functions, such as ω-3 fatty acids, arginine, and nucleic acid [2-7]. Inflammatory mediators derived from ω-3 fatty acids such as prostaglandin (PG) E3, thromboxane (TX) A2, and leukotriene (LT) 5 have mild physiologic activities and anti-inflammatory effects [8]. Arginine and nucleic acid also have immunopotentiating and cell proliferating effects and are expected to promote wound healing and help stabilize the intestinal mucosa [9,10]. Excessive postoperative inflammation and immunosuppression can be controlled by massive preoperative intake of oral nutritional preparations containing high levels of ω-3 fatty acids, arginine, and nucleic acid.

According to reports concerning surgical site infections (SSI), the incidence of SSI in the liver-biliary-pancreas region is as high as 17%, second only to the esophagus and colon [11]. In view of the current aging of the population, perioperative nutritional management is important for reducing postoperative compli-

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Abbreviations: AA, arachidonic acid; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; Arg, arginine; Ccr, creatinine clearance; DHR, delayed hypersensitivity responses; EPA, eicosapentaenoic acid; FFA, free fatty acids; IgG, immunoglobulin G; IL-6, interleukin 6; LT, leukotriene ; Orn, ornithine; PG, prostaglandin; Pre Alb, transthyretin; RBP, retinol binding protein; SSI, surgical site infections; Tf, transferrin; TG, triglycerides; TNF, tumor necrosis factor; TX, thromboxane; WBC, white blood cell count.

cations [12]. Many studies have been performed regarding immunonutrition and the esophagus, stomach, and colon, but there have been no reports indicating the effectiveness of immunonutrition in hepatectomy. Immunonutrition before hepatectomy is not as prevalent as that before surgery of the esophagus, colon and other parts of the digestive tract. However, as complications after extensive hepatectomy may be fatal, preoperative immunonutrition to control postoperative complications could have important implications.

In this study, we evaluated the effectiveness of preoperative immunonutrition on perioperative management of patients undergoing hepatectomy.

PATIENTS AND METHODS

The subjects were patients undergoing segmentectomy or more extensive hepatectomy not including biliary tract reconstruction for liver tumors (hepatocellular carcinoma, cholangiocellular carcinoma, metastatic liver cancer, and carcinoid) between February 2005 and December 2008 at the Department of Surgery, Kurume University. The exclusion criteria were marked renal dysfunction (Ccr<30 ml/min), severe diabetes requiring insulin injection, chemoradiotherapy within 1 month before surgery, and inability to take oral nutrition. Patients meeting any of these criteria were excluded.

This protocol was approved by the Ethical Review Board of Kurume University. Written informed consent was obtained directly from all subjects. Forty-one patients who provided consent were randomized to IM and C groups, consisting of 25 and 16 patients, respectively.

The IM group was given IMPACT (Ajinomoto Pharma, Tokyo, Japan) at 750 ml/day (750 kcal/day) and half meals (half-size hospital meals, 1,000 kcal/day) to avoid excessive energy intake from 5 days before to the day before surgery. The C group was given conventional hospital meals (1,800 kcal/day). Both groups were given ordinary hospital meals from two days after surgery.

Serum albumin (Alb) and transthyretin (Pre alb) were measured as nutritional indices before surgery; white blood cell count (WBC) and serum interleukin 6 (IL-6) were used as indices of inflammatory reaction; aspartate transaminase (AST) and alanine aminotransferase (ALT) were used as indices of liver function; and levels of eicosapentaenoic acid (EPA), which is an $\omega 3$ fatty acid, arachidonic acid (AA), which is an $\omega 6$ fatty acid, triglycerides (TG), and free fatty acids (FFA) were used as indices of fatty acid metabolism. Alb and Pr Alb were measured 5 days before (Pre5), and one day before (Pre1) surgery; AST, ALT, EPA, TG, and FFA were measured at Pre5, Pre1, 3 days after (Post3), and 7 days after (Post7) surgery. WBC was measured at Pre5, Pre1, immediately after surgery (Post0), Post3, and Post7. IL-6 was measured on Post0 and Post3.

As clinical outcomes, age, gender, BMI, preoperative liver function, extent of hepatectomy, operation time, volume of intraoperative blood loss, Pringle time, postoperative complications, and duration of postoperative hospital stay were recorded.

The data were analyzed by ANOVA using JMP version 8 (Windows, Tokayo, Japan), and $p<0.05$ was considered significant.

RESULTS

Although 41 patients were registered between February 2005 and December 2008, 15 (43.0%) were lost from the study. These included 10 in whom the treatment was changed, 1 who experienced diarrhea as an adverse effect, 1 who complained of abdominal distension, 1 who disliked the taste, and 2 who declined to participate. Eventually comparisons were made between 13 patients each in the IM and C groups (Fig. 1).

Concerning the patients' characteristics, no significant difference was noted between the two groups in terms of age, gender, preoperative liver function, extent of hepatectomy, operation time, volume of blood loss, or Pringle time (Table 1). Also, no significant difference was noted between the two groups in the values of Alb, Pre alb, AST, ALT, TG, or FFA. On Pre5, the WBC was normal in both groups but was signifi-

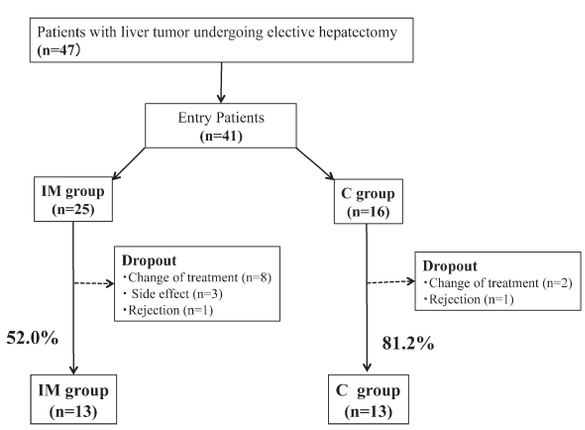

Fig. 1. Study diagram .
IM group, immunonutrition group; C group, control group.

cantly higher in the C group (p=0.024).

On Pre1, the EPA level and EPA/AA ratio were significantly higher in the IM group (Fig. 2). No difference was noted between the two groups in the preoperative or postoperative changes in Alb or Pre alb, which are nutritional indices. The increase in WBC

TABLE 1.
Clinical features of the enrolled patients.

	IM group (n=13)	C group (n=13)	P value
Age (years)	67.5±11.3	61.5±10.2	n.s.
Sex (M : F)	10 : 3	8 : 5	n.s.
Preoperative BMI	23.6±3.8	21.5±4.4	n.s.
Liver function			
NL / CH / AL	8 / 3 / 2	8 / 5 / 0	n.s.
Hepatectomy			
1 segment	6	5	n.s.
2 segment	6	7	n.s.
3 segment	1	1	n.s.
Duration of surgery (min)	376.5±74.9	424.4±111.8	n.s.
Operative blood loss (ml)	823.5±667.8	723.3±490.4	n.s.
Pringle time (min)	20.1±20.6	14.9±15.5	n.s.

IM group, immunonutrition group: C group, control group: NL: normal liver, CH: chronic hepatitis, AL: alcoholic hepatitis, n.s.: not significant.

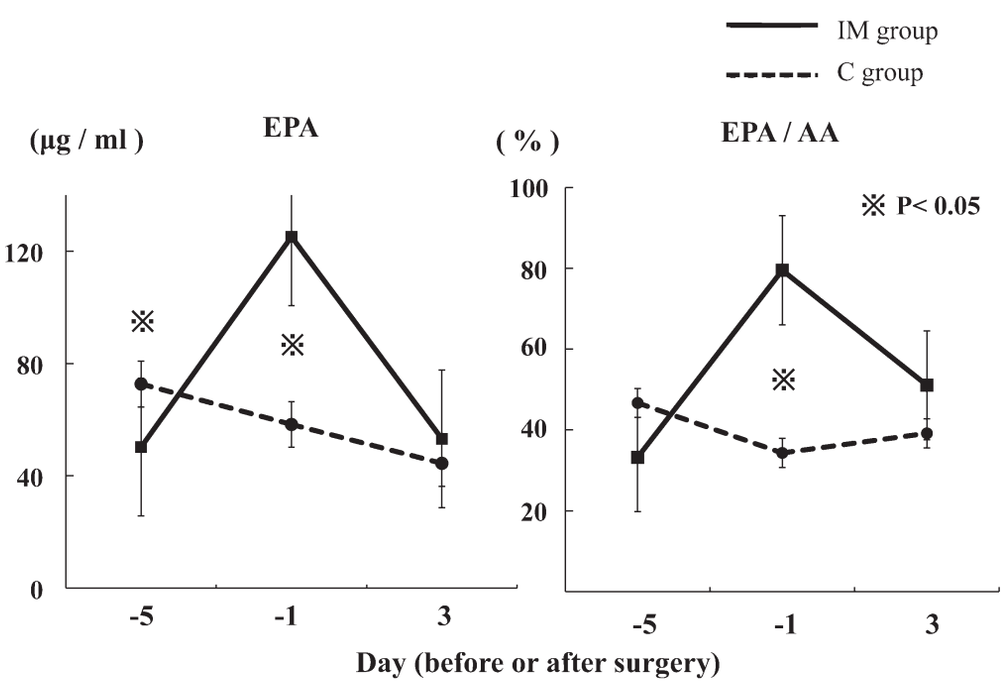

Fig. 2. Change in ω-3 fatty acid and ω-3 fatty acid/ω-6 fatty acid ratio during the perioperative period.

The changes in ω-3 fatty acid such as eicosapentaenoic acid (EPA) and ω-3 fatty acid/ω-6 fatty acid ratio such as EPA/arachidnic acid (AA) ratio during the perioperative period are shown. The serum concentrations of EPA and EPA/AA ratio were higher in the IM group than in C group at the immediate preoperative day (day 1) ($p<0.05$).

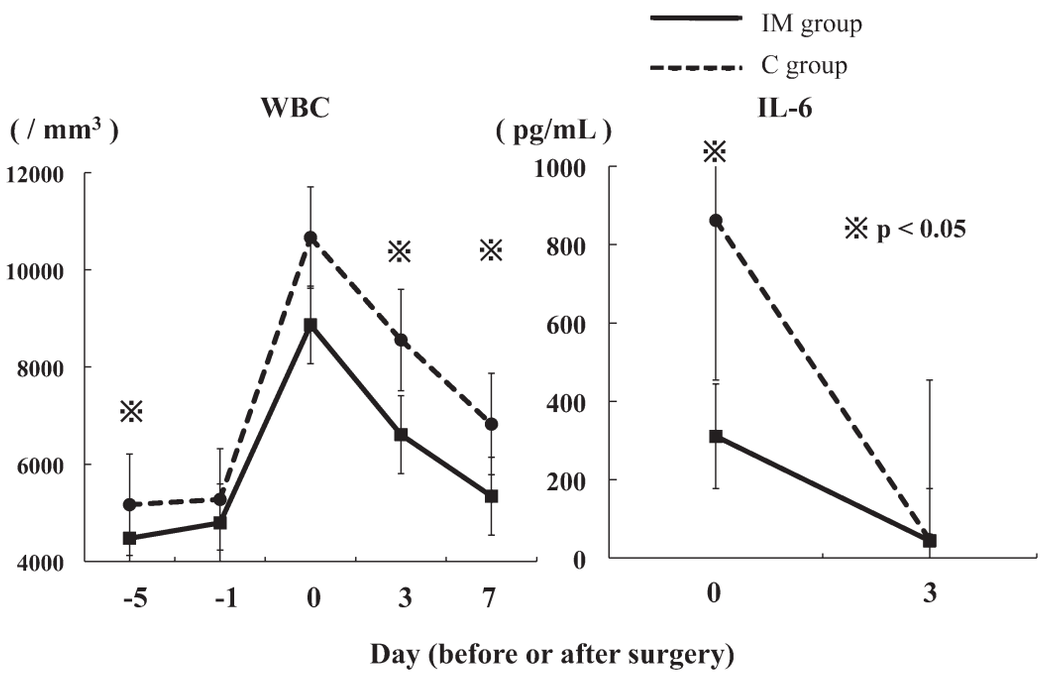

Fig. 3. Change in the inflammatory variables during the perioperative period.

The changes in inflammatory variables such as white blood cell (WBC) and interleukin-6 (IL-6) during the perioperative period are shown. The serum concentrations of WBC were lower in the IM group than in C group between postoperative day 3 and day 7 ($p<0.05$). The serum concentrations of IL-6 were lower in the IM group than in C group at the immediate postoperative day (day 0) ($p<0.05$).

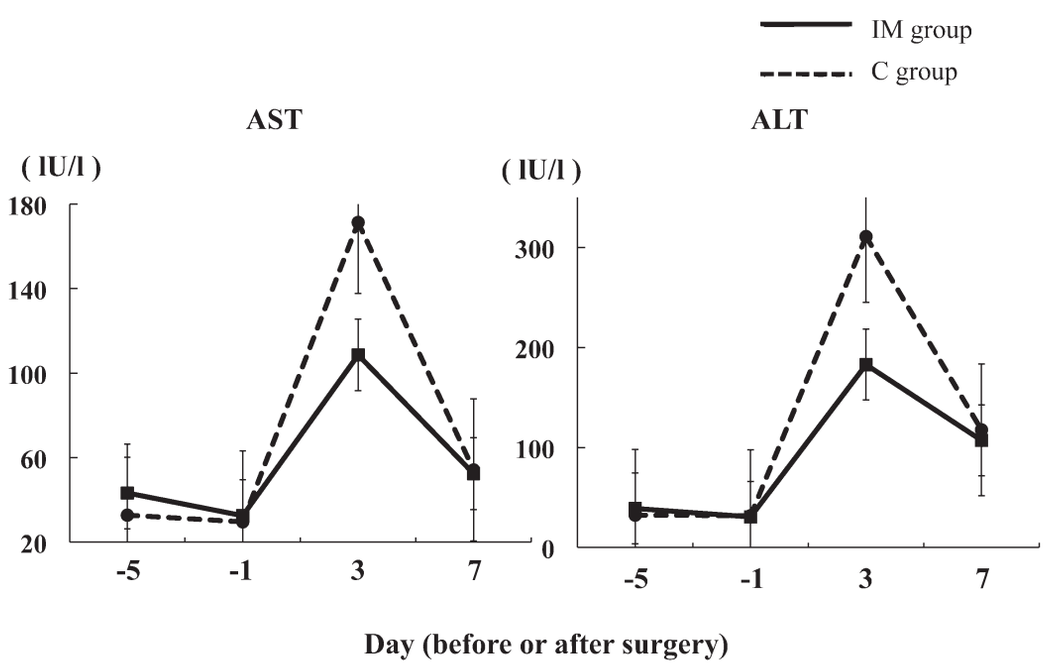

Fig. 4. Change in the liver dysfunction variables during the perioperative period.

The changes in liver dysfunction variables such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) during the perioperative period are shown. No significant differences were observed in them between the IM group and C group.

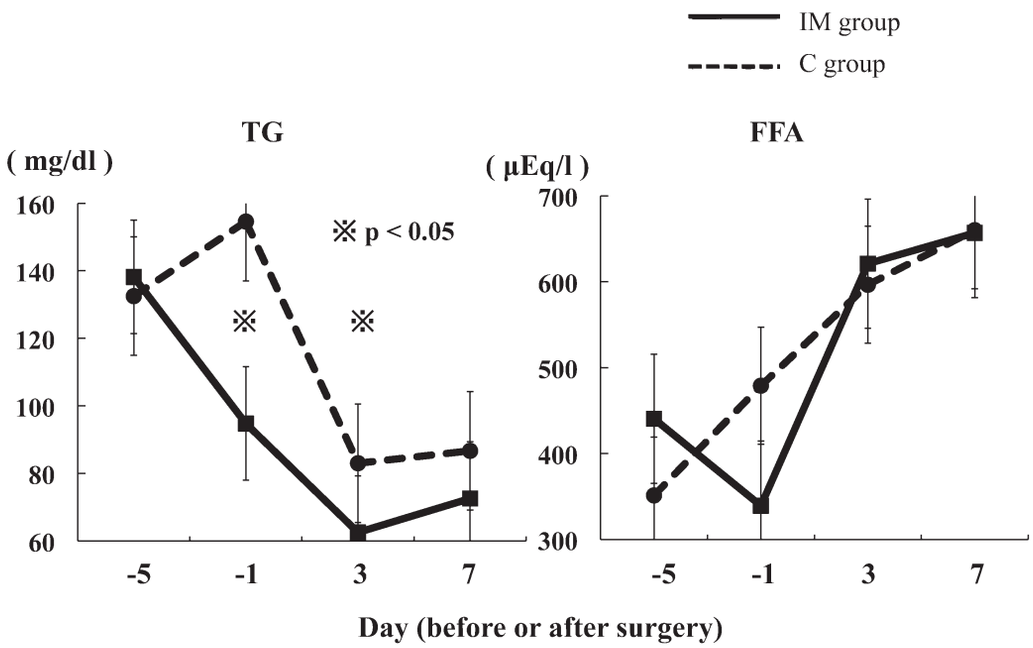

Fig. 5. Change in the lipidolytic variables during the perioperative period.

The changes in lipidolytic variables such as triglyceride (TG) and free fatty acid (FFA) during the perioperative perio are shown. The serum concentrations of TG were lower in the IM group than in C group between the immediate preoperative day (day -1) and postoperative day 3 ($p<0.05$). No significant differences were observed in FFA between the IM group and C group.

TABLE 2.
Outcome variable.

	IM group (n=13)	C group (n=13)	P value
Patients with complications	1 (7%)	3 (23%)	n.s.
Infectious complications	0	1 (7%)	n.s.
・Urinary tract infection	0	1 (7%)	
Noninfectious complications	1 (7%)	2 (15%)	n.s.
・ Ileus	1 (7%)	0	
・Atelectasis	0	2 (15%)	
Length of central hospital stay after operation (day)	16.3	14.5	n.s.

IM group, immunonutrition group: C group, control group: n.s., not significant.

was significantly suppressed in the IM group on Post3 (p=0.02) and on Post7 (p=0.001). The inflammatory cytokine IL-6 level was significantly lower in the IM group on Post0 (p=0.04) (Fig. 3). Concerning postoperative liver function, AST and ALT levels were lower in the IM group than in the C group on Post3, although the differences were not significant (AST: p=0.15, ALT: p=0.05) (Fig. 4). The TG level was significantly lower in the IM group on Pre1 and Post3 (Pre: p=0.0001, Post3: p=0.01). The FFA level did not differ significantly but was lower in the IM group on Pre1 and showed changes similar to those in the C group after surgery (p=0.24) (Fig. 5).

As for postoperative infectious complications, urinary tract infection was noted in 1 patient of the C group. Noninfectious complications observed in the

IM and C groups were adynamic ileus and atelectasis. No significant difference was noted between the two groups in the duration of postoperative hospital stay (Table 2).

DISCUSSION

Recent reports have shown that postoperative infectious complications were reduced by the intake of oral preparations containing nutrients that enhance immune functions, such as ω-3 fatty acids, arginine, and nucleic acid [2-7], but most of these studies concerned patients with colorectal or stomach neoplasms [1,4,6,13-17] (Table 3). There have been no reports of immunonutrition in patients with neoplasms of the liver. In this study, administration of immunonutrients containing ω3 fatty acid, arginine, and nucleic acid before hepatectomy reduced inflammation, protected liver function, and improved lipid metabolism postoperatively.

ω3 fatty acids have greater affinity for metabolic enzymes than ω6 fatty acids. An increase in the ω3 (EPA)/ω6 (AA) fatty acid ratio shifts fatty acid metabolism in the body to the ω3 fatty acid pathway [8], and the production of eicosanoids (PGE3, TXA3, LT5), which are metabolites of ω3 fatty acids and inflammatory mediators, becomes predominant [18,19]. Eicosanoids (PGE2, TXA2, LT4) derived from ω6 fatty acids also show strong physiologic activities, such as leukocyte aggregation, taxis, and migration, and promote the synthesis of inflammatory cytokines. However, the activity of eicosanoids derived from ω3 fatty acids is only 1/100 that of eicosanoids derived from ω6 fatty acids [20]. Eicosanoids derived from ω3 fatty acids stimulate peripheral monocytes and inhibit the synthesis of inflammatory cytokines [21]. One study reported that inflammatory cytokines were suppressed by the perioperative administration of an enteral nutritional preparation containing EPA in patients undergoing esophageal surgery [22]. In the present

TABLE 3.
Reports of immunonutrition

Author (year)	Patients	Administration method	Immune response	Protein metabolism et al.	Infectious complications
Daly et al. (1992)	85 patients with upper gastrointestinal malignancies	postoperative	Lymphoid system ↑	N-balance ↑ Alb, Tf ↑	↓
Braga et al. (1996)	60 patients with gastric and pancreatic cancer	postoperative	IL-6 ↓	Pre Alb, RBP ↑ Alb, Tf →	→ Septic score ↓
Gianotti et al. (1997)	260 patients with gastric and pancreatic cancer	postoperative	DHR ↑ IL-6 ↓	Pre Alb ↑	↓
Kumen et al. (1995)	42 patients with upper gastrointestinal cancer	postoperative	CD3+,CD4+ ↑ B lymphocyte ↑	Alb, Tf →	→
McCarter et al. (1998)	38 patients with upper gastrointestinal tumors	preoperative	TNF,IL-6 → PGE2, LTB4 →	Arg → Orn ↑	→
Braga et al. (1999)	206 patients with neoplasm of colorectum, stomach, or pancreas	perioperative	IL-6 ↓	Pre Alb,RBP ↑ Alb,Tf → CRP ↓	↓
Gianotti et al. (2002)	305 patients with cancer of gastrointestinal tract	Pre and post-operative			↓
Janmin et al. (2006)	60 patients with colorectal or gastrointestinal cancer	preoperative	IgG,CD4/CD8 ↑	Pre Alb,Tf ↑	↓

study, administration of IMPACT elevated the serum $\omega 3$ fatty acid concentration and $\omega 3/\omega 6$ fatty acid ratio preoperatively, neutrophil aggregation, taxis, and migration were suppressed by the actions of eicosanoids derived from $\omega 3$ fatty acids, and the postoperative serum WBC was reduced. Also, the postoperative IL-6 level was lower than in the control group due to inhibition of the suppression of cellular immunity [22,23] and stabilization of biological membranes [19] by $\omega 3$ fatty acids. Our findings indicated that $\omega 3$ fatty acids produced an anti-inflammatory effect by these mechanisms in patients undergoing hepatectomy.

Concerning liver function, increases in AST and ALT levels early after surgery were suppressed in the IM group although the differences were not significant. While there are no studies concerning the preventive effect of $\omega 3$ fatty acids on liver dysfunction, there have been reports of animal experiments in which administration after hepatectomy of an inhibitor of TXA2, a metabolic product of $\omega 6$ fatty acids, promoted portal and liver tissue blood flows, mitigated microcirculation disorders, and prevented liver dysfunction associated with liver devascularization [24,25]. The protective effect on liver function observed in the present study is considered to have been derived from the suppression of TXA2 production due to the shift of the metabolic pathway from $\omega 6$ to $\omega 3$ fatty acids. On the other hand, arginine is converted in the body to nitrogen monoxide, which improves the microcirculation of organs [26]. If excessive doses of arginine are administered to the body, active oxygen is produced from nitrogen monoxide and can damage the organs. The optimum dose of arginine to treat stress is 20-30g per day [27]. We used a dose of 21g/day in the present study. $\omega 3$ fatty acids and arginine are considered to exert favorable effects on liver damage due to devascularization during hepatectomy.

Concerning lipid metabolism, preoperative serum FFA and TG levels were significantly lower in the IM group. Fatty acid metabolism may have exerted a favorable effect on hepatocytes before surgery. Nakatani T et al. [28] reported that energy metabolism changes with hepatectomy and that hepatocytes within 24 hours after hepatectomy, in which fatty acid metabolism becomes dominant with the suppression of sugar metabolism, obtain adenosine triphosphate primarily by β-oxidation of free fatty acids rather than by using glucose as the energy substrate. Also, Delahunty TJ et al. [29] reported that within 24 hours after hepatectomy the remaining hepatocytes increase their uptake of free fatty acids and accumulate TG to obtain energy for cell proliferation. Our present findings suggest that lipid metabolism became dominant in hepatocytes preoperatively, improving the energy efficiency.

In this study, a remarkable elevation of the blood level of EPA, a $\omega 3$ fatty acid, was noted preoperatively by the intake of IMPACT (750 ml/day) from 5 days prior to surgery. In Western countries, it has been reported that the administration of IMPACT at about 1,000 ml/day from 5-7 days before surgery in patients undergoing elective surgery reduced postoperative infections by 50% [3,30]. Taking into account the smaller body build of Japanese, an oral intake of 750 ml/day for 5 days before surgery is considered to suffice, and this treatment may well have been a factor contributing to the successful completion of surgery in all our patients.

No significant difference was noted between the two groups in postoperative infectious complications or duration of hospital stay. Improvements in preoperative imaging examinations and development of liver function assessment and superior surgical techniques are considered to have markedly contributed to these results. Therefore, when determining the indications of immunonutrition for patients undergoing hepatectomy, the cost of the oral preparations containing the nutrients that enhance immune functions will be an important consideration in future.

One study has reported that preoperative immunonutrition has no preventive effect on infections in patients undergoing gastrointestinal surgery. [31] However, the results of the present study suggest that preoperative immunonutrition is effective both preoperatively and postoperatively in controlling inflammation, protecting liver function, and improving lipid metabolism. We expect that immunonutrition before hepatectomy may help to prevent an excessive inflammatory reaction and protect the liver early after surgery, but additional studies will be needed to confirm this hypothesis.

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Original Contribution

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Comparison of Leukotriene Receptor Antagonists and Anti-Histamines as an Add-On Therapy in Patients with Asthma Complicated by Allergic Rhinitis

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Summary: Patients with asthma are often complicated by allergic rhinitis, and the intimate pathophysiological association between allergic rhinitis and asthma often imposes a significant morbidity on affected individuals. The present study was conducted to assess the clinical efficacies of leukotriene receptor antagonists (LTRAs) and anti-histamines on asthma as an add-on therapy in patients with asthma complicated by allergic rhinitis. Consecutive patients with asthma were recruited to fill in systematic self-administered questionnaires concerning symptoms and conditions related to asthma and allergic rhinitis. The questionnaire was conducted twice, one month apart, and the attending physicians gave detailed information on disease control and medications on both occasions. In the study 3,140 patients with asthma participated, and 634 had concomitant allergic rhinitis (mean age: 53.1, 389 female). The second survey disclosed that treatment with LTRAs or anti-histamines had been added in 26 patients and 19 patients, respectively, without any changes in other medications. There were no significant differences in age, gender, severity of disease, or baseline treatments. The initial survey indicated that the patients who were treated with LTRAs had significantly more severe asthma-related symptoms (i.e. wheeze, cough and sleep disturbance) and experienced greater dissatisfaction with the treatment than did those who were treated with anti-histamines. The second survey disclosed significant reductions in sneezing (p=0.03), rhinorrhea (p=0.01), dyspnea (p=0.046), sleep disturbance (p=0.02), over-all asthma symptoms (p=0.013), and an improvement in satisfaction with treatment (p=0.019) in patients to whom LTRAs were added-on, whereas the patients receiving anti-histamines reported no significant changes in these symptoms. These results suggest that LTRAs are more effective than anti-histamines as an add-on therapy in symptomatic patients with asthma complicated by allergic rhinitis.

Key words allergic rhinitis, asthma, anti-histamine, leukotriene receptor antagonist, add-on therapy

INTRODUCTION

The association between asthma and allergic rhinitis has been gaining attention as part of a continuum of airway pathology, as these two disorders not only coexist frequently but also have intimate clinical and pathological associations. For instance, clinical observations have documented that asthma attacks are coincident with a worsening of nasal symptoms [1], and that cough in patients with asthma complicated by allergic rhinitis is more severe than that in patients with asthma alone [2]. A shared pathophysiology of

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Abbreviations: LTRAs, leukotriene receptor antagonists.

the two disorders is illustrated by the existence of a significant correlation between the number of nasal eosinophils and forced expiratory volume in one sec [3], and by an exaggerated responsiveness of the lower airways induced by allergic nasal challenge [4] in patients with asthma complicated by allergic rhinitis.

Although recent findings suggest allergic rhinitis as a possible therapeutic target for asthma control [5,6], there are few reports available concerning the association of the responses to therapeutic agents for the two disorders. Here we had an opportunity to evaluate the clinical efficacies of leukotriene receptor antagonists (LTRAs) and anti-histamines in patients with asthma complicated by allergic rhinitis in practice.

METHODS

Study design

Consecutive patients with asthma with/without concomitant allergic rhinitis were recruited at 217 medical institutions in eight prefectures of the Kyushu district of Japan between May and December 2003 [6]. Recruited subjects in the study were non-smoking ambulatory adult patients being treated at one of the participating institutions who gave written consent to the survey. The survey consisted of systematic self-administered questionnaires that were collected twice, one month apart, to obtain information on subjective symptoms, self-evaluated disease control and satisfaction with treatment. Physicians provided a complete list of medications for asthma and allergic rhinitis on both occasions. The questionnaire also included items for medications. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by institutional board of ethical committees, and all participants gave written informed consent.

Definitions of asthma and allergic rhinitis

The diagnosis of asthma was based on the Global Initiative for Asthma guideline [7]. Patients were considered as having allergic rhinitis if they presented with sneeze or nasal itching, watery nasal discharge, and nasal obstruction, and either eosinophilia in nasal discharge or positive results for positive skin prick or serum specific IgE for common antigens (house dust and pollens).

Self-administered questionnaire

Patients completed the questionnaire by selecting one of the relevant ratings for each items [6]. Items related to allergic rhinitis included sneeze (0:none, 1:1 to 5, 2:more than 6 times a day), rhinorrhea (0:none, 1:1 to 5, 2: nose blowing more than 6 times a day), nasal obstruction (0:none, 1:mild, 2:moderate to severe), and over-all nasal symptoms (1:excellent, 2:good, 3:worse than good). Items related to asthma included wheeze (0:none, 1:1 to 2, 2:more than 3 days a week for morning, daytime, nighttime separately), dyspnea (same rating as wheeze), cough (0:none, 1:1 to 2, 2:more than 3 days a week), sputum (same rating as cough), and over-all asthma symptoms (same rating as over-all nasal symptoms) and satisfaction with treatment (1:satisfied, 2: mostly satisfied, 3:other than 1 and 2).

Statistical analysis

Comparisons between the groups were performed by Mann-Whitney non-parametric U test or chi-square test where appropriate. Wilcoxon signed-rank test was used for the paired comparisons of the same individuals. All statistical analyses were performed using SPSS software 13.0J (Spss Japan Inc., Tokyo, Japan).

RESULTS

The questionnaire was distributed to 3,270 patients with asthma who gave consent to the survey, and was completed by 3,140 of them. Of these, 634 patients had physician-diagnosed allergic rhinitis in addition to asthma, including 19 patients who began receiving anti-histamines (loratadine in 6, ebastine in 4, fexofenadine in 2, olopatadine in 2, and azelastine, epinastine, emadastine, chlorpheniramine, mequitazine in 1 patient each) immediately after the first survey, without any other changes in medications, and 26 patients who began to receive LTRAs (pranlukast for 21 patients and montelukast for 5 patients) without any other treatment modifications during the same period. Demographics and treatments of these patients were summarized in Table 1. When these two groups of patients were compared, there were no significant differences in gender, age, base-line medications (inhaled, intranasal and oral corticosteroids and bronchodilators) or severity of asthma as judged by the medications.

Comparisons of the nasal and asthma symptoms between the two patient groups on the first survey (Table 2) revealed that there were significant differences in some of the symptoms related with asthma: patients who were treated with LTRAs had significantly more severe wheezes in the morning, daytime and nighttime, daytime dyspnea, cough, sleep disturbance, and were significantly less satisfied with the asthma treatment in comparison with the patients who received antihistamines. There were no significant dif-

TABLE 1.
Patient characteristics

	Anti-histamines	LTRAs	*p*
n	19	26	
Female (%)	8 (42.1)	11 (42.3)	0.62
Age (SD) [year]	50.2 (19.2)	46.2 (19.9)	0.78
β2 agonists* (%)	3 (15.8)	8 (30.8)	0.24
Theophylline (%)	9 (47.4)	17 (65.4)	0.36
INS (%)	4 (21.1)	5 (19.2)	1.0
ICS (%)	18 (94.7)	19 (73.1)	0.06
ICS dose (SD) [mg]	412.5 (185.7)	450.0 (225.1)	0.52
Oral steroid	1 (0.05)	3 (0.1)	0.63

*includes dermal patch and inhalation formula
LTRAs, leukotriene recptor antagonists; INS, intranasal corticosteroid; ICS, inhaled corticosteroid Paretheses indicate SD

TABLE 2.
Comparison of the symptoms on the first survey

	Sum of the ranks		*p*
	Anti-histamies	LTRAs	
Sneeze	397	593	0.80
Rhinorrhea	330	660	0.46
Nasal obstruction	388	647	0.18
Over all nasal	392	553	0.81
Limitation in daily activity	336	610	0.14
Morning wheeze	314	677	0.009
Morning dyspnea	310	637	0.058
Daytime wheeze	323	623	0.035
Daytime dyspnea	335	611	0.049
Nighttime wheeze	334	656	0.022
Nighttime dyspnea	377	613	0.352
Cough	309	595	0.041
Sputum	348	598	0.133
Sleep disturbance	272	674	0.001
Over all asthma	365	670	0.059
Satisfaction to treatment	350	686	0.025

ferences in the initial symptoms related with rhinitis.

Comparisons of the nasal and asthma symptoms between the first and second questionnaire were summarized in Table 3. In nasal symptoms, there were no significant changes in the patients treated with anti-histamines. In contrast, the survey results demonstrated that there were significant improvements in sneeze and rhinorrhea in patients treated with LTRAs. Nasal obstruction tended to be improved in patients treated with LTRAs, but not in those treated with anti-histamines.

There were no significant changes in any of asthma-related symptoms in patients treated with anti-histamines, whereas there were significant improvements in morning dyspnea, sleep disturbance, over-all asthma symptoms, and satisfaction with asthma treatment in

TABLE 3.
Efficacies of anti-histamines and LTRAs

	Anti-histamines				LTRAs			
	First	Second	z	*p*	First	Second	z	*p*
Sneeze	1.0 (0.49)	0.94 (0.54)	-0.45	0.65	1.04 (0.53)	0.68 (0.69)	-2.18	0.03
Rhinorrhea	0.94 (0.64)	1.00 (0.76)	-0.45	0.65	1.35 (0.63)	1.00 (0.76)	-2.5	0.01
Nasal obstruction	1.26 (0.45)	1.22 (0.43)	-0.45	0.65	1.46 (0.51)	1.24 (0.44)	-1.89	0.06
Over all nasal	1.94 (0.24)	1.76 (0.43)	-1.73	0.08	1.96 (0.20)	1.80 (0.41)	-1.63	0.1
Limitation in daily activity	0.06 (0.24)	0 (0)	-1	0.32	0.23 (0.43)	0.16 (0.37)	-0.71	0.48
Morning wheeze	0.17 (0.51)	0.11 (0.32)	-0.58	0.56	0.77 (0.86)	0.5 (0.71)	-1.46	0.14
Morning dyspnea	0.24 (0.56)	0.22 (0.43)	0	1	0.65 (0.80)	0.36 (0.57)	-2	0.046
Daytime wheeze	0 (0)	0 (0)	0	1	0.31 (0.62)	0.35 (0.56)	-0.33	0.73
Daytime dyspnea	0.11 (0.32)	0 (0)	-1.41	0.16	0.56 (0.82)	0.42 (0.75)	-1	0.32
Nighttime wheeze	0.06 (0.23)	0.12 (0.33)	-0.57	0.56	0.54 (0.81)	0.38 (0.64)	-1.26	0.2
Nighttime dyspnea	0.17 (0.38)	0.18 (0.39)	0	1	0.38 (0.7)	0.38 (0.7)	-0.09	0.93
Cough	0.06 (0.24)	0 (0)	-1	0.32	0.44 (0.71)	0.26 (0.67)	-1.02	0.3
Sputum	0.22 (0.55)	0.16 (0.37)	-0.58	0.56	0.6 (0.87)	0.38 (0.7)	-1.73	0.08
Sleep disturbance	0 (0)	0.11 (0.32)	-1.41	0.16	0.65 (0.8)	0.25 (0.61)	-2.33	0.02
Over all asthma	1.79 (0.42)	1.67 (0.49)	-1	0.32	2.15 (0.73)	1.81 (0.57)	-2.5	0.013
Satisfaction to treatment	1.32 (0.58)	1.18 (0.39)	-1	0.32	1.85 (0.83)	1.46 (0.65)	-2.35	0.019

LTRAs, leukotriene receptor antagonists
Parentheses indicate SD.

those treated with LTRAs. Sputum tended to be improved in patients treated with LTRAs, but not in those treated with anti-histamines.

DISCUSSION

The present study focused on the clinical efficacy of anti-histamines and LTRAs in patients with asthma complicated by allergic rhinitis, and our results showed that the initiation of LTRAs but not anti-histamines was associated with significant improvement in asthma-related symptoms. Published reports indicate that appropriate management of concomitant allergic rhinitis confers a better control of asthma in patients with both diseases. For instance, treatment with intranasal corticosteroid for allergic rhinitis resulted in decreased cough and severity of concomitant asthma [8]. A retrospective cohort study has documented that treatment of concomitant allergic rhinitis was associated with reductions in emergency visits or hospitalizations caused by asthma exacerbations [9]. In this context, anti-histamines and LTRAs, which are both commonly prescribed drugs, deserve attention as therapeutic agents not only for allergic rhinitis itself but also to achieve better control of concomitant asthma in patients with both diseases. A randomized study involving patients with asthma complicated by allergic rhinitis has documented that subjects treated with cetirizine, an anti-histamine, showed significant improvements in nasal and asthma symptoms, although pulmonary function was comparable with those who received a placebo [10], whereas another study has reported that the administration of cetirizine resulted in a significant improvement in lung function in subjects treated with the drug in comparison with the subjects who received placebo in patients with mild-to-moderate asthma [11]. In contrast, the present study did not support the efficacies of anti-histamines during the study period. Reasons for this discrepancy are unknown, however, several plausible explanations deserve mentioning. The first survey indicated that patients treated with LTRAs generally had had worse symptoms related with rhinitis and asthma, some of which were statistically significant, in comparison with patients treated with anti-histamines. It is possible that the difference in the severity of initial symptoms contributed to the observed difference noted in the second survey. Second, several varieties of anti-histamines were used

in the present study, while only two kinds of LTRAs were prescribed, probably reflecting the difference in the number of available drugs. Since there is a significant variation in potency among anti-histamines [12], some of the anti-histamines or the doses used may not have been adequate to produce clinical improvements in our limited study period. Duration of treatment is another factor that may have affected the observed results. For instance, a significant reduction in bronchial hyperreactivity has been observed in patients treated with cetirizine for two weeks [13], whereas montelukast, a LTRA, showed its effectiveness in a shorter period in patients with asthma [14]. This may also explain the insignificant improvements in the nasal symptoms in patients treated with anti-histamines.

The results of the present study have demonstrated that some nasal and asthma symptoms improved significantly in patients treated with LTRAs . Interestingly, satisfaction with asthma treatment was also significantly improved in patients who started LTRAs. Therapeutic effects of LTRAs on asthma itself [15] and, as aforementioned, on nasal symptoms are both likely to have contributed to the improvement in patient satisfaction. A meta-analysis indicated that the efficacies of LTRAs are comparable with those of anti-histamines but less than those of nasal corticosteroids in patients with seasonal allergic rhinitis [16]. It would be interesting to compare the clinical efficacies of LTRAs and nasal corticosteroids as a treatment option in the management of patients with asthma complicating allergic rhinitis.

The primary limitation of the present investigation arises from its cross-sectional uncontrolled observational design, which may harbor a potential bias in the subjects for comparisons, although they were recruited consecutively from multiple institutions. A second limitation is the fact that the results solely depended on subjective evaluations of the symptoms and were not endorsed by objective parameters. In addition, limited information on medications hindered a detailed assessment of the efficacies of the drugs. Despite these limitations, however, the present investigation provided a unique opportunity to evaluate the efficacies of therapeutic agents in daily practice, and supported the intimate association between allergic rhinitis and asthma from a therapeutic viewpoint. Importantly, the results of the present investigation suggest a considerable difference in the therapeutic efficacy of medications used in the management of asthma complicating allergic rhinitis. Since the two diseases often co-exist, optimization of currently available treatments is needed to improve quality of care for affected individuals.

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Original Contribution

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Propofol Protects against Anandamide-Induced Injury in Human Umbilical Vein Endothelial Cells

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Summary: Endocannabinoid anandamide, arachidonylethanolamine (AEA), is considered to be a causative mediator of hemorrhagic or septic shock, inducing death of several types of cells by producing free radicals such as reactive oxygen species (ROS). Propofol contains a phenolic hydroxyl group that donates electrons to the free radicals, and thus functions as an antioxidant. The purpose of this study was to investigate the protective effect of propofol against AEA-induced cell injury. After incubation with propofol at concentrations of 10, 50 or 100 μM, human umbilical vein endothelial cells (HUVECs) were stimulated with 10 μM of AEA for 24 h. ROS production, caspase-3 activity, and cell viability were evaluated 1, 8, and 24 h after the administration of 10 μM of AEA, respectively. Propofol (50 μM) significantly attenuated cell death induced by AEA, showing a protective effect against ROS production and caspase-3 activity. These results suggest that propofol at concentrations used during clinical anesthesia protects HUVECs against AEA-induced injury, in part by suppressing apoptosis.

Key words propofol, anandamide, apoptosis, reactive oxygen species, antioxidant, fatty amide acid hydrolase, human umbilical vein endothelial cell

INTRODUCTION

The endocannabinoid anandamide, (i.e., arachidonylethanolamine (AEA)) has been isolated from porcine brain lipid extract as an endogenous ligand for cannabinoid receptors in the central nervous and immune systems [1]. AEA is synthesized from N-arachidonoyl phosphatidylethanolamine in depolarized neurons, macrophages, endothelial cells and platelets [2-4], and quickly degraded by the fatty amide acid hydrolase (FAAH) into arachidonic acid and ethanolamine. In normal humans, AEA exists at low levels in blood and cerebrospinal fluid [5-7]. However, it has been demonstrated that the serum levels of AEA increase dramatically during the shock caused by either hemorrhage [8] or septis [9], and play a crucial role in the pathogenesis of hypotension [10,11]. Furthermore, in several types of cells, elevated levels of AEA can induce apoptosis by producing free radicals such as reactive oxygen species (ROS), and the production of ROS is exacerbated by the inhibition of FAAH [12-14].

Vascular endothelial cells have important physiologic functions as barriers, and in maintaining cardiovascular homeostasis and vascular stability. However, this function may be impaired in septic shock and ischemia-reperfusion injury, resulting in cellular necrosis and apoptosis [15,16]. On the other hand,

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Abbreviations: Ac-DEVD-*p*NA, N-acetyl-Asp-Glu-Val-Asp-*p*-nitroanilide; AEA, arachidonylethanolamine; EGM-2, endothelial growth medium-2; FAAH, fatty amide acid hydrolase; FBS, fetal bovine serum; carboxyl H_2DCFDA; 5-(and-6)-carboxy-2´,7´-dichlorodihydrofluorescein diacetate, HUVECs, human umbilical vein endothelial cells; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; *p*NA, *p*-nitroanilide; ROS, reactive oxygen species.

propofol (2,6-diisopropylphenol), an intravenous general anesthetic, possesses an antioxidant property because it contains a phenolic hydroxyl group that gives electrons to the free radicals generated during ischemia and reperfusion [17,18]. The purpose of the present study was to examine the protective effect of propofol against AEA-induced cell injury using human umbilical vein endothelial cells (HUVECs).

MATERIALS AND METHODS

Cell culture

The initial batch of HUVECs was purchased from Lonza, Inc. (Basel, Switzerland), and cultured in endothelial growth medium-2 (EGM-2), consisting of ascorbic acid, fibroblast growth factor, hydrocortisone, insulin-like growth factor-1, vascular endothelial growth factor, gentamicin, amphotericin-B, and 10% fetal bovine serum (FBS). The cells were grown in a humidified incubator at 37°C containing 95% air and 5% of carbon dioxide with media replenishment every 3 days. Following growth to 90% confluence, the cells were split (passage 2) and grown to confluence again. Before the experimental intervention, confluent HUVECs with 2-5 passages were incubated in a starved medium supplemented with 1% of FBS for 4 h. In the ROS production assay and the caspase-3 activity assay, HUVECs were divided into three experimental groups characterized by culture medium conditions as 1) control, 2) cultured with AEA alone, or 3) pretreatment with propofol for 30 min, then co-incubated with AEA.

Evaluation of HUVECs viability exposed to AEA

As shown in Figure 1A, the HUVECs were coincubated with AEA (0, 0.01, 0.1, 1, 2.5, 5, 7.5 and 10 μM) at 37°C for 24 h. Then, the cell viability was evaluated using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. In brief, 10 μL of MTT (Sigma Chemical, St. Louis, USA) solution (5 mg/L) was administered to each incubating well, and the wells were incubated at 37°C for 5 h. The formazan in each well, produced by the MTT assay, was dissolved in 100 μL of dimethyl sulfoxide. The absorbance of this colored solution was measured at 570 nm by a spectrophotometer. According to the results of this experiment, 10 μM of AEA was utilized as a positive control for AEA-induced cell injury in all subsequent experiments.

Effect of propofol on HUVEC viability

Propofol was prepared by diluting Diprivan (AstraZeneca, London, UK) with EGM-2 to a concentration of 10, 50, or 100 μM. After pretreatment of the culture medium with propofol for 30 min at the above concentrations, the HUVECs were stimulated without or with 10 μM of AEA and incubated at 37°C for 24 h. Thereafter, the cell viability was observed employing the MTT assay as mentioned above (Fig. 1B).

Analysis of ROS production

The Image-iT^{TM} live green reactive oxygen species detection system (Molecular Probes, Eugene, OR), counterstained with Hoechst 33342 for nuclei, was used to visualize reactive oxygen species in live HUVECs under a microscope (Olympus FV1000, Tokyo, Japan), using fluorescein filter sets.

Intracellular ROS formation was detected using 5-(and-6)-carboxy-2´,7´-dichlorodihydrofluorescein diacetate (carboxyl H_2DCFDA) as previously reported [19]. Briefly, starved HUVECs, seeded at a density of 2.0×10^4 cells /well, were loaded with the redox sensitive dye carboxyl H_2DCFDA for 45 min, washed and pretreated with propofol (50 μM), and then stimulated with AEA alone (10 μM) or in combination with propofol (50 μM) at 37°C for 1 h (Fig. 1C). Then, ROS levels were measured with a multiwell fluorescence plate reader (Tecan, Männedorf, Switzerland), using excitation and emission filters of 485nm and 535 nm, respectively.

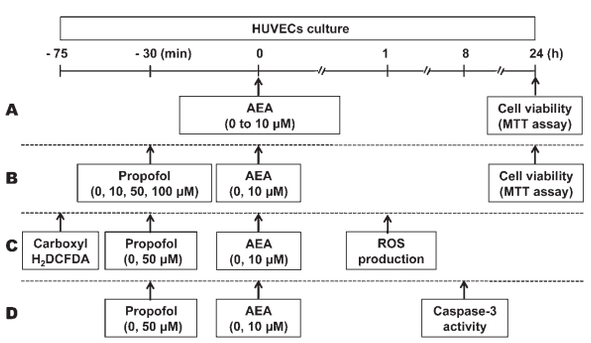

Fig. 1. Experimental protocol. (A) The HUVECs viability was examined using an MTT assay 24 h following the exposure to 0-10 μM of AEA. (B) The effect of propofol (0-100 μM) on the HUVECs viability was evaluated with the use of an MTT assay 24 h after the exposure to 0, 10 μM of AEA. (C) The intracellular ROS production in HUVECs was detected by spectrophotometry 1 h after the stimulation by AEA (10 μM) or coexistence with propofol (50 μM). (D) The caspase-3 activity in HUVECs was colorimetrically measured 8 h following the exposure to AEA (10 μM) or coexistence with propofol (50 μM).

Caspase-3 activity assay

The caspase-3 activity in the incubated HUVECs was colorimetrically assayed 8 h following treatment with AEA alone (10 μM) or in combination with 50 μM of propofol (Fig. 1D). The cells were washed, lysed, and incubated with the caspase-3 specific labeled substrate, N-acetyl-Asp-Glu-Val-Asp-*p*-nitroanilide (Ac-DEVD-*p*NA), on ice for 15 min. The chromophore *p*-nitroanilide (*p*NA), which was released from Ac-DEVD-*p*NA upon cleavage by caspase-3, could be quantified using a microtiter plate reader at 405 nm. The relative increase in caspase-3 activity was determined by comparing the absorbance of *p*NA from an apoptotic sample to an uninduced control.

Statistical analysis

All data represent the mean of three independent experiments ± S.D. Statistical comparisons were made with a paired *t*-test or one sample test, followed by the Bonferroni test. Statistical analysis was performed with SAS ver.9.2 (SAS Institute Inc., Cary, NC, USA). A value of $P<0.05$ was considered to be statistically significant.

RESULTS

Reduction in HUVECs viability due to AEA

Evaluating cell viability by an MTT assay 24 h after the AEA exposure showed that 5 μM, 7.5 μM and 10 μM of AEA caused a significant deterioration of cultured HUVECs viability to 79.2±2.3%, 58.3±1.2% and 38.5±2.1%, respectively, compared with the control (Fig. 2).

Protective effect of propofol on HUVECs viability

Propofol itself did not affect the cell viability at the concentrations of 10-100 μM. Of great importance was that pretreatment with 50 and 100 μMs of propofol significantly increased viability in cells exposed to 10 μM of AEA from 29.7±3.2%, to 67.9±11.0% and 78.4±6.5%, respectively, although 10 μM of propofol had no protective effect (Fig. 3).

Decrease in ROS production by propofol

HUVECs stimulated with AEA alone were ROS-positive (green) (Fig. 4B), whereas the pretreatment of cells with propofol significantly attenuated the green ROS signal (Fig. 4C), and almost no green ROS signal was observed in controls (Fig. 4A).

ROS production in the cultured HUVECs 1 h after exposure to 10 μM of AEA was significantly attenuated by 50 μM of propofol, falling from 113.8±2.0% in the AEA-exposed cells to 103.7±1.0% in the propofol treated cells. (Fig. 4D)

Protected caspase-3 activity by propofol

Caspase-3 activity 8 h after the exposure to 10 μM of AEA in the cultured HUVECs was significantly ameliorated by 50 μM of propofol, dropping from 277.6±83.3% in the AEA-exposed cells, to 132.1± 12.0% in the propofol-treated cells (Fig. 5).

DISCUSSION

This study demonstrated the protective effects of propofol against AEA-induced cell injury. One of the crucial mechanisms of cell injury due to anandamide is surmised to be ROS production followed by apopto-

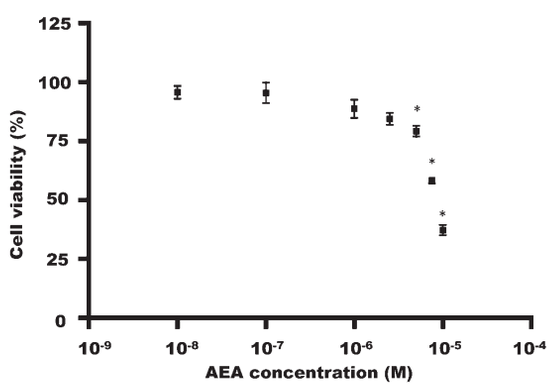

Fig. 2. Cytotoxicity of AEA in HUVECs. The HUVECs viability was significantly attenuated at 5 μM, 7.5 μM and 10 μM of AEA to 79.2±2.3%, 58.3±1.2% and 38.5±2.1% of the control, respectively. *P<0.05 vs. non-treated cells.

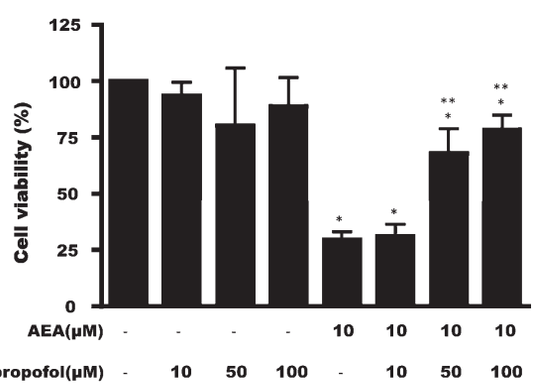

Fig. 3. Protection of HUVECs viability by propofol against AEA-induced injury. Propofol in the concentration of 50 and 100 μM protected the cell viability damaged by AEA to 67.9±11.0% and 78.4±6.5%, respectively. *P<0.05 *vs.* non-treated cells, **P<0.05 *vs.* AEA alone.

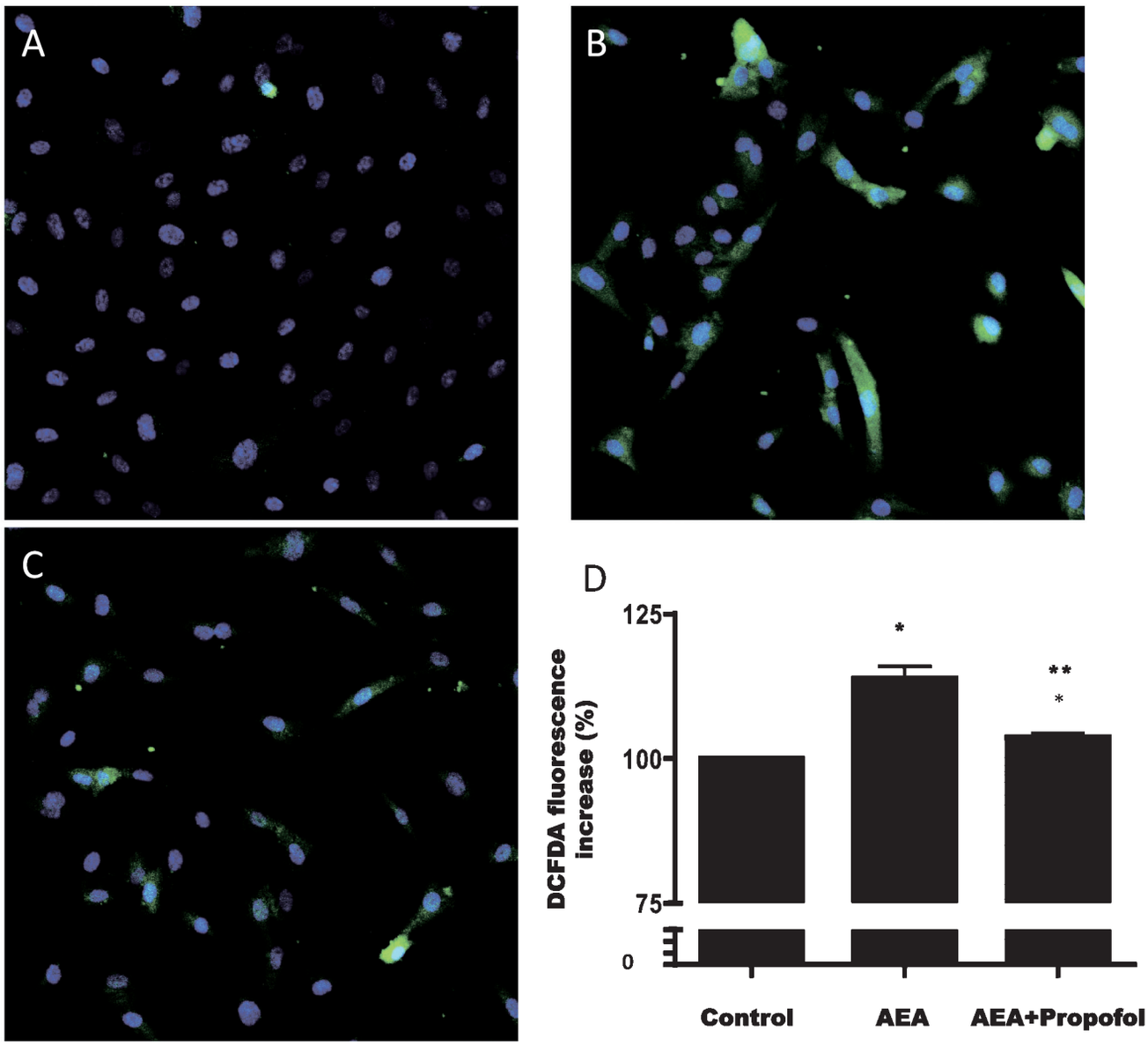

Fig. 4. Attenuation of intracellular ROS production by propofol. The representative photographs of visualized ROS formation in the control (A), 10 μM of AEA-exposed (B) and 50 μM of propofol-treated (C) HUVECs were shown. (D) The ROS production was significantly increased by 10 μM of AEA (113.8±2.0%). Propofol significantly attenuated the AEA-derived ROS production to 103.7±1.0%. *P<0.05 *vs*. control, **P<0.05 *vs*. propofol treated.

sis. Siegmund et al. [20] reported that glutathione, an antioxidant, attenuated the AEA-derived ROS formation and effectively suppressed the death of primary hepatic stellate cells. Propofol is also known to have antioxidant activity in scavenging ROS and suppressing apoptosis, coinciding with our results [17,18,21-25].

Lipid rafts, localized in gamma-aminobutyric acid A receptors, are supposed to play an important role in AEA-induced cell death [12,26]. One possible protective mechanism of propofol might be its action on these receptors [27].

As mentioned above, AEA is metabolized by FAAH and the inhibition of FAAH could enhance AEA-induced cellular toxicity. Meanwhile, propofol is thought to be an FAAH inhibitor [28]. However, Schelling et al. [29] observed no remarkable increase in blood level of AEA during general anesthesia using propofol. It is not clear whether the mechanism by which propofol protected HUVECs against AEA-induced injury in this study involved the inhibition of FAAH.

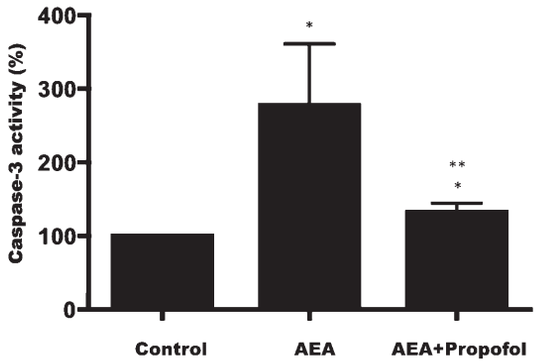

Fig. 5. Protection of AEA-induced increase in caspase-3 activity by propofol. The caspase-3 activity elevated by 10 μM of AEA (277.6± 83.3%) was significantly protected by 50 μM of propofol (132.1±12.0%). *P<0.05 *vs.* control, **P<0.05 *vs.* AEA alone.

It is notable that in the present study propofol exerted a protective effect at a blood concentration level used clinically to achieve general anesthesia, (i.e., 10-60 μM). This finding suggests the clinical usefulness of propofol as a general anesthetic for patients with shock caused by hemorrhage, endotoxin, and so forth.

There have been a number of reports on the blood concentration of AEA in normal humans, most of which were conducted on the nM-level [3,9,12]. However, this could increase to the μM-level in endotoxic shock, and a level of over 10 μM, at which the death of cells was observed, could be considered a pathologic state. Concerning anandamide-induced cell death, the involvement of nitric oxide and several receptors of cannabinoid and capsaicin, and the differences in pathway leading to cell death depending on the types of cell have been suggested [2,13,30,31]. Further investigations are needed to clarify both the mechanism of and the therapeutic strategy for anandamide-induced cell death.

In conclusion, our results suggest that propofol at clinically used blood concentrations protects HUVECs against AEA-induced injury, in part by suppressing ROS production and subsequent apoptosis.

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Original Contribution

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Computer-Assisted Total Knee Arthroplasty: Comparisons with the Conventional Technique

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Summary: For successful total knee arthroplasty (TKA), it is very important to gain an accurate grasp of the mechanical axis of the lower limb and establish a suitable ligament balance. Recently, TKA using navigation systems has been developed to accomplish more accurate component placement and to achieve a better understanding of the mechanical axis. The purpose of this study was to compare the radiological results of computer-navigated TKA with those of conventional TKA. We prospectively evaluated 75 primary TKAs (75 subjects) that were performed using a cruciate-retaining prosthesis of the same model at our institution. The subjects were allocated alternately to a navigation group (37 knees) and a conventional group (38 knees). Postoperative radiographs were taken in the standing position at 12 weeks after surgery, and were evaluated in accordance with the report of Bäthis et al. [1]. No significant difference in preoperative profiles was observed between the two groups. At the postoperative radiographic evaluation, significantly better results were obtained in the navigation group with regard to the mechanical axis and the component, but the results were less conclusive in the lateral femoral component position. Our findings suggest that computer-navigated TKA is useful for obtaining more accurate results. However, the present study was limited by the small number of subjects and short follow-up period, and therefore further study involving more subjects and a longer-term follow-up will be needed.

Key words computer-assisted total knee arthroplasty, cruciate-retaining prosthesis, radiographic evaluation, mechanical axis, alignment of the component

INTRODUCTION

Total knee arthroplasty (TKA) has been established as a surgical method for treatment of osteoarthritis of the knee. Previous studies with long-term follow-up have demonstrated that 80% of patients who undergo TKA are satisfied with the results [2,3]. Such studies consistently showed that the mechanical axis and ligament balance are important factors to consider for obtaining good clinical results.

The postoperative mechanical axis in TKA is usually within ±3° of the planned axis, and deviation from this can lead to early loosening [4-7]. A postoperative mechanical axis within ±3° after TKA was noted in 74% of patients (37 of 50) in a study by Petersen and Engh [8], and 75% (469 of 637) in a study by Mahaluxmivara et al. [9].

Varus/valgus placement of the femoral and tibial components can similarly lead to loosening [10]. A change in the joint line affects the range of motion [11], as does retroversion of the tibial component [12,13].

Navigation systems have been developed to obtain a more accurate grasp of the mechanical axis and aid in placement of the components in TKA. Mielke et al.

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Abbreviations: TKA, total knee arthroplasty; HKA angle, hip-knee-ankle angle; FFC angle, frontal femoral component angle; FTC angle, frontal tibial component angle; LFC angle, lateral femoral component angle; LTC angle, lateral tibial component angle; FTA, femorotibial angle.

[14] compared the use of a navigation system with the conventional method and reported that the former achieved better postoperative alignment. Conversely, Jenny and Boeri [15] stated that there was no significant difference between the use of a navigation system and the conventional approach. In the present study, we performed a radiographic evaluation of a CT-free navigation system, and compared it with the conventional method.

MATERIALS AND METHODS

Subjects

Primary TKA was performed on 281 patients at the Kurume University Medical Center between April 2003 and December 2005. Of these patients, 75 were chosen as the study subjects, and 37 were allocated to a navigation group and 38 to a conventional group. The same type of implant (TC Plus, EndoPlus, Switzerland) was used for all patients in both groups. Before surgery, the purpose of the present study was explained to the patients, and their informed consent was obtained.

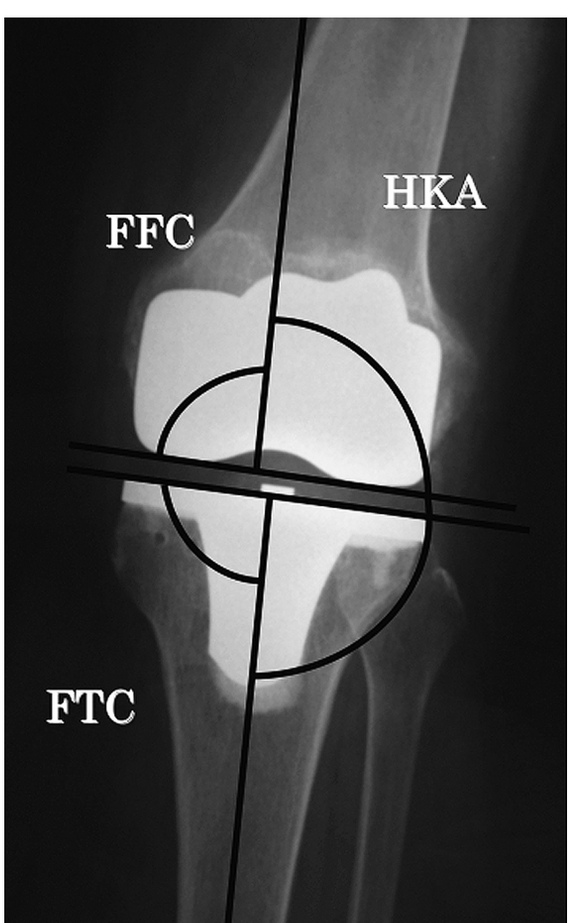

Fig. 1A.

Surgical technique

The surgical procedure was performed in accordance with the manufacturer's instructions. Specifically, femoral osteotomy was performed using an intramedullary rod through medial parapatellar approach, and an external rotation of 3° was the index for femoral rotation with reference to the posterior condylar line. Tibial osteotomy was performed using an extramedullary rod, and the posterior inclination was set at 5°.

Computer-assisted technique

A CT-free navigation system (Garireo, Endplus, Switzerland) was used in the navigation group. This is a system for detecting waves that are reflected from a marker on a spherical object using an infrared camera. The marker was firmly fixed to the distal femur, the femur was moved in an arbitrary direction around the hip joint, and 16 points were obtained. In addition, 24 reference points were input using a stylus with a marker. The resulting measurements were analyzed, and a model of the femur was generated by a computer, followed by adjustment of the alignment, and the rotation as well as the varus-valgus line was checked visually using an alignment guide. Based on this approach, the sites for osteotomy were established so that the cut block attached to the femur was aligned with the mechanical axis from the front view and had a flexion angle of 5° on the front face of the femoral component

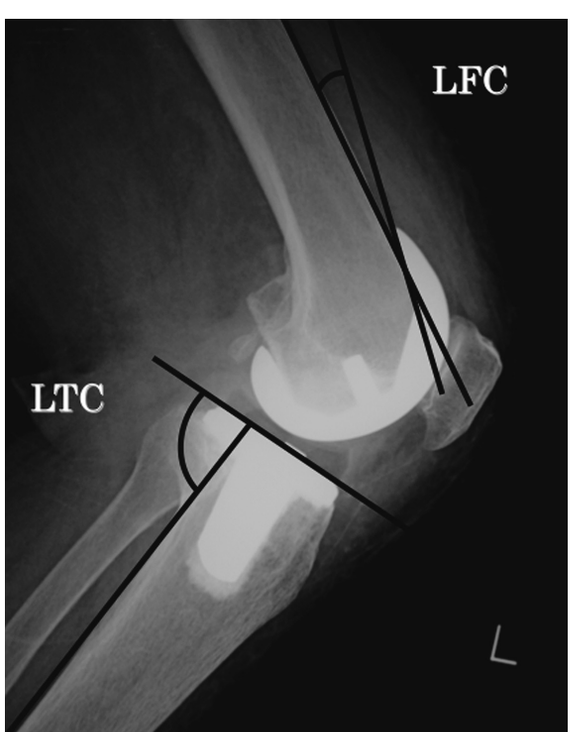

Fig. 1B.

from the lateral view, and each osteotomy was performed under visual observation.

On the tibial side, a tibial base plate was placed at the distal tibia and a marker was fixed to it. Six arbitrary reference points were input, and a model of the tibial bone was reproduced on the computer, in the same way as for the femur. On this basis, the posterior inclination of the tibia was set at 5°, and the bone was cut perpendicularly to the tibial axis.

After the osteotomy, a trial placement was conducted, and the range of motion and the varus-valgus alignment were verified on the image via flexion and extension of the knee joint.

Radiological measurement

For postoperative radiographic evaluation, X-ray films were obtained in the frontal and sagittal views at 12 weeks after the surgery with the patient in a standing position. Measurements were performed in accordance with the method of Bäthis, et al. [1]. For the mechanical axis and frontal alignment, the hip-knee-ankle (HKA) angle (= mechanical axis of the limb), the frontal femoral component (FFC) angle, and the frontal tibial component (FTC) angle were measured (Fig. 1A). For the sagittal view, the lateral femoral component (LFC) angle and the lateral tibial component (LTC) angle were evaluated (Fig. 1B).

These measurements were performed by an experienced orthopedist who was not involved in the present study.

Statistical analysis

The ideal range of each angle and "outliers" were defined based on a range of ±3° varus/valgus and ±3° flexion/extension [16]. For statistical evaluation, the t test, the Fisher test, and the Mann-Whitney test were used. A P value of <0.05 was considered to indicate a significant difference.

RESULTS

Preoperative profiles in the navigated and conventional groups

It was possible to evaluate all of the 75 patients enrolled. There were 5 males and 32 females in the navigation group, with an average age of 74.7 (range: 62 years to 86) years, including 31 with osteoarthritis (OA) and 6 with rheumatoid arthritis (RA). The average preoperative femorotibial angle (FTA) was 185.7° (range: 140° to 200°). In the conventional group, there were 8 males and 30 females, with an average age of 74.0 (range: 46 years to 89) years, including 32 with OA and 6 with RA. The average FTA was 185.3° (range: 170° to 204°). There was no significant difference in these preoperative factors between the two groups (t-test). Details are summarized in Table 1.

Mechanical axis of the leg

The average postoperative mechanical axis (HKA) was 180.6±2.8° in the navigation group and 181.2±4.1° in the conventional group, the mechanical axis of the navigation group being significantly closer to 180° (P=0.0232, F-test). Outlier values of the mechanical axis were seen for 6 patients (16.3%) in the navigation group and 16 patients (42.1%) in the conventional group. Details are shown in Table 2.

Alignment of the component

The average FFC angle was 90.1±1.8° in the navigation group and 89.4±2.7° in the conventional group, being significantly closer to 90° in the former (P=0.0198, F-test). Outlier values of the FFC angle were seen in 1 patient (2.8%) in the navigation group and 5 patients (13.2%) in the conventional group. The outliers in both groups were within 90°±5°. The FTC angle was 90.2±1.5° in the navigation group and 89.7±2.2° in the conventional group, being significantly closer to 90° in the former (P=0.014, F-test). Outlier values of

TABLE 1.
Preoparative profiles

	Navigation system	Conventional technique	P-value
Age	74.8 (5.4)	74.0 (7.5)	0.6288
Male	5	8	0.5437
Female	32	30	
OA	31	32	1.000
RA	6	6	
FTA	185.7° (12)	185.3° (7.8)	0.8693

TABLE 2.
Coronal axis alignment

	Navigation system		Conventional technique		P-value
	n		n		
HKA	37	180.6° (2.8)	38	181.2° (4.1)	0.0232
outlier		16.3%		42.1%	
FFC	37	90.1° (1.8)	38	89.4° (2.7)	0.0198
outlier		2.8%		13.2%	
FTC	37	90.2° (1.5)	38	89.7° (2.2)	0.014
outlier		0.0%		15.6%	

TABLE 3.
Sagital alignment

	Navigation system		Conventional technique		P-value
	n		n		
LFC	37	8.5° (3.5)	38	8.5° (3.1)	0.4955
outlier		45.9%		42.1%	
LTC	37	3.8° (1.9)	38	3.5° (2.8)	0.0118
outlier		7.9%		27.0%	

the FTC angle were seen in 0 (0%) of the navigation group and 6 patients (15.6%) in the conventional group. The outliers in the conventional group were within 90°±5°. Details are shown in Table 2.

The average LFC angle was 8.5±3.5° in the navigation group and 8.5±3.1° in the manual group, being non-significantly closer to 5° in the navigation group (P = 0.4955, F-test). There were 17 (45.9%) LFC angle outliers in the navigation group and 16 (42.1%) in the conventional group. The average LTC angle was 3.8± 1.9°in the navigation group and 3.5±2.8° in the conventional group, being significantly closer to 5° in the former (P=0.0118, F-test). There were 3 (7.9%) LTC angle outliers in the navigation group and 10 (27%) in the conventional group. Details are shown in Table 3.

In the present series, there was no instance in which the procedure was changed from navigation to conventional during surgery, and no significant complications were encountered. The operation time was 106±21 min for the navigation group and 95±10 min for the conventional group (p=0.0163, Mann-Whitney test). The average length of the skin incision was 24.8 cm in the navigation group and 19.5 cm in the conventional group (p<0.0001, Mann-Whitney test).

DISCUSSION

Proper mechanical limb alignment in TKA is an important factor for obtaining good postoperative results. Malposition of the TKA implant results in early loosening and accelerated polyethylene wear [4,7,16]. Valgus/varus malalignment can result in early postoperative complications, including loosening, instability, and polyethylene wear may occur [4-7].

To obtain a proper mechanical axis in TKA, the use of a navigation system has been developed and analyzed in previous studies comparing the radiological accuracy of the component placement between navigated and conventional TKA. However, plain radiographs have been commonly used for radiological evaluation [16], despite the limitations imposed by imaging errors [16,17-19], possibly leading to a statistical bias in analysis of the radiological results. In the present study, the consistency of alignment for each radiological parameter was assessed by setting outliers based on ±3° varus/valgus or ±3° flexion/extension, in accordance with the approach of Jung et al. [16].

For TKA using a navigation system, the mechanical axis was reported to be within ±3° in 96% of subjects (77 of 80) in a study by Bäthis et al. [1], 92% (217 of 235) in a study by Jenny et al. [20], 71% (26 of 32) in a study by Inoue et al. [19], and 87% (13 of 15) in a study by Taki et al. [21]. In the present investigation, the axis was within 3° in 84% of subjects (31 of 37) who underwent TKA with the navigation system, and was within 5° in the remaining 16% (6 of 37). Our results also demonstrated that the proportion of patients in whom the postoperative mechanical axis was within

3° was significantly greater in the navigation group than in the conventional TKA group.

Conventional TKA aims to achieve a mechanical axis within 180±3° [4-9]. Petersen and Engh [8] reported that the mechanical axis was within 180±3° in 74% (37 of 50) of patients who underwent conventional TKA, compared with 72% (170 of 235) in the study by Jenny et al. [20], 69% (22 of 32) in the study by Inoue et al. [19], and 47% (7 of 15) in the study by Taki et al. [21]. In the present study, the mechanical axis was within 180±3° in 58% of subjects (22 of 38) after conventional TKA, and within 180±5° in the remaining 42% (16 of 38).

Previous reports have demonstrated variability of the LFC angles in conventional TKA [1,17,18]. With the conventional technique, the LFC position is not always optimal, because it depends on the diameter of the intramedullary rod, the insertion point, and the length of the rod. By contrast, the LFC can be placed more accurately by navigated TKA, with reference to the center of the femoral head and the direction of the femoral axis [20]. The present study, however, demonstrated no significant difference in LFC between the two groups. This may indicate a degree of measurement error due to anterior bowing of the femur in navigation TKA [22], or pointing error for the center of the femoral head [1]. As with the CT-based navigation system, these errors may be reduced by creating an accurate 3D model [24].

The present study demonstrated that the LTC angle was more accurate in navigated TKA than in conventional TKA, in agreement with previous reports [1,17,18]. In the conventional method, the LTC angle may vary because of differences of the tibial posterior slope in each patient [1], cutting error due to deflection of the bone saw [23], and/or stylus pointing error [25].

Limitations of the present study included the small number of subjects analyzed and the short follow-up period. However, we were able to demonstrate the characteristics of navigated TKA for component placement in comparison with conventional TKA. Future studies involving a larger number of subjects and a longer period of follow-up will be needed. Furthermore, comparison with a CT-based navigation system may also be necessary.

In the present study, we compared the mechanical axis of the lower limb and the position of the component placement in TKA using a CT-free navigation system with those of conventional TKA. The results indicated that the mechanical axis and component placement were more accurate with navigated TKA, except for the LFC angle. The potential benefits of navigated TKA in terms of long-term outcome and functional improvement await further clarification.

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Original Contribution

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Effects of Emotionally Affect Adult and Baby' Photographs in Healthy Controls and Schizophrenic Patients Evaluating by Exploratory Eye Movements

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Summary: The relationship between mother and baby is of fundamental importance in the development of cognitive function and emotion. In this study we investigated the effects of affective photographs of a mother and baby (crying or smiling faces) and other stimuli (neutral mother or baby faces) on visual cognitive function in schizophrenic patents. We recorded exploratory eye movements in 22 healthy controls and 22 age-matched schizophrenic patients. Total number of right and left field gaze points (right TNGP, left TNGP) in the visual fields were determined using an eye-mark recorder as subjects viewed affectively charged or neutral photographs (crying, smiling or neutral faces). Left TNGP for all mother photographs (crying, smiling or neutral) were significantly larger in controls than patients, and right TNGP for neutral mother photographs were significantly larger in controls than in patients. Right TNGP for photographs of smiling babies were significantly larger in controls than patients, and left TNGP for photographs of both smiling and crying babies were significantly larger in controls than patients. Within the patient group, right TNGP were significantly larger than left TNGP for all mother photographs (crying, smiling or neutral). Left TNGP for photographs of mothers and babies correlated negatively with negative symptom scores. These results suggest that exploratory eye movements when viewing emotionally laded twin stimuli such as photographs of a mother and baby are a useful marker of visual cognitive function in both healthy controls and schizophrenic patients.

Key words exploratory eye movements, healthy control, schizophrenia, affective photograph, laterality, visual recognition

INTRODUCTION

Humans obtain a particularly large amount of information for adapting to their environment visually as opposed to other types of sensory input. Specific information is selected from a wide variety of visual stimuli, and then processed to guide behavior. Affection and emotion are critical elements of human relationships: generally, negative emotions impair quality of life, while positive emotions make life pleasurable. Affective stimuli have been shown to influence event-related potentials such as P300 components [1,2] and potentials related to eye movements [3-5]. The relationship between mother and baby, in particular, is of fundamental importance in the development of cognitive function and emotion [6].

Schwartz et al. [7] compared responses of healthy adults between emotional and none-motional figure

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Abbreviations: ANOVA, analysis of variance; EMR, eye-mark recorder; PANSS, Positive and Negative Symptom Scale; RSS, responsive search score; TNGP, total number of gaze points.

recognition tasks, noting that the eyes more often moved to the left during the emotional tasks. Turning the eyes to the left suggests activity of mechanisms tending supply visual information to the right cerebral hemisphere, indicating a relationship between the right brain and emotion [7,8]. Furthermore, in terms of brain function, one study of emotional perception used eye movements across a screen to demonstrate that the right hemisphere plays a dominant role in retention and recall of emotionally related facial expressions, with a higher frequency of eye movements to the left during such tasks [9]. Since leftward shift of gaze fixation suggests direction visual information to the right cerebral hemisphere, that hemisphere appears to be concerned with emotional visual processing. Indeed, responsive search score (RSS) measured by exploratory eye movements was related to the right brain function [9].

It has been observed that schizophrenic patients have deficient positive emotion perception. However, little direct evidence regarding the effects of affection on eye movements has been reported [3,4]. Thus, the effect of positive emotion on cognitive function linked to exploratory eye movements is an important new area of study. Loughland et al. [5] suggested that this deficit might reflect a failure to integrate visual information. Nishiura et al. [10] also reported that viewing images with positive affective content, such as smiling photographs, reduced exploratory eye movements in schizophrenic patients. Moreover, this impairment particularly involves scanning of the left field of the screen. The authors suggested that eye movements increase in distance and frequency as a result of an increased allocation of mental resources for maintenance of attention. We previously suggested that exploratory eye movements in schizophrenic patients have a more limited scanning range than in healthy controls [11], with longer maintenance of gaze when viewing simple figures such as a circle, similar to the findings of Kojima et al. [12]. Schizophrenic patients may gaze aimlessly at an inappropriate part of a picture rather than focusing attention on a more appropriate part. This finding suggests the possibility of impaired visual information processing in schizophrenic patients, especially concerning positive emotion presented to the left visual field of sight [10].

In the present study, we investigated the effects of emotionally laden photographs, such as a mother and child smiling or crying, and other photographs unrelated to emotion, upon exploratory eye movements, comparing healthy subjects and schizophrenic patients using an eye-mark recorder (EMR). A second aim was to determine whether any particular eye movement response was related to the ability to form human relationships.

METHODS

Subjects

Healthy paid volunteers (n=22; mean ±SD, 26.9± 5.7), as well as age-matched schizophrenic patients (n=22; mean±SD, 27.9±5.7) were enrolled. Schizophrenia was of the paranoid type in 16 patients, and non paranoid in 6 patients. All healthy controls and patients were right handed and had normal visual and auditory ability. Controls had no history of psychiatric or neurological disease or of drug addiction. All subjects gave written informed consent for study participation. The Ethics Committee of Kurume University approved the present study.

Eye mark recording

Eye movements were recorded using an eye-mark recorder (Mac, EMR-8, Tokyo, Japan). Infrared light sources (850 nm) were positioned in front of each lower eyelid. The camera on the top of the cap recorded the pictures shown on the screen. After a camera controller superimposed these recordings with a 0.01 sec electronic timer, the combined recording was stored on a compact disc. Movement of more than 1˚ with duration greater than 0.1 sec was scored as an eye movement. In the present study, exploratory eye movements were analyzed in terms of one parameter, total number of gaze points (TNGP), as reported previously [13,14]. We also recorded two versions: Version 1 used photographs showing the mother in the left half of the screen, and version 2 showed the mother on the right side, and we recorded left TNGP and right TNGP, respectively [10]. Central, lateral (20˚ visual angle), and vertical (12˚ visual angle) positions were confirmed beforehand. Lateral differences in gaze points were analyzed based on data with confirmed positions [10].

Eye movement recording procedure

Subjects were instructed to identify each photograph exactly as it was presented. All subjects also were instructed to view and fixate upon several corner points to check their eye movements for neurological deficits and low-level eye movement disturbances such as reflex organic saccades. Deficits were not found in any subjects. Exploratory eye movements and fixation points were recorded during viewing. Photographs were projected onto a screen to form images 120 cm

wide and 90 cm high. Maximum angle of sight lines were 40˚ horizontally and 24˚ vertically. Each block consisted of a series of four photographs, each presented for 15 sec [11,12]. Six kinds of photographs were used (Fig. 1 and 2).

Version 1: Picture 1 showed a smiling mother on the left and smiling baby on the right to study the effect of positive affect. Picture 2 showed a crying mother on the left and crying baby on the right to study the effect of negative affect. Photograph 3 showed a neutral mother on the left and neutral baby on the right to study the effect of nonemotional content.

Version 2: The mother and baby were transposed from right to left and vice versa. Versions 1 and 2 were presented in a counterbalanced manner and two recordings were carried at one-week intervals.

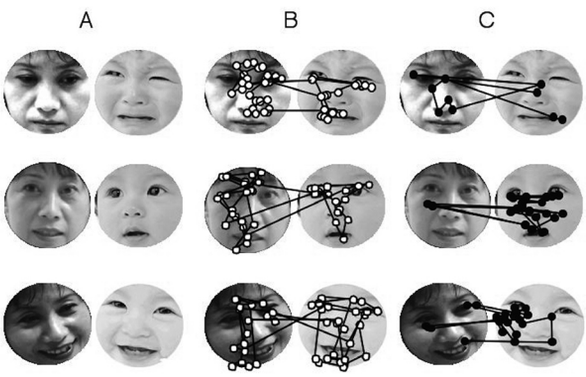

Fig. 1. Typical series of exploratory eye movements under version 1 (left Mother and right Baby) when viewing crying (upward), neutral (middle) and smiling (lower) photographs in a healthy subjects (B) and schizophrenic patients (C). Each dot indicates a gaze point and each line, eye movement. The gaze points were located rightward in patients.

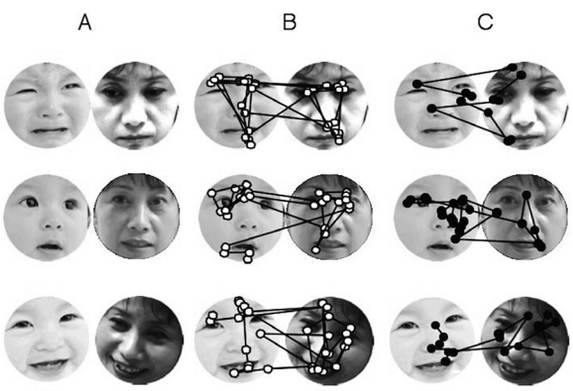

Fig. 2. Typical series of exploratory eye movements under version 2 (right Mother and left Baby) when viewing crying (upward), neutral (middle) and smiling (lower) photographs in a healthy subjects (B) and schizophrenic patients (C). Each dot indicates a gaze point and each line, eye movement. The gaze points were located rightward in patients.

In the present study, we used two similar pictures transposed left and right to examine differences in eye movement and to evaluate the perceived relationships between mother and baby. In a basic study, three kinds of photographs of mothers and babies were viewed by 100 healthy controls. All reported that the figures in picture 1 were crying and feeling sad, those in picture 2 were smiling and feeling pleasure, and those in photograph 3 were neither crying nor smiling and were feeling no emotion. Thus we utilized these photographs in the present study.

Recording was performed as follows. Session 1 (free task): All subjects were instructed, “Look at the photographs in front of you freely. After the task, I will ask you how the people shown were feeling, for example happy, sad or nothing.” Session 2 (memory task): All subjects were instructed, “Look at the photographs in front of you and try to remember carefully what you see. After the task, I will ask you what kind of pictures you saw.” Session 3 (confidence task): All subjects were instructed, “note any differences between the photographs you are seeing now and the ones you saw previously” to test confidence and attention. Data from right and left eyes were analyzed and found to be similar [11,15].

Clinical evaluation and medication

The clinical state of all patients was assessed using the Positive and Negative Symptom Scale (PANSS) [16] by two psychiatrists within 1 week after eye movement recording. The positive symptom score was 24.3±5.9 and the negative symptom score 22.3±4.6. When scores differed between the two psychiatrists, final scores were determined by negotiation before being analyzed as data. All patients were treated with neuroleptics (mean daily dose in chlorpromazine equivalent, 279.4±107.5 (mg/day) [13].

Statistical analysis

The present study considered only data obtained from the confidence task (session 3), since the confidence task has been reported to best reflect visual cognitive function [11]. First, three-way analysis of variance (ANOVA) (version, group, stimulus) was performed. Then two-way ANOVA was performed (group, stimuli) in version1 and version 2. Finally, one-way ANOVA was performed, with or without interaction, for each version (version 1: mother on left, version 2: mother on right), group (patients or con-

trols) and stimuli (smiling, crying or neutral). Post hoc analyses were conducted using Scheffe tests. Pearson's correlation coefficient was used to identify significant relationships between symptom scores, measures of eye movements, and dose of medication. A p value below 0.05 was taken to indicate statistical significance.

RESULTS

Representative sequences of exploratory eye movements from a healthy control and from a schizophrenic patient while viewing the three photographs in version 1 are shown in Figure 1, and eye movements from version 2 are shown in Figure 2. The control subject's eye movements were coherent, focusing on the baby's eyes and mouth in both the left and right visual fields (a double inverted triangle pattern). The patient's eye movements appeared to be random, no organizing strategy was apparent, and they were relatively limited in aggregate length.

Mother (Table 1, Fig. 3).

Three-way ANOVA (group, version, stimulus) demonstrated significant group ($F=113.3$, $p<0.0001$) and version ($F=6.00$, $p<0.05$) differences. Significant interaction was observed between group and stimuli ($F=6.00$, $p<0.05$), group and version ($F=25.9$, $p<0.0001$). Two-way ANOVA (group, stimulus) demonstrated significant group differences in version 1 ($F=133.2$, $p<0.0001$) and in version 2 ($F=14.4$, $p<0.0001$).

By one-way ANOVA, TNGP in version 1 (left mother) differed between the two groups with regard to crying ($F=42.55$, $p<0.0001$), neutral photographs ($F=75.5$, $p<0.0001$) and smiling ($F=25.3$, $p<0.0001$). In version 2, TNGP in controls (right mother) were significantly larger than in patients (neutral: $F=11.48$, $p<0.001$), but not for crying and smiling photographs. TNGP for version 1 in controls was significantly larger than for version 2 ($F=4.99$, $p<0.05$). In patients, TNGP for version 2 was significantly larger than for version 1 (crying: $F=8.97$, $p<0.01$,neutral: $F=6.08$, $p<0.05$, smiling: $F=16.2$, $p<0.001$) (not shown in figure).

Baby (Table 1, Fig. 4).

Three-way ANOVA (group, version, stimulus) demonstrated significant main group ($F=9.57$, $p<0.01$), version ($F=7.8$, $p<0.01$) differences. Significant interaction was observed between group and version ($F=3.9$, $p<0.05$). Two-way ANOVA (group, stimulus) in version 2 demonstrated group difference ($F=8.79$, $p<0.01$).

By one-way ANOVA, TNGP in patients (version 1: left mother) was significantly smaller than in controls (smiling: $F=4.0$, $p<0.05$), but not for crying and neutral photographs. TNGP in patients (version 2: right mother) was significantly smaller than that in controls (crying: $F=5.9$, $p<0.05$, smiling: $F=4.77$, $p<0.05$), but not for neutral photographs. In version 1, significant stimuli difference of TNGP was observed only in patients ($F=4.2$, $p<0.05$). TNGP for the neutral picture was significantly larger than for crying ($p<0.05$) and for smiling ($p<0.05$) photographs.

The only significant difference was noted between version 1 and 2 viewing neutral photographs ($F=4.36$ $p<0.05$). TNGP for version 1 was significantly larger than for version 2 ($p<0.05$) (not shown in figure).

Symptom scores and eye measures (Table 2)

In version 1 (left mother), a significant correlation was obtained between negative symptom scores and TNGP for the crying baby (right) ($r=-0.393$, $p<0.01$),

TABLE 1.
Value of the measurements of the exploratory eye movements under confidence condition

		TNGP of mother (*n*)		TNGP of baby (*n*)	
		Controls	Patients	Controls	Patients
Version 1	Crying	15.4±6.1	7.9±4.0 [a]	12.7±4.6	12.0±5.5
Left Mother Right baby	Neutral	16.8±3.1	8.0±5.5 [a]	12.9±4.5	14.3±6.0 [c]
	Smiling	14.8±5.5	9.2±4.5 [a]	13.6±4.4	11.9±3.1 [d]
Version 2	Crying	13.1±4.5	11.1±5.4	12.7±4.3	9.4±6.9 [d]
Right Mother Left baby	Neutral	15.4±5.1	11.1±5.9 [b]	12.4±6.1	11.5±6.1
	Smiling	14.8±5.1	13.3±4.8	12.9±4.3	10.5±5.5 [d]

Data are given as mean±standard deviation.
a: $p<0.001$,vs.controls. b: $p<0.01$,vs.controls. c: $p<0.05$,vs.clying and smiling of patienrs. d: $p<0.01$,vs.controls.

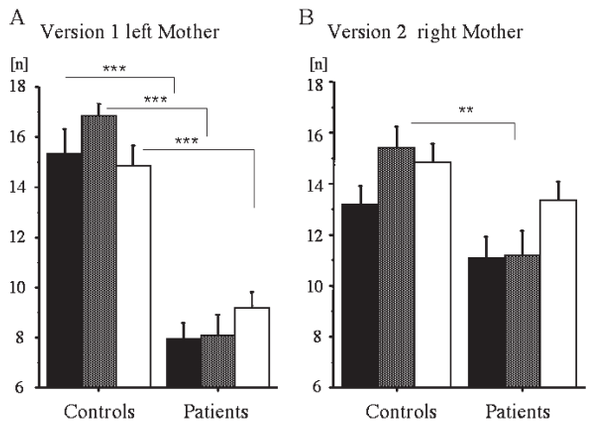

Fig. 3. A: Total number of gaze points (TNGP; ordinate) in the left field (version 1, Mother presentation) was plotted against stimuli and group. B: Total number of gaze points (TNGP; ordinate) in the right field (version 2, Mother presentation) was plotted against stimuli and group. Closed column: crying photographs. Dotted column: neutral photographs. Open column: smiling photographs. *: $p<0.05$. **: $p<0.01$. ***: $p<0.001$. Bars indicate the standard errors.

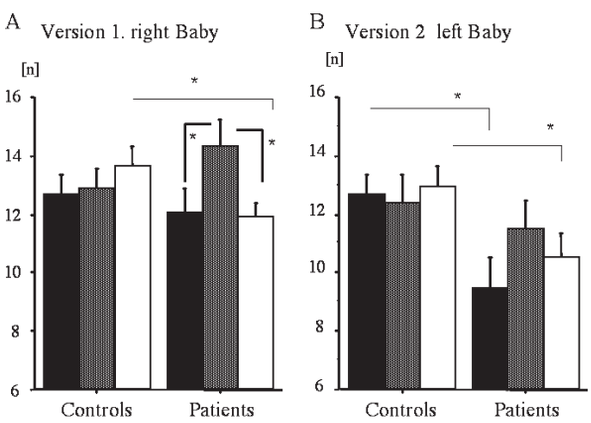

Fig. 4. A: Total number of gaze points (TNGP; ordinate) in the right field (version 1, Baby presentation) was plotted against stimuli and group. B: Total number of gaze points (TNGP; ordinate) in the left field (version 2, Baby presentation) was plotted against stimuli and group. Closed column: crying photographs. Dotted column: neutral photographs. Open column: smiling photographs. *: $p<0.05$. **: $p<0.001$. Bars indicate the standard errors.

TABLE 2.
Relationships between TNGP and negative symptoms in patients

		TNGP of mother (*n*)		TNGP of baby (*n*)	
		Left Mother	Right Mother	Right baby	Left baby
Version 1	Crying	-0.217		-0.393[b]	
Left Mother Right baby	Neutral	-0.521[a]		-0.323	
	Smiling	-0.552[a]		-0.027	
Version 2	Crying		0.037		0.029
Right Mother Left baby	Neutral		0.070		-0.410[b]
	Smiling		-0.367[c]		-0.086

a: $p<0.001$. b: $p<0.01$. c: $p<0.05$

for neutral mother (left) ($r=-0.521$, $p<0.001$), and for smiling mother (left) $r=-0.552$, $p<0.001$). In version 2 (right mother), a significant correlation was obtained between negative symptom scores and TNGP of neutral baby (left) ($r=-0.410$, $p<0.01$) and for smiling mother (right) ($r=-0.367$, $p<0.05$).

In version 1, a significant correlation was obtained between positive symptom scores and TNGP of crying baby (right) ($r=-0.475$, $p<0.01$), and in version 2 between positive symptom scores and TNGP of crying baby (left) ($r=-0.350$, $p<0.05$). No significant correlation was obtained for either negative or positive symptom scores and drug intake.

DISCUSSION

TNGP was significantly larger in controls than in the schizophrenic patients. In the patients, right TNGP were larger than left TNGP.

The most important finding of the present study was that emotionally charged adult (mother) and baby photographs proved to be a useful tool in investigating characteristics of exploratory eye movements in healthy subjects and also in patients with schizophrenia, most notably in eye scanning when viewing smiling and neutral pictures on the left side of the visual field.

The relationship between mother and baby should

be the most important factor in enabling human beings to establish human relationships. An impairment of this relation may cause various dysfunctions in social relationships between humans [7]. However, no reports have concentrated on the role of affection in the mother-baby relationship on cognitive function as evaluated by physiological methods such as event related potential or eye movements. Kojima et al. [10,16] investigated exploratory eye movements using specially constructed S-shaped geometric figures, demonstrating exploratory eye movement to be a useful biologic marker of visual cognitive function in patients with schizophrenia. The present study examined effects of emotionally charged and non-emotional stimuli on gaze points in the left or the right scanning fields, and more particularly examined the scanning for a mother or baby.

Mother

Significant differences of TNGP were noted between controls and patients for the smiling, neutral and crying photographs in the left field (version 1), but only for the neutral pictures in the right field (version 2). Indeed, in patients, TNGP in version 2 (right mother) were significantly larger than under version 1 (left mother) for smiling, neutral and crying pictures. This enhancement was not observed with the photographs of the baby (see below). This indicates that left field scanning in patients of the mother image tended to be inhibited, thus the left adult affective stimuli may generally be impaired without regard to stimuli differences. Moreover, the increases in TNGP under version 2 for neutral photographs were rather smaller than for the other stimuli.

Baby

Significant differences of TNGP were noted between controls and patients only for the smiling photographs in the left field (version 1), and for the crying and the smiling photographs in the right field (version 2). TNGP for neutral pictures both in version 1 and version 2 were about the same in both groups. Interestingly, TNGP for neutral photos among patients was larger than that for crying and smiling photographs in both version 1, and version 2, although the difference was not significant. These findings indicate that neutral photographs may enhance the attention and eye scanning in patients, especially in the left field of vision. Indeed, no significant difference between version 1 and version 2 for the crying and smiling pictures was noted. Significant differences were observed only for the neutral picture: TNGP for the neutral photo with the baby on the right side (version 1) was larger than that with the baby on the left. Photos with the neutral baby in the right field tended to attract enhanced attention in patients, but not in the left. Furthermore, TNGP in patients for smiling and crying pictures in the right field were somewhat higher than for those in the left. These indicate that the left scanning in patients was generally impaired, as was observed in the case of photos of a mother. However, the dysfunction when viewing a baby appeared to be weaker than when viewing a mother.

Symptoms and eye movements

Negative psychiatric symptoms have been reported to correlate negatively with exploratory eye movements [11]. In our study, a significant negative correlation was observed between the TNGP of version 1 (left mother) for the neutral and smiling picture and negative symptom scores, but not in version 2 (right mother). TNGP of right baby (version 1) for the crying and neutral photographs was negatively correlated with negative symptom scores. TNGP of left baby (version 2) for the neutral and smiling photographs correlated negatively with negative symptom scores. These results strongly indicate that the left TNGP for smiling or neutral pictures is the best index and revealed a fundamentally important dysfunction of the schizophrenic patients regardless of whether the photo viewed was a mother or baby. Our findings strongly suggest that exploratory eye movements may be a clinically useful prognostic indicator of negative symptoms. Correlations between scanning measurements and symptoms showed that negative symptoms were related to scanning measures such as fixation numbers, and total scan path length of face [14]. The authors suggest that visual organization impairments may be related to cognitive inflexibility and frontal dysfunction.

Positive symptom scores were negatively correlated to TNGP of right baby in version 1 (left mother) and TNGP of right mother in version 2 (left baby) only for crying photographs. These results indicate that negative affective stimuli may relate to positive symptoms only in the right field of vision. These results taken together suggested that negative symptoms might be related to right brain function and positive symptoms to left brain function.

Conclusions and psychophysiological significance

Phillips et al. [3] reported that schizophrenic patients had difficulty in redirection of focus of attention to left-field stimuli, proposing left- specific scan paths as a marker of attention processes in schizophrenic patients. Ishi et al. [17] reported that left TNGP

was smaller in schizophrenia patients under positive affection with voice and suggested that left eye scanning function could be a trait marker of schizophrenia, similar to previous reports [10]. In the present study, left TNGP under both versions (version 1: left mother, version 2: left baby) differed between patients and controls, especially depending on the location (left or right) of the mother. These indicated the left scanning dysfunction should occur regardless of the stimulus. This function was seen also in when viewing neutral baby photograph. Thus, the left-sided ocular scanning may be a particularly good trait marker of visual cognitive dysfunction in schizophrenic patients.

We hypothesize that if patients see themselves in the baby photographs, the neutral mother face may tend to cause confusion, thus patients may avoid looking at the mother and prefer to look at the self (baby) on the right side [18]. This hyper activation of viewing in case of the neutral baby may be one of the characteristics of the cognitive function of schizophrenic patients.

From these reports, schizophrenic patients may have an impairment of the right frontal cortex especially under pleasurable and neutral conditions. Indeed, the RSS of exploratory eye movement viewing the letter "S" was reported to reflect right brain function [19]. This dysfunction should make human social relationships more difficult. Finally, exploratory eye movements while viewing certain pictures showed certain differences between schizophrenic patients and healthy controls in the left field of screen using adult or baby' photographs. Thus, exploratory eye movements appear to include clinical and hemispheric functional markers that could be useful for exploring human visual cognition.

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Original Contribution

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A Comparative Study of Treatments for Chronic Subdural Hematoma: Burr Hole Drainage versus Burr Hole Drainage with Irrigation

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Summary: Although chronic subdural hematoma (CSDH) is one of the most common entities encountered in neurosurgical practice, optimal surgical treatment for CSDH remains controversial. This study retrospectively compared results for CSDH between burr hole drainage alone and burr hole drainage with irrigation. Ninety-two patients with CSDH underwent surgery at our institution from January 1998 through December 2009. Fifty-eight patients received burr hole drainage alone (Group A), while 34 patients were treated using burr hole drainage with irrigation (Group B). Outcomes, recurrence rates, and death rates for the two groups were analyzed.Age, sex ratio, consciousness level on admission, radiodensity of hematoma on computed tomography before surgery, and duration of hospitalization were nearly the same in both groups. No significant differences were seen in good outcomes or death rates between groups, but poor outcomes were significantly more frequent in Group A (p=0.009). The recurrence rate was higher in Group A compared to Group B (10.3% vs. 2.9%). The authors used logistic regression analysis to identify factors associated with the outcome of CSDH, and found that duration of hospital stay, anti-coagulant therapy, presence of dementia and burr hole drainage alone were significantly associated with poor outcome of CSDH. These results indicate that burr hole drainage with irrigation has a significantly stronger association with good outcomes compared to drainage alone, and could be a reliable and effective operative method for the treatment of CSDH with a lower recurrence rate.

Key words chronic subdural hematoma, computed tomography, recurrence, burr hole surgery, drainage, irrigation

INTRODUCTION

Chronic subdural hematoma (CSDH) is a well-known clinical entity among elderly patients and is encountered in daily neurosurgical practice. Although surgical therapy is generally accepted for treatment (e.g., twist drill craniostomy, burr hole craniostomy and craniotomy or craniectomy), optimal surgical procedures remain contentious [1,2].

Burr hole drainage has recently been reported to be the method of choice for the initial treatment of CSDH [3] and some reports have described low recurrence rates for burr hole irrigation followed by drainage [4,5]. However, few studies compared results for CSDH between burr hole drainage alone and burr hole drainage with irrigation [2,7,10,15].

This retrospective study examined whether any differences exist in outcomes, recurrence rates and death rates between surgical treatment involving drainage alone and drainage with irrigation.

PATIENTS AND METHODS

Subjects comprised 92 patients (59 men, 33 women)

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Abbreviations: CSDH, chronic subdural hematoma; CT, computed tomography, GOS, Glasgow Outcome Scale.

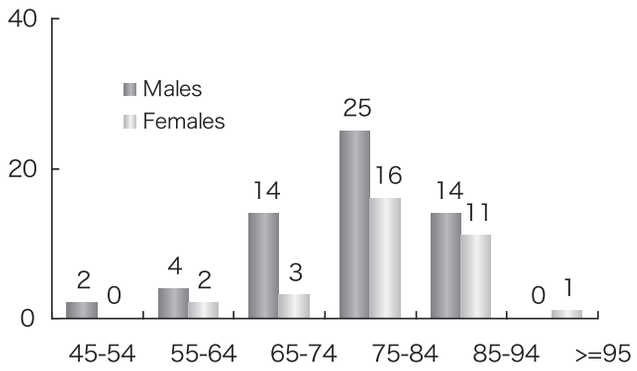

Fig. 1. Age distributions of the 59 male and 33 female.

who underwent surgery for CSDH at our institution between January 1998 and December 2009. Median age was 78.6 years (range, 52-95 years). Incidence gradually increased with age, peaking in the seventh decade (Fig. 1). The 92 patients were classified into 2 groups according to a randomly allocated operative procedure: Group A (n=58), one burr hole with closed system drainage without irrigation; and Group B (n=34), one burr hole with closed system drainage after irrigation. Baseline characteristics of patients in each group are given in Table 1. Patients were neurologically evaluated using the Japan Coma scale [6] and mental state was analyzed with the revised Hasegawa Dementia Scale [7]. Postoperative condition was assessed at discharge using the Glasgow Outcome Scale (GOS) [8]. Patients with GOS showing good recovery or moderate disability were considered to have good outcomes. Patients with GOS showing severe disability, vegetative state or death were judged as having poor outcomes. Patients who had dementia or neurological deficits due to cerebrovascular disease preoperatively and regained their previous condition after surgical intervention were considered to show good outcomes.

For Group A, a burr hole was drilled under local anesthesia and a drainage catheter was inserted and connected to a collection bag (FORTE GROW MEDICAL VIETNAM CO., LTD, TINH DUONG, VIETNAM). For Group B, a burr hole was drilled under local anesthesia, then a 5-Fr Nelaton tube was inserted into the cavity and the subdural hematoma was washed out with warm sterile saline until the irrigation fluid ran clear. A drainage catheter was then inserted and connected to a collection bag. All patients were in bed in a supine position with a collection bag on the bed. Drainage was extracted when ineffectiveness in reducing residual hematoma was noted 1 or 2 days postoperatively.

CSDH was defined as the presence of a typical neomembrane and liquefied blood in the hematoma cavity. These findings were confirmed during surgery in all patients. Patients showing reappearance of neurological symptoms with increasing hematoma cavity volume on the operated side within a few months after surgery were considered to have recurrence and underwent a repeated operation.

Rates of good and poor outcomes, recurrence and death were compared between surgical groups. Statistical analysis was conducted using univariate and multiple logistic regression analysis.

RESULTS

Group A consisted of 58 patients (40 men, 18 women) and Group B consisted of 34 patients (19 men, 15 women). Median age in Group A was 77.9±8.5 years (range, 52-95 years), compared to 79.1±10 years (range, 59-94 years) in Group B (Table 1-1).

On preoperative computed tomography (CT), hematomas in Group A showed low density in 8 patients, iso-density in 15, high density in 24, and mixed density in 11. In Group B, hematomas showed low density in 3 patients, iso-density in 12, high density in 10, and mixed density in 9. CSDHs were unilateral in 52 patients in Group A and 31 patients in Group B and bilateral in 6 patients in Group A and 3 patients in Group B. No significant differences between groups were seen for clinical characteristics such as age, sex, preoperative hematoma density on CT, or duration of hospitalization (Table 1-1, 2). Good outcomes were obtained in 48 of 58 patients (82.0%) in Group A and in all 34 patients (100%) in Group B. Poor outcomes were noted for 10 patients (18.0%) in Group A and no patients (0.0%) in Group B. Two patients (3.4%) died in Group A. No deaths were directly related to surgery, but 1 patient died of recurrent acute myocardial infarction 3 days after surgery and the other died due to aspiration pneumonia 1 year postoperatively. No patients had died as of the final follow-up after surgery in Group B. No significant differences in rates of good outcomes and deaths were apparent between groups. However, poor outcomes (including the 2 deaths) were significantly more frequent in Group A (p=0.009) (Table 1-2). The authors analyzed factors associated with the outcome of CSDH by logistic regression analysis, and found that duration of hospital stay, anticoagulant therapy, presence of dementia and burr hole drainage alone were significant independent risk factors in CSDH (Table 2-1, 2). Thus, drainage with irri-

TABLE 1-1.
Baseline characteristics of 92 patients with CSDH

Characteristics	Group A (n=58)	Group B (n=34)	Total (N=92)	p
Age (years)	77.9 (8.5)	79.1 (10.0)	78.7 (9.5)	0.579
Sex (male%)	40 (68.9)	19 (55.9)	59 (64.1)	0.150
Hospitalization	29.2 (25.2)	25.0 (20.2)	27.6 (23.4)	0.412
Hypertension	18 (31.0)	18 (52.9)	36 (39.1)	0.032
Diabetes mellitus	7 (12.1)	4 (11.8)	11 (11.9)	0.621
Hyperlipidemia	5 (8.6)	6 (17.6)	11 (11.9)	0.169
Renal failure	3 (5.2)	2 (5.9)	5 (5.4)	0.613
Cardiac arrhythmia	13 (22.4)	4 (11.8)	17 (18.5)	0.161
Cerebral infarction	10 (17.2)	3 (8.8)	13 (14.1)	0.212
Cerebral hemorrhage	2 (3.4)	0 (0.0)	2 (2.2)	0.390
Anticoagulant drug	6 (10.3)	2 (5.9)	8 (8.7)	0.374
Antiplatelet drug	5 (8.6)	3 (8.8)	8 (8.7)	0.626

(Values in parentheses represent standard deviation or percentage)

TABLE 1-2.
Baseline characteristics of 92 patients with CSDH

Characteristics	Group A (n=58)	Group B (n=34)	Total (N=92)	p
Dementia	26 (44.8)	9 (26.5)	35 (38.0)	0.062
Low density on CT	8 (13.8)	3 (8.8)	11 (12.0)	0.362
Consciousness disturbance	13 (22.4)	4 (11.8)	17 (18.5)	0.161
Recurrence	6 (10.3)	1 (2.9)	7 (7.6)	0.191
Good outcome	48 (82.0)	34 (100)	82 (89.1)	0.058
Poor outcome	10 (18.0)	0 (0.0)	10 (10.9)	0.009
Death	2 (3.4)	0 (0.0)	2 (2.1)	–

(Values in parentheses represent percentage)

gation had a stronger association with good outcomes as compared with drainage alone.

Recurrence was identified in 1 patient in Group B (2.9%) and 6 patients in Group A (10.3%). All except one recurrence occurred within 3 weeks after surgery, with residual hematomas found on CT within a few days after surgery in 5 of 7 recurrences. Although no significant difference was noted between groups, the recurrence rate was 3-fold higher in Group A (10.3%) than in Group B (2.9%, p=0.191) (Table 1-2).

DISCUSSION

Burr hole surgery is currently the most common therapeutic surgical treatment for CSDH and burr hole drainage has been reported to be superior to burr hole irrigation [9]. However, whether drainage alone or drainage with irrigation is better for patients with CSDH remains unclear [1,2,4,5,10-17].

Zakararia et al. [2] reported good outcomes in 83.3% of patients who underwent drainage and 87% of patients who received drainage with irrigation. Muzii et al. [1] stated that 90.9% of patients who received drainage and 70.8% of patients who underwent drainage with irrigation showed complete recovery. No significant differences in good outcomes between the two surgical techniques were identified in either report. In the present study, good outcomes were seen

TABLE 2-1.
Factors associated with the outcome of CSDH analyzed by the logistic regression analysis

Variables	Regression coefficient	Standard error	p-value	Relative risk (95% C.I.)
Age (years)	0.042	0.035	0.227	1.043 (0.974-1.116)
Sex (male)	0.348	0.590	0.555	1.417 (0.446-4.504)
Hospitalization	0.023	0.011	0.003	1.023 (1.002-1.045)
Hypertension	−0.172	0.604	0.776	0.842 (0.258-2.751)
Diabetes mellitus	−0.648	1.092	0.553	0.523 (0.062-4.444)
Hyperlipidemia	0.245	0.842	0.771	1.278 (0.245-6.655)
Renal failure	1.427	0.964	0.139	4.167 (0.629-27.584)
Cardiac arrhythmia	1.117	0.640	0.081	3.056 (0.872-10.712)
Cerebral infarction	1.121	0.690	0.104	3.067 (0.794-11.849)
Cerebral hemorrhage	1.859	1.448	0.199	6.417 (0.376-109.581)
Anticoagulant drug	2.011	0.783	0.011	7.400 (1.594-34.352)
Antiplatelet drug	1.382	0.799	0.084	3.982 (0.832-19.052)

C.I., Confidence interval.

TABLE 2-2.
Factors associated with the outcome of CSDH analyzed by the logistic regression analysis

Variables	Regression coefficient	Standard deviation	p-value	Relative risk (95% C.I.)
Dementia	2.644	0.803	0.001	14.348 (2.973-69.247)
Low density on CT	0.648	1.092	0.553	1.912 (0.225-16.241)
Consciousness disturbance	1.117	0.640	0.081	3.056 (0.872-10.712)
Drainage with irrigation	−2.255	1.063	0.034	0.105 (0.013-0.842)

C.I., Confidence interval.

in 82% of Group A patients and 100% of Group B patients, comparable to previous reports. In contrast, 18% of patients in Group A and no patients in Group B showed poor outcomes. Poor outcomes were significantly more frequent in Group A (p=0.009) (Table 1-2) and furthermore, the logistic regression analysis indicated that drainage with irrigation had a significantly stronger association with good outcomes as compared to drainage alone. Duration of hospital stay, anti-coagulant therapy, and presence of dementia were also significant factors associated with poor outcomes of CSDH.

Despite various surgical treatment options, CSDH recurs in some patients. Muzii et al. [1] reported recurrence rates of 4.5% for the group with drainage alone and 20% for the group with drainage and irrigation, showing no significant difference. Zakararia et al. [2] demonstrated recurrence rates of 14.3% in the drainage group and 10% in the drainage with irrigation group, again showing no significant difference. Kuroki et al. [11] reported recurrence rates of 1.8% with drainage alone and 11.1% with drainage and irrigation. The recurrence rate was significantly lower for drainage alone than for drainage with irrigation. In the present study, although no statistical difference was noted between groups, the recurrence rate was 3-fold higher in drainage alone (10.3%) than in drainage with irrigation (2.9%, p=0.191) (Table1 1-2). The present findings thus support the efficacy of irrigation followed by drainage for the treatment of CSDH with a lower recurrence rate.

The present study was a non-randomized, retrospective study. Therefore, the authors could not deny the possibility of bias in selection of surgical technique. It is conceivable that patients in Group A might have been selected for treatment with drainage alone rather than drainage with irrigation because of poorer clinical conditions, as drainage without irrigation is

simpler and quicker than drainage with irrigation.

As the subject cohort in this series was insufficient to reach definitive conclusions regarding the optimal surgical technique for CSDH, investigations using a larger group of patients are needed to confirm these preliminary data.

CONCLUSION

These results indicate that burr hole drainage with irrigation has a significantly stronger association with good outcomes compared to drainage alone, and could be a reliable and effective operative method for the treatment of CSDH with a lower recurrence rate.

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