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CASE REPORT Open Access

Development of microscopic polyangiitis-related pulmonary fibrosis in a patient with autoimmune pulmonary alveolar proteinosis

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Abstract

Background: Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disease caused by the autoantibody against granulocyte-macrophage colony stimulating factor (GM-CSF). The clinical course of aPAP is variable; in severe cases, patients develop lethal respiratory failure due to pulmonary fibrosis. However, the pathogenesis of pulmonary fibrosis in aPAP has never been delineated.

Case presentation: Here, we describe a rare case of aPAP that was subsequently complicated by microscopic polyangiitis-related pulmonary fibrosis. The patient was a 75-year-old Japanese man diagnosed with aPAP based on the crazy-paving appearance on high-resolution computed tomography (HRCT), "milky" appearance of broncho-alveolar lavage fluid (BALF), and elevated serum levels of the anti-GM-CSF antibody. The patient was followed-up without aPAP-specific treatment for 3 years. During this period, both hematuria and proteinuria appeared; in addition, serum myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA) turned positive and increased markedly. The second BAL performed one year after the diagnosis, showed that the "milky" appearance had resolved. The HRCT showed that fibrotic changes had developed and that the crazy-paving appearance had disappeared. These data suggest an association between pulmonary fibrosis that developed during the natural course of aPAP and ANCA-related systemic vasculitis.

Conclusion: This is the first case report that suggests the existence of a pathogenetic relationship between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis. The link between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis requires further investigation.

Keywords: Pulmonary alveolar proteinosis, Pulmonary fibrosis, Myeloperoxidase antineutrophil cytoplasmic antibody

Background

Autoimmune pulmonary alveolar proteinosis (aPAP), which causes 90% of all PAP cases, is an autoimmune disease caused by the presence of an autoantibody against granulocyte-macrophage colony stimulating factor (GM-CSF) [1]. The suppression of GM-CSF signaling by anti-GM-CSF autoantibody disrupts the surfactant catabolism, resulting in the accumulation of surfactant lipids and proteins in pulmonary alveolar macrophages and alveoli. The clinical course of aPAP is variable. In the contemporaneous cohort of 223 Japanese aPAP patients, 3 patients (1.4%) were complicated by severe respiratory failure due to pulmonary fibrosis [2]. And so far, there have been, at least, 5 case reports, which highly suggested the pathogenetic relationship between aPAP and pulmonary fibrosis [3-7].

The pathogenesis of pulmonary fibrosis in aPAP is unknown. It has been hypothesized that the retention of lipoproteinaceous material in the alveoli, silica exposure, and/or superimposed pulmonary infections induces damage to cells lining the alveoli and causes pulmonary fibrosis in aPAP patients [5]. In rats, the

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overexpression of GM-CSF in the lung by adenovirus-vector leads to pulmonary fibrosis, suggesting an inconclusive relationship between GM-CSF therapy and pulmonary fibrosis in patients with aPAP [8].

Anti-neutrophil cytoplasmic antibody (ANCA) is a sensitive and specific marker for ANCA-associated systemic vasculitis, as observed in granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), "idiopathic" necrotizing crescentic glomerulonephritis and allergic granulomatous angiitis [9]. In vitro and in vivo studies provide compelling evidence that ANCA play a critical role in the pathogenesis of ANCA-associated systemic vasculitis [10]. Pulmonary fibrosis due to alveolar capillaritis is a common complication in ANCA-associated systemic vasculitis. However, ANCA-related pulmonary fibrosis has never been reported in association with aPAP.

Case presentation

A 75-year-old Japanese man, who self-identified as a chronic smoker (30 pack-years), was referred to our hospital because of a cough, which had been continued for 2 months, and an abnormal chest X-ray. He had no significant past medical history. He was an owner of a liquor shop and had no prior exposure to harmful dust. The physical examination revealed fine crackles bilaterally over the lower lung. The laboratory findings showed elevated levels of lactate dehydrogenase (376 U/L; normal range, 120-242), Krebs von den Lungen-6 (17330 U/mL; normal range, 0-500), surfactant protein-D (293.0 ng/mL; normal range, 0–110), carcinoembryonic antigen (12 ng/mL; normal range, 0–5.0), and CYFRA21.1 (cytokeratin-19 fragments) (26.5 ng/mL; normal range, 0–20.0) in the serum. Serum antinuclear antibody titer was 1:40 (normal range, <1:40), and myeloperoxidase (MPO)-ANCA testing was negative. The chest X-ray showed diffuse bilateral ground-glass opacities, and high-resolution computed tomography (HRCT) showed a crazy-paving appearance (Figure 1A). Bronchoscopy was performed; the broncho-alveolar lavage fluid (BALF) from the left lingura (B^5) showed a

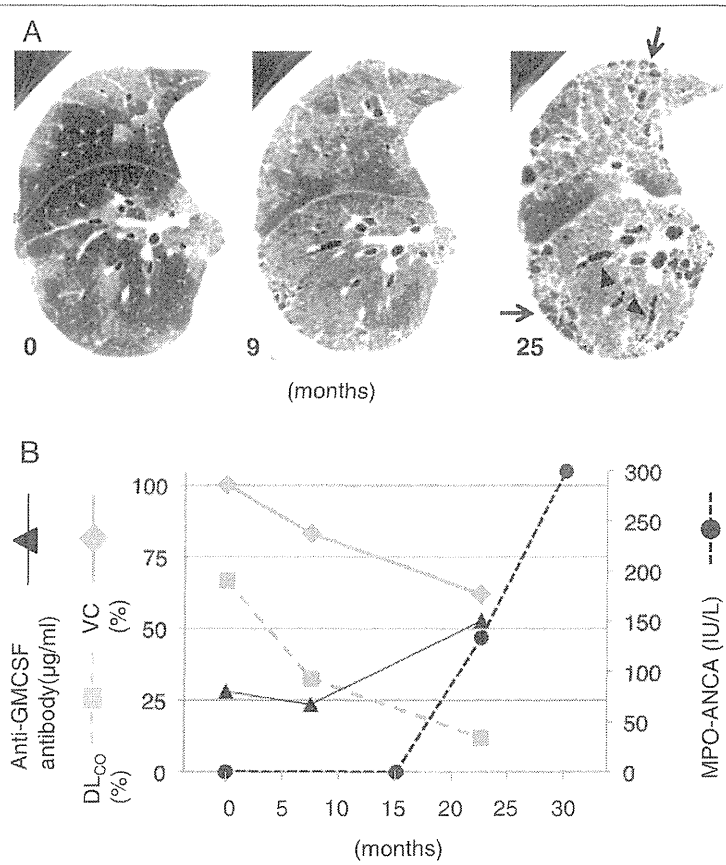

Figure 1 During the clinical course of aPAP in this patient, HRCT images showed increased evidence of pulmonary fibrosis: reticular opacity (arrows) and traction bronchiectasis (arrowheads). (A) Serum MPO-ANCA testing became positive and then increased significantly (circle), while the results of pulmonary function tests, including vital capacity (VC, diamond) and CO diffusing capacity (DLCO, square), deteriorated. Serum anti-GM-CSF antibody concentrations kept high and increased **(B)**.

typical "milky" appearance. The total cell count in BALF was 320/μL. Differential cell count revealed 50% alveolar macrophages, 36% lymphocytes, 12% neutrophils, 2% eosinophils. Pathological examination of a transbronchial lung biopsy sample revealed periodic-acid-Schiff stain-positive material along the alveolar wall. After the serum anti-GM-CSF autoantibody concentration (28 μg/mL; normal range, <0.5) was confirmed and the comorbidity of hematological diseases, such as chronic myelocytic leukemia, myelodysplastic syndrome, or monoclonal gammopathy of undetermined significance, were excluded, the patient was diagnosed with aPAP.

Because the patient refused any specific treatment for aPAP, including whole-lung lavage and GM-CSF inhalation therapy, he was followed in the outpatient department. Nine months later, his cough had worsened and he began to experience dyspnea upon exertion, which was classified using the modified Medical Research Council Dyspnea Scale (mMRC) as grade 2. The chest HRCT obtained at this visit showed that the crazy-paving pattern had been replaced by fibrotic changes, i.e., subpleural honeycombing and traction bronchiectasis (Figure 1A). In contrast to the results obtained at the time of diagnosis, the BALF was transparent, without a "milky" appearance. Serum anti-GM-CSF autoantibody concentration was 23.5 μg/mL. Surprisingly, serum MPO-ANCA testing was positive (134 IU/L) and subsequently continued to rise (Figure 1B). In accordance with the fibrotic changes seen on HRCT images, the patient's respiratory failure had worsened since diagnosis (Figure 1B). The patient also showed signs of hematuria and proteinuria. Although neither kidney nor lung biopsies were performed because of the patient's general condition, the findings presented above met the most recent criteria for MPA [11]. Because the patient refused steroid and immunosuppressant treatment, he has been followed-up for MPA without any specific therapy.

Many studies have shown that ANCA production is key to the pathogenesis of MPA. ANCA is known to activate neutrophils and allow their accumulation at the endothelial portion of a vasculitic lesion [12]. ANCA is also an excellent diagnostic marker of MPA with specificity of 96.3-99.1% [13]. Based on these findings, the European League against Rheumatism and the American College of Rheumatology established new criteria that emphasized serum ANCA in the diagnosis of MPA [14]. A new criterion of MPA, proposed by Watts, lays more emphasis on the role of ANCA in MPA diagnosis, wherein histopathological signs of vasculitis are not essential for the diagnosis [11]. Our case met these criteria due to the patient's high level of MPO-ANCA and the associated urinary findings.

There are several reports of pulmonary fibrosis that developed in patients with aPAP. In these cases, as in ours, the features of PAP disappeared as pulmonary fibrosis progressed [5,7]. As Luisetti et al. mentioned, it is not possible for us to exclude that some subjects diagnosed with diffuse fibrotic lung disease actually represented the end-stage evolution of a previous pulmonary alveolar proteinosis process [7]. If a patient's BALF or HRCT does not show a typical PAP appearance at the time of admission, serum GM-CSF autoantibody is not usually measured. Thus, the link between PAP and pulmonary fibrosis must be explored. In this report, we suggest the role of ANCA-associated systemic vasculitis in the pathogenesis of aPAP-related pulmonary fibrosis. We sought to verify the existence of ANCA-associated systemic vasculitis in patients with aPAP-related pulmonary fibrosis, because in these cases, steroids or immunosuppressants (including rituximab) that are not usually used for the treatment of aPAP may be effective for the treatment of pulmonary fibrosis [15]. There is one reported case of secondary PAP with high levels of MPO-ANCA [16]. Further research will be necessary to elucidate the link between aPAP and ANCA-associated systemic vasculitis. Serum ANCA levels should be examined in cases of aPAP complicated by pulmonary fibrosis.

It is generally thought that autoimmune diseases are induced by dysfunctional immunotolerance to self-antigens due to genetic as well as environmental factors [17]. Clinical evidence shows that the coexistence of autoimmune diseases within an individual (i.e., polyautoimmunity) is not uncommon, suggesting that these autoimmune diseases have a common genetic or environmental root [18]. It is also reported that aPAP sometimes accompanies other systemic or organ-specific autoimmune diseases. Seymour et al. reviewed 410 cases of PAP and reported seven cases (1.7%) with coexisting autoimmune disorders or positive autoimmune serology (rheumatoid arthritis, two cases; anti-smooth muscle antibody positive, two cases; multiple sclerosis, one case; IgA nephropathy, one case; and celiac disease, one case) [19]. Inoue et al. reported three cases among 212 patients with aPAP that were complicated by other autoimmune diseases including polymyalgia rheumatica, GPA, and autoimmune hemolytic anemia [2]. Whether the coexistence of aPAP and ANCA-associated systemic vasculitis in our case was anecdotal or due to shared underlying mechanisms remains to be elucidated. However, it is known that air pollution and/or infections sometimes overwhelm immunotolerance to MPO, even in healthy individuals [20]. Owing to their genetic tendency toward autoimmune disease and the altered immunologic milieu in their lungs, aPAP patients might be prone to developing an autoimmune reaction to MPO, triggered by an unknown environmental factor.

Conclusion

Previous research has not succeeded in explaining why pulmonary fibrosis occurs in patients with aPAP, or how we should treat this complication, which is often associated with a poor prognosis. This is the first case report to suggest a pathogenetic relationship between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis. The link between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis must be explored with further research.

Consent

Because the patient passed away due to the progression of respiratory failure, written informed consent was obtained from the patient's wife for publication of this case report and any accompanying images. A copy is available for review by the Editor of this journal.

Abbreviations

aPAP: Autoimmune pulmonary alveolar proteinosis; GM-CSF: Granulocyte-macrophage colony stimulating factor; HRCT: High-resolution computed tomography; BALF: Broncho-alveolar lavage fluid; MPO: Myeloperoxidase; ANCA: Anti-neutrophil cytoplasmic antibody; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YK, HK, and YI analyzed and interpreted the patient's data and drafted the manuscript. MH performed the ELISA for anti-GM-CSF antibody. AN, YT, YH, KF, HH, KI, TM, IN, YT, TF, TK, and AK revised the clinical data and supervised drafting of the case report. All authors read and approved the final manuscript.

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Effects of Remifentanil on In-Hospital Mortality and Length of Stay Following Clipping of Intracranial Aneurysm: A Propensity Score-matched Analysis

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Background: Remifentanil is an ultrashort-acting μ-opioid receptor agonist and is especially suitable for neuroanesthesia. We previously reported that general anesthesia with remifentanil for brain tumor resection was associated with lower postoperative mortality and shorter postoperative length of stay (LOS) when compared with surgeries without remifentanil. This phenomenon may also exist during clipping of intracranial aneurysms (ICAs), where brain tissue frequently suffers ischemia and reperfusion injury. We performed a propensity score-matching study to compare in-hospital mortality and postoperative LOS with and without remifentanil in such patients.

Methods: We used the Diagnosis Procedure Combination inpatient database in Japan that includes 926 acute care hospitals to identify patients who underwent clipping of ICAs under general anesthesia between July and December 2007.

Results: Of the 4502 patients who underwent ICA clipping, 1380 propensity-matched pairs (n = 2760) were included for outcome comparison. The remifentanil group had significantly lower in-hospital mortality than the nonremifentanil group (4.2% vs. 7.7%; $P < 0.001$). Use of remifentanil was an independent factor for lower in-hospital mortality (odds ratio = 0.52; 95% confidence interval, 0.37-0.74; $P < 0.001$). By contrast, postoperative LOS did not differ significantly between the 2 groups. There was no difference in the occurrence of postoperative complications except for hydrocephalus, which was more common with remifentanil.

Conclusions: This retrospective observational study demonstrated a possible relationship between the use of remifentanil for neuroanesthesia and reduced mortality of patients undergoing clipping of ICAs with open craniotomy. Prospective interventional studies are necessary to confirm this relationship.

Key Words: remifentanil, clipping of intracranial aneurysm, subarachnoid hemorrhage, postoperative mortality, general anesthesia, Diagnosis Procedure Combination, propensity score matching, large administrative claim database

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Remifentanil, a μ-opioid receptor agonist, has a unique pharmacokinetic profile, including a short half-life.[1] The clinical efficiency of remifentanil is especially recognized in neuroanesthesia, where rapid postoperative emergence is often desirable.[2] Using a Japanese nationwide administrative database,[3] we recently reported that general anesthesia with remifentanil is associated with reduced postoperative mortality as well as shorter postoperative length of stay (LOS) compared with fentanyl alone in patients undergoing brain tumor resection.[4] In patients undergoing rectal cancer surgery with intraoperative epidural anesthesia, the above phenomenon was not observed, possibly indicating that the surgical stress response that can be suppressed by epidural anesthesia may affect postoperative outcome. This response may also be efficiently suppressed by remifentanil in neurosurgery, consequently creating better outcomes.[4]

Ruptured intracranial aneurysm (ICA) constitutes 15% of all cerebrovascular accidents, with an incidence of

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> 700,000 cases per year in the United States.[5] Thirty-day mortality is reported to be approximately 45% in the United States[5] and 34% in Japan[6] and half of the survivors suffer irreversible brain damage.[5] Postoperative neurological deficits are common due to factors such as brain retraction, vessel occlusion, and intraoperative hemorrhage,[7] especially in ruptured ICA.

In our previous report, we included patients without any preoperative changes in consciousness (Japan Coma Scale [JCS] = 0),[8] to exclude those with preoperative brain damage/ischemia that may have affected the postoperative outcome.[7] Until now, it was unknown how general anesthesia with remifentanil affects early postoperative outcomes in patients with increased intracranial pressure.

In the present study, we hypothesized that general anesthesia supplemented with remifentanil works favorably to early postoperative outcome in patients undergoing clipping of ICAs. To address this hypothesis, we retrospectively surveyed a large administrative claims database in Japan and applied propensity score-matched analyses to compare factors related to postoperative outcome between remifentanil and nonremifentanil patients who underwent clipping of ruptured/unruptured ICAs.

METHODS

Data Source

The details of the Diagnosis Procedure Combination (DPC) database have been described previously.[3,4,9] Briefly, the DPC is a Japanese case-mix classification system linked with a lump-sum payment system launched in 2002 by the Ministry of Health, Labour, and Welfare of Japan. All 82 academic hospitals in Japan are obliged to use the DPC system, whereas community hospitals can use it voluntarily. In 2007, 926 hospitals, approximately 3 million patients were enrolled in the system that represents about 45% of all inpatient admissions to acute care hospitals in Japan. A survey of DPC-participating hospitals is conducted between July 1 and December 31 annually by the DPC-Research Group, funded by the Ministry of Health, Labour, and Welfare.[10,11]

The database includes the following information: unique identifier for each hospital; age and sex, diagnoses at admission, comorbidities, in-hospital complications recorded using text data in the Japanese language and the International Classification of Diseases 10th Revision codes; medical procedures coded using original Japanese codes; duration of anesthesia (min); list of drug and the dates when it was used; and LOS and discharge status. The level of consciousness at admission for all patients was evaluated using JCS, which is widely used by Japanese clinical facilities including emergency services for assessment of consciousness level. The JCS and the Glasgow Coma Scale are well correlated.[8]

This study was based on a secondary analysis of administrative claims data. Given the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the Institutional Review Board of the Graduate School of Medicine at the University of Tokyo (IRB# 3501).

Patient Selection

From the 3 million inpatients recorded between July 1 and December 31, 2007, we selected patients who underwent clipping of ruptured/unruptured ICA with open craniotomy under general anesthesia. We then selected patients who received fentanyl or remifentanil during general anesthesia and divided them into 2 subgroups: (a) patients who received both remifentanil and fentanyl; and (b) those who received fentanyl alone. We excluded patients who died within 3 days after admission because we suspected that the preoperative brain damage in these patients was so serious that physiological derangement would have occurred, and that this might have led the anesthesia care provider to choose conventional opioids such as fentanyl.[12] Figure 1 shows a diagram illustrating how the patients were included for the analysis.

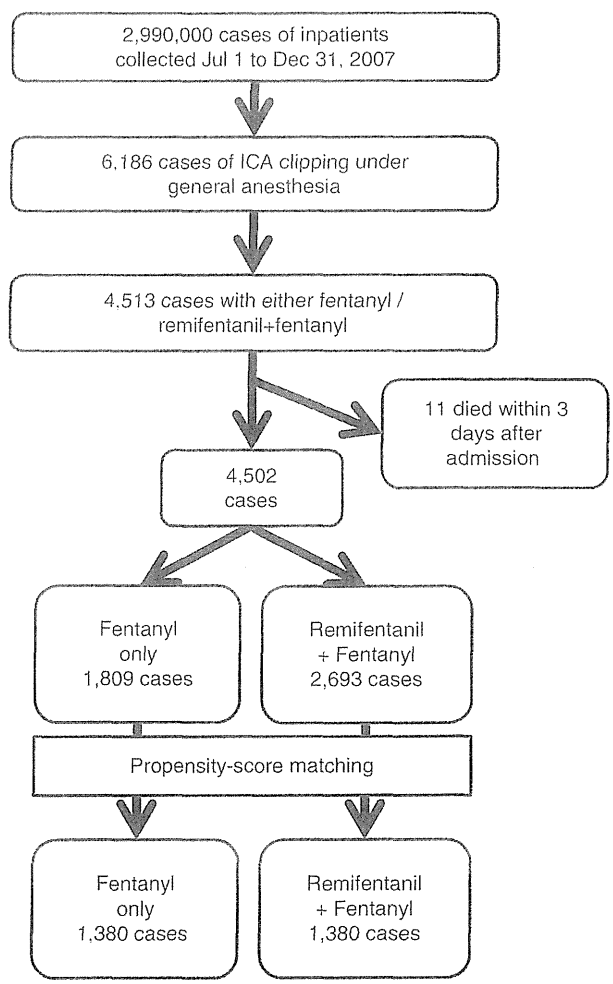

FIGURE 1. Patient inclusions and exclusions. The numbers of patients included/excluded based on each inclusion/exclusion criterion are demonstrated. ICA indicates intracranial aneurysm.

Patient Background Data

Patient background data that could potentially affect the study end points, such as age, sex, and comorbidities, were assessed. The comorbidities were as follows: hypertension, diabetes, chronic heart disease (ischemic heart disease, valvular heart disease, cardiomyopathy, or congenital heart disease), chronic lung disease (emphysema, chronic bronchitis, bronchiectasis, asthma, interstitial lung disease, or pulmonary hypertension), liver cirrhosis, and chronic renal failure. We also evaluated the use of volatile anesthetic agents (sevoflurane, isoflurane, enflurane, or halothane), nitrous oxide, and propofol for each patient. We assessed the type of hospital (academic, nonacademic) and hospital inpatient volumes for ICA clipping, because these factors could potentially affect postoperative outcomes, including mortality.[13] Hospital volumes were determined by the number of ICA clipping procedures performed during the study period, using the unique identifier for each hospital. Numbers of clipping and duration of anesthesia, which may indicate whether surgical difficulties occurred, were included. Use of blood transfusion, which is correlated with intraoperative bleeding, was also included because it affects postoperative outcomes.

For postoperative complications, we extracted postoperative cerebral infarction, cerebrovascular spasm, cerebral hemorrhage, hydrocephalus, pulmonary complications, cardiovascular complications, sepsis, and diffuse intravascular coagulation according to the Japanese text and International Classification of Disease-10 codes in the database.

End Points

The primary end point was in-hospital mortality. Postoperative LOS, postoperative complications including hydrocephalus, brain infarction, and cardiovascular and respiratory complications were assessed as a secondary end point.

Statistical Analysis

As the patients were not randomly assigned to receive remifentanil, we used propensity score matching[11,14] to adjust for differences in baseline characteristics. We applied one-to-one matched analysis on the basis of the estimated propensity scores for each patient. The log odds of the probability that a patient received remifentanil were modeled for potential confounders including age, sex, type of aneurysm (unruptured or ruptured), preoperative consciousness level, number of clippings, preoperative comorbidities (hypertension, diabetes mellitus, chronic lung disease, cardiovascular disease, liver cirrhosis, or chronic renal failure), duration of anesthesia, blood transfusion, type of hospital, and hospital volume. We also included anesthetic agents other than opioids that can affect postoperative recovery, such as nitrous oxide, volatile anesthetics, and propofol. The *C*-statistic for evaluating the goodness of fit was calculated. Each patient who received remifentanil was matched with a patient who did not receive remifentanil with the closest estimated propensity on the logit scale within a specified range (≤ 0.6 of the pooled SD of estimated logits).[11,14]

We compared in-hospital mortality rates and postoperative LOS between the remifentanil and nonremifentanil groups using the χ^2 test and the log-rank test, respectively. The multivariate logistic regression model included age, sex, remifentanil use, and other covariates used for propensity score matching, while also adjusting for clustering of patients within hospitals using a generalized estimating equation.[15]

We compared the proportion of patients discharged from hospital between the subgroups in each covariate using the Kaplan-Meier method and log-rank tests. Cox proportional hazards regression analysis was performed to model the concurrent effects of various factors on the proportion of patients discharged, including age, sex, remifentanil use, and other covariates used for propensity score matching.

We presented odds ratios and 95% confidence intervals (95% CIs) for the logistic regressions and hazard ratios and 95% CIs for the Cox regressions. The threshold for significance was $P < 0.05$. All statistical analyses were conducted using IBM SPSS version 19.0 (IBM SPSS, Armonk, NY).

RESULTS

Of the 3 million inpatients, we identified 6186 ICA clipping procedures performed between July and December, 2007. After inclusion of patients who were administered either fentanyl or remifentanil, we selected 4502 patients who underwent clipping of unruptured or ruptured ICAs under general anesthesia (2693 with both remifentanil and fentanyl and 1809 with fentanyl alone) (Table 1). Using one-to-one propensity score matching, we selected 1380 pairs from the remifentanil and nonremifentanil groups. The *C*-statistic was calculated to be 0.733.

Table 1 shows background data for patients in the remifentanil and nonremifentanil groups who underwent ICA clipping, before and after propensity score matching. Remifentanil was more likely to be used in patients with an unruptured ICA, those with longer duration of anesthesia, and those treated in academic hospitals. Mean hospital volume for clipping was higher in the remifentanil group. Remifentanil was less likely to be used in patients with cardiovascular disease. Before propensity score matching, the proportions of remifentanil patients receiving nitrous oxide or volatile agents were significantly lower than those of nonremifentanil patients, whereas propofol was more frequently used in the remifentanil group than in the nonremifentanil group. After propensity score matching, patient distributions were closely balanced between the remifentanil and nonremifentanil groups.

Table 2 shows the results of χ^2 tests for postoperative in-hospital mortality and log-rank tests for postoperative LOS comparing the remifentanil and nonremifentanil groups. There was a significant difference in in-hospital mortality between the 2 groups (4.2% vs.

TABLE 1. Patient Backgrounds and Use of Volatile Agents

	Before Propensity Score Matching			After Propensity Score Matching		
	Remifentanil and Fentanyl (n = 2693)	Fentanyl Alone (n = 1809)	*P*	Remifentanil and Fentanyl (n = 1380)	Fentanyl Alone (n = 1380)	*P*
Patient background						
Age (mean ± SD)	61.2 ± 11.8	61.8 ± 12.3	0.115	61.7 ± 11.9	61.6 ± 12.3	0.786
Sex (male) (n [%])	915 (34.0)	611 (33.8)	0.889	491 (35.6)	465 (33.7)	0.298
Diagnosis and consciousness level (n [%])						
Unruptured ICA	1289 (47.9)	665 (36.8)	< 0.001	552 (40.0)	538 (39.0)	0.484
Ruptured ICA with JCS grade 0	416 (15.4)	299 (16.5)		232 (16.8)	213 (15.4)	
Ruptured ICA with JCS grade 1	391 (14.5)	334 (18.5)		234 (17.0)	229 (16.6)	
Ruptured ICA with JCS grade 2	294 (10.9)	239 (13.2)		176 (12.8)	184 (13.3)	
Ruptured ICA with JCS grade 3	303 (11.3)	272 (15.0)		186 (13.5)	216 (15.7)	
No. clippings						
1	2277 (86.3)	1561 (84.6)	0.104	1175 (85.1)	1182 (85.7)	0.706
≥ 2	416 (15.4)	248 (13.7)		205 (14.9)	198 (14.3)	
Comorbidities (n [%])						
Hypertension	783 (29.1)	502 (27.8)	0.334	409 (29.6)	396 (28.7)	0.586
Diabetes	121 (4.5)	66 (3.6)	0.164	53 (3.8)	52 (3.8)	0.921
Cardiovascular diseases	78 (2.9)	73 (4.0)	0.037	53 (3.8)	57 (4.1)	0.697
Chronic lung diseases	88 (3.3)	43 (2.4)	0.081	42 (3.0)	39 (2.8)	0.735
Liver cirrhosis	3 (0.1)	2 (0.1)	0.993	2 (0.1)	2 (0.1)	1.000
Chronic renal failure	14 (0.5)	18 (1.0)	0.063	7 (0.5)	12 (0.9)	0.250
Duration of anesthesia (mean ± SD) (h)	6.1 ± 2.4	5.8 ± 2.1	< 0.001	5.9 ± 2.3	5.9 ± 2.2	0.907
Blood transfusion (yes [%])	276 (10.2)	212 (11.7)	0.120	150 (10.9)	160 (11.6)	0.547
Academic hospital (n [%])	647 (24.0)	168 (9.3)	< 0.001	141 (10.2)	162 (11.7)	0.201
Hospital volume for clipping surgery (per 6 mo [mean ± SD])	35.1 ± 49.1	27.1 ± 28.0	< 0.001	27.8 ± 37.9	29.0 ± 30.4	0.366
Use of other anesthetics (n [%])						
Nitrous oxide	264 (9.8)	507 (28.0)	< 0.001	238 (17.2)	271 (19.6)	0.105
Volatile agents	1884 (70.0)	1627 (89.9)	< 0.001	1183 (85.7)	1212 (87.8)	0.103
Propofol	2460 (91.3)	1477 (81.6)	< 0.001	1186 (85.9)	1180 (85.5)	0.744

ICA indicates intracranial aneurysm; JCS, Japan Coma Scale.

7.7%; $P < 0.001$). This phenomenon was observed in patients with ruptured ICAs with worse preoperative level of consciousness (ie, JCS Grade 3). Only 1 in-hospital death occurred among the patients with unruptured ICAs. Postoperative LOS was not significantly different between the 2 groups. The occurrence of postoperative neurological, cardiovascular, pulmonary, and infectious complications did not differ significantly between the

TABLE 2. Comparison of In-Hospital Death and Postoperative Complications by χ^2 Test and Comparison of Postoperative Length of Stay by Log-Rank Test

	Remifentanil and Fentanyl (n = 1380)	Fentanyl Alone (n = 1380)	*P*
In-hospital death (n [%])			
Overall	58 (4.2)	106 (7.7)	< 0.001
Diagnosis and consciousness level			
Ruptured ICA with JCS grade 0	3/232 (1.3)	11/213 (5.2)	0.019
Ruptured ICA with JCS grade 1	19/234 (8.1)	20/229 (8.1)	0.812
Ruptured ICA with JCS grade 2	14/176 (8.0)	25/184 (13.6)	0.086
Ruptured ICA with JCS grade 3	22/186 (11.8)	49/216 (22.7)	0.004
Unruptured ICA	0/552 (0)	1/538 (0.2)	0.311
Postoperative LOS (mean [95% CI]) (d)	37.7 (35.9-39.4)	36.7 (34.9-38.4)	0.433
Postoperative complications (n [%])			
Cerebral infarction	93 (6.7)	113 (8.2)	0.147
Cerebrovascular spasm	117 (8.5)	112 (8.1)	0.730
Cerebral hemorrhage	13 (0.9)	10 (0.7)	0.530
Hydrochephalus	185 (13.4)	150 (10.9)	0.041
Pulmonary complications	90 (6.5)	101 (7.3)	0.409
Cardiovascular complications	23 (1.7)	24 (1.7)	0.883
Sepsis, DIC	17 (1.2)	19 (1.4)	0.737
Postoperative LOS (mean [95% CI]) (d)	37.7 (35.9-39.4)	36.7 (34.9-38.4)	0.433

CI indicates confidence interval; DIC, disseminated intravascular coagulation; ICA, intracranial aneurysm; JCS, Japan Coma Scale; LOS, length of stay.

groups except for hydrocephalus, which was more common in the remifentanil group.

Table 3 shows the results of logistic generalized estimating equation regression analysis of in-hospital mortality following ICA clipping. The remifentanil group had a significantly lower mortality than the nonremifentanil group (odds ratio = 0.52; 95% CI, 0.37-0.74; $P < 0.001$). Greater age and male sex were significantly associated with higher mortality. Worse preoperative consciousness level and intraoperative blood transfusion were also associated with higher in-hospital mortality. Academic hospital and preoperative hypertension were associated with lower mortality. Number of clippings, duration of anesthesia, and hospital volume were not significant predictors for in-hospital mortality. Use of other anesthetic agents including propofol, nitrous oxide, and volatile agents was not significantly associated with in-hospital mortality.

Table 4 shows the results of Cox proportional hazards regression analysis of the proportion of patients discharged from hospital following ICA clipping. Greater age, male sex, diabetes, cardiac disease, chronic renal failure, intraoperative blood transfusion, and longer duration of anesthesia were significantly associated with a lower proportion of discharge. Better preoperative consciousness level and treatment in an academic or high-volume hospital were significantly associated with the higher proportion of discharge. Use of anesthetic agents including remifentanil was not significantly associated with the proportion of patients discharged.

TABLE 3. Logistic Regression Analysis of In-Hospital Mortality

	OR	95% CI	P
Age (y)			
≤49	Reference		
50-59	1.27	0.71-2.28	0.421
60-69	1.64	0.90-2.99	0.105
70-79	1.75	0.94-3.25	0.077
≥80	2.58	1.25-5.32	0.01
Sex			
Male	Reference		
Female	0.61	0.43-0.86	0.004
Comorbidities			
Hypertension	0.65	0.43-0.97	0.035
Diabetes	1.17	0.48-2.85	0.733
Cardiac disease	1.47	0.61-3.56	0.397
Chronic lung disease	1.67	0.87-3.19	0.122
Liver cirrhosis	2.39	0.36-16.00	0.367
Chronic renal failure	2.05	0.56-7.54	0.278
Diagnosis and consciousness level			
Unruptured ICA	0.03	0.01-0.25	0.001
Ruptured ICA with JCS grade 0	Reference		
Ruptured ICA with JCS grade 1	2.85	1.53-5.31	0.001
Ruptured ICA with JCS grade 2	3.53	1.85-6.72	< 0.001
Ruptured ICA with JCS grade 3	5.79	2.98-11.25	< 0.001
Blood transfusion			
No	Reference		
Yes	2.50	1.67-3.75	< 0.001
No. clippings			
1	Reference		
≥2	1.03	0.60-1.77	0.919
Type of hospital			
Nonacademic	Reference		
Academic	0.53	0.29-0.96	0.035
Duration of anesthesia (h)	1.00	1.00-1.00	0.616
Hospital volume (/y)	0.99	0.98-1.00	0.159
Anesthetic agent used			
Fentanyl alone	Reference		
Remifentanil and fentanyl	0.52	0.37-0.74	< 0.001
Nitrous oxide	0.88	0.55-1.41	0.595
Volatile agent	0.70	0.41-1.20	0.200
Propofol	1.12	0.69-1.80	0.655

CI indicates confidence interval; ICA, Intracranial aneurysm; JCS, Japan Coma Scale; OR, odds ratio.

TABLE 4. Cox Regression Analysis of Hospital Discharge

	HR	95% CI	P
Age (y)			
≤49	Reference		
50-59	0.87	0.76-0.98	0.028
60-69	0.72	0.63-0.81	< 0.001
70-79	0.56	0.49-0.64	< 0.001
≥80	0.47	0.38-0.60	< 0.001
Sex			
Male	Reference		
Female	1.10	1.01-1.20	0.024
Comorbidities			
Hypertension	1.00	0.92-1.09	0.968
Diabetes	0.70	0.57-0.87	0.001
Cardiac disease	0.81	0.66-0.99	0.039
Chronic lung disease	0.82	0.64-1.05	0.114
Liver cirrhosis	1.45	0.47-4.54	0.520
Chronic renal failure	0.36	0.21-0.61	< 0.001
Diagnosis and consciousness level			
Unruptured ICA	3.13	2.78-3.52	< 0.001
Ruptured ICA with JCS grade 0	Reference		
Ruptured ICA with JCS grade 1	0.74	0.65-0.85	< 0.001
Ruptured ICA with JCS grade 2	0.63	0.54-0.73	< 0.001
Ruptured ICA with JCS grade 3	0.44	0.38-0.51	< 0.001
Blood transfusion			
No	Reference		
Yes	0.65	0.57-0.75	< 0.001
No. clippings			
1	Reference		
≥2	0.90	0.81-1.01	0.069
Type of hospital			
Nonacademic	Reference		
Academic	1.30	1.15-1.47	< 0.001
Duration of anesthesia (h)	0.91	0.90-0.93	< 0.001
Hospital volume (/y)	1.003	1.001-1.004	< 0.001
Anesthetic agent used			
Fentanyl alone	Reference		
Remifentanil and fentanyl	1.06	0.98-1.14	0.163
Nitrous oxide	1.01	0.91-1.12	0.885
Volatile agent	0.81	0.72-0.91	0.885
Propofol	0.91	0.82-1.02	0.120

CI indicates confidence interval; HR, hazard ratio; ICA, Intracranial aneurysm; JCS, Japan Coma Scale.

DISCUSSION

On propensity score-matched analysis, patients who underwent ICA clipping under general anesthesia with remifentanil had significantly lower in-hospital mortality than those anesthetized without remifentanil, but there was no significant difference in postoperative LOS, or the incidence of postoperative neurological, cardiovascular,

or respiratory complications except for hydrocephalus between the remifentanil and nonremifentanil groups.

Male sex, greater age, blood transfusion, and worse preoperative consciousness level were significantly associated with increased mortality, as in previous publications.[16–18] After adjustment for preoperative and intraoperative variables that are associated with outcome, use of remifentanil was an independent factor for low in-hospital mortality. Mortality was significantly lower in the remifentanil group even in patients with ruptured ICA with preoperative JCS grade 3 (11.8% vs. 22.7%; $P = 0.004$, Table 2), indicating a possible association between the use of remifentanil and lower mortality even in patients with preexisting brain damage and increased intracranial pressure because of rupture of aneurysms.

Limitations

Because our data were based on an administrative claims database, several limitations should be acknowledged and our results interpreted carefully. First, and most importantly, this is a nonrandomized retrospective study. Although we used propensity score matching to adjust for differences in baseline characteristics, the results could have been biased by several unmeasured confounders. For example, no data were available regarding the size and location of aneurysms, or clot thickness evaluated by computed tomography.[18] We did not have commonly used clinical grading scales for subarachnoid hemorrhage in the database such as Hunt & Hess grade, Fisher grade, or World Federation of Neurosurgical Societies grade estimated by GCS combined with the presence of motor deficit that were known to be closely associated with outcome after subarachnoid hemorrhage,[19] although we used JCS that was known to correlate well with GCS.[8] In the present study, worse JCS was significantly associated with higher mortality, confirming the legitimacy of using the JCS for propensity score matching. We also did not have records of surgical procedures that could have affected the patients' outcomes, such as temporary clipping, although we adjusted for the duration of anesthesia because of its presumed association with the surgical difficulty.

Second, we could not evaluate the doses of intraoperative anesthetics and concurrent effects of various other drugs that could potentially have affected the postoperative outcomes. Although our logistic regression analyses for other anesthetics showed that no other agents were significantly contributed to in-hospital mortality, further prospective studies are required to confirm the present results and explore the underlying mechanism behind the better postoperative outcome observed in the remifentanil group.

Third, we could not completely exclude the possibility that outcome was associated with individual anesthesia care providers' choices made according to their patients' preoperative physiological status. In the present study, we adjusted preoperative cardiovascular comorbidities between groups. However, we should be aware of other factors that could not be extracted from the present data set. For example, one may not choose remifentanil for those patients with serious physiological derangement due to lethally increased intracranial pressure. We excluded those who died within 3 days postoperatively before propensity score matching. Even if we included these patients in the analysis, results were not altered. Postoperative neurological, cardiovascular, pulmonary, and infectious complications did not differ significantly between groups except for hydrocephalus, which was more common in the remifentanil group. This observation indicates that preoperative and intraoperative physical status may not be significantly different between groups and cannot solely account for postoperative complications or mortality.

Fourth, our propensity score matching was based on complete pooling of the characteristics information across hospitals, which might have caused residual confounding by the site effect. We did not use the nonpooling approach (ie, matching patients in each hospital) because of the paucity of data available to support the propensity score estimation within each hospital alone.

Fifth, choice of drug may be somewhat correlated with quality of care, which may affect postoperative outcome. Generally, nitrous oxide is recognized as harmful to brain in neurosurgery, especially for those with increased intracranial pressure[20] (although recent studies had conflicting results[21,22]) and its use may represent inferior care that is associated with increased mortality. In our present data set, use of nitrous oxide was not associated with mortality. Similarly, those who did not choose to use remifentanil might have given poor intraoperative and postoperative care to the patients, which might have contributed to the poor outcomes. In the present study, hospital volume for ICA clipping had no significant effect on postoperative mortality. Besides, the remifentanil group did not show significant improvement in postoperative LOS and mortality among patients who underwent rectal cancer surgery extracted from the same database.[4] However, we should be aware of this possible bias, which cannot be excluded.

Speculations on the Neuroprotective Mechanisms of Remifentanil

There are a number of previous papers that describe the physiological/biochemical factors that could affect postoperative outcome for patients undergoing ICA clipping that may be modulated by the use of remifentanil. These include the suppression of stress-related endocrine responses, hyperglycemia, and inflammation.

Hyperglycemia in SAH is known to be associated with worse outcomes.[23,24] General anesthesia with remifentanil may suppress further increases in blood glucose during surgery[25,26] that could damage intact as well as ischemic neurons. Remifentanil with propofol suppresses intraoperative increases in blood glucose during craniotomy.[27]

Several lines of evidence indicate that remifentanil strongly suppresses surgical stress-related endocrine responses compared with fentanyl-based or sevoflurane

anesthesia.[25,26] This effect of remifentanil persists into the early postoperative period[25,28,29] and may serve better postoperative recovery.

In addition, several publications also suggest that remifentanil may suppress inflammatory reactions after surgical insults in rats,[30] mice,[31] and humans.[32] Systemic inflammation is known to be associated with worse postoperative outcomes[33] and suppression of postoperative inflammatory reactions in general anesthesia with remifentanil might be associated with better outcomes.

Furthermore, the use of remifentanil may provide better brain conditions for surgery. Opioids including fentanyl and remifentanil do not have any effects on carbon dioxide reactivity or intracranial pressure,[34,35] whereas volatile anesthetics contribute to brain swelling by their vasodilatory effect.[36] Remifentanil patients might be exposed to smaller amounts of volatile anesthetics than nonremifentanil patients and this may help to avoid brain swelling, which may be deleterious to the brain when intracranial pressure is increased due to SAH.[36,37]

In our previous report, remifentanil use was associated with shorter LOS in patients undergoing brain tumor resection without preoperative disorders in consciousness.[4] However, in the present study, use of remifentanil was not significantly associated with shorter LOS although preoperative and intraoperative factors associated with increased mortality were also associated with greater LOS. One possible reason for the present results is that there were more survivors among remifentanil patients than among nonremifentanil patients. Those patients were suspected to have greater brain damage and may have required prolonged intensive care. ICA clipping accompanied by decompression craniotomy required patients to stay in hospital until further surgery to repair their skull defect. These factors may have contributed to diminishing the difference in early postoperative recovery between the 2 groups. After surgery, patients may receive hypnotics/narcotics other than remifentanil for sedation and that can mask differences in recovery. Prolonged postoperative use of hypnotics is reported to be a cause of postoperative cognitive impairment.[38] Besides, generally longer postoperative LOS in Japan than in the United States due to differences in health care delivery systems[39] may also mask differences in patients' postoperative early recovery.

The above descriptions are speculations and based on the limitations described earlier, we should be prudent to make any definitive statement from the present study that may change our regular clinical practice before obtaining other prospective studies that confirm our present results.

CONCLUSIONS

In conclusion, this propensity score-matched retrospective survey in Japan indicates a possible association between remifentanil use and less postoperative mortality in patients undergoing clipping of ICAs. The present data should be confirmed by other prospective investigations before reaching any conclusions that could change our clinical practice.

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Section Editor: Avery Tung

The Effects on Gastric Emptying and Carbohydrate Loading of an Oral Nutritional Supplement and an Oral Rehydration Solution: A Crossover Study with Magnetic Resonance Imaging

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BACKGROUND: Preoperative administration of clear fluids by mouth has recently been endorsed as a way to improve postoperative outcomes. A carbohydrate-containing beverage supplemented with electrolytes or proteins may have additional benefits for patients' satisfaction. However, effects on gastric residual, nausea, and emesis and the effectiveness of these beverages for improving patients' hydration status have not been well defined.

METHODS: We evaluated changes in gastric volume over time by magnetic resonance imaging, as well as blood glucose levels, before and after administration of 500 mL oral rehydration solution (ORS) containing 1.8% glucose and electrolytes in 10 healthy volunteers. The same volume of an oral nutritional supplement (ONS) containing 18% glucose and supplemental arginine (545 mOsm/kg) was given to the same population using a crossover design.

RESULTS: The mean (median, 95% confidence interval) gastric fluid volume at 1 hour after oral ingestion was 55.0 (55.3, 39.0–70.9) mL in the ORS group, whereas 409.2 (410.9, 371.4–447.0) mL in the ONS group ($P = 0.0002$). The gastric fluid volume of all participants in the ORS group returned to <1 mL/kg at 90 minutes after ingestion, whereas none reached <1 mL/kg at 120 minutes in the ONS group. The ONS group showed a sustained increase in the blood glucose level after ingestion ($P < 0.0001$ to baseline at 30, 60, 120 minutes), while the ORS group showed an initial increase ($P < 0.0001$, $P = 0.01$, $P = 0.205$ at each time point).

CONCLUSIONS: ORS supplemented with a small amount of glucose showed faster gastric emptying, which may make it suitable for preoperative administration. In contrast, ONS supplemented with arginine with a relatively low osmolality was associated with a longer time for gastric emptying, although it showed a sustained increase in blood glucose level. (Anesth Analg 2014;118:1268–73)

During the past decade, based on the assumption that so-called clear fluids should be cleared from the stomach by 2 to 3 hours, several international guidelines[1–4] shortened preoperative fasting periods for clear fluids from overnight (>10 hours) to 2 to 3 hours before induction of anesthesia, though neither a strict formula for clear fluids nor a maximum safe volume for preoperative administration has been determined.

Recently, preoperative administration of fluid supplemented with glucose has even been endorsed to restore dehydration, ameliorate patients' discomfort, and reduce the incidence of postoperative insulin resistance,[5–9] which should improve overall postoperative outcomes. After the announcement of the Enhanced Recovery After Surgery protocol, an additional nutritional supplement in the beverages has been preferred for preoperative use; 400 mL of a 12.5% carbohydrate-containing drink has been shown to be safe in patients undergoing major abdominal surgery.[5,10–14]

Glucose-supplemented oral rehydration solution (ORS) (OS-1®, Otsuka Pharmaceutical Factory, Tokushima, Japan) contains both salts and glucose, and its osmolality is similar to that of serum; it is advocated for hydration purposes, especially for dehydrated patients. The beverage is assumed to be quickly eliminated from the stomach and is preferable for preoperative hydration for patients undergoing surgery. ORS is reported to be safe for preoperative use in the low-risk Japanese surgical population,[15] although the precise performance of ingested beverages in vivo has not been reported.

An arginine-containing oral nutritional supplement (ONS) (Arginaid Water®, Nestle Health Science Company, Tokyo, Japan) is a clear fluid supplemented with 18% glucose, 2% protein including arginine, and 0.008% zinc, and it

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has an osmolality of 545 mOsm/kg. Its calorie (0.8 kcal/mL) and glucose content (18%) are sufficient to fulfill the Enhanced Recovery After Surgery protocol.[16] Arginine facilitates healing from pressure ulcers[17] and from surgical wounds,[18] and it enhances the immunity of trauma patients.[19] Serum zinc decreases after surgery,[20] and zinc supplementation has been reported to be protective in an endotoxemic mouse model.[21] Therefore, perioperative administration of this beverage may help patients recover faster after surgery. However, the relatively higher glucose content and additives such as arginine in the beverage might compromise gastric emptying. There has been a limited number of papers on the efficacy and safety of this beverage in terms of gastric emptying.[22]

Magnetic resonance imaging (MRI) creates high-resolution images that distinguish gastric liquid from air and gastric wall, allowing direct measurement of gastric volume to be determined in real time.[10,23–25]

In the present study, the time course changes in gastric fluid volume (GFV) were evaluated by MRI, and carbohydrate loading efficiency was evaluated by measuring blood glucose levels after the administration of either ORS or ONS to 10 healthy volunteers in a crossover design to validate the efficacy and safety of these 2 beverages for preoperative use.

Methods

Study Design, Setting, and Ethics

The protocol for this randomized, double-blind, crossover study involving healthy volunteers was approved by the Ethics Committee of the Graduate School of Medicine, University of Tokyo (IRB#3476), and it was conducted in accordance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects and with the Ethical Guidelines for Clinical Research issued by the Ministry of Health, Labour, and Welfare in Japan. Written, informed consent was obtained from all participants before enrollment.

Participants

Ten healthy adult men (28–53 years), with no risk factors for delayed gastric emptying (e.g., morbidly obese, diabetes mellitus on medical treatment, past gastrointestinal disorders that required in-hospital treatment) and suitable for MRI scanning (e.g., no metal/implants in the body), were studied. A medical questionnaire was administered before recruitment to confirm the participants' background.

Interventions

Each participant was randomized in a crossover manner to groups ONS (Arginaid Water® Nestle Healthcare Science Company, Tokyo, Japan) or ORS (OS-1®, Otsuka Pharmaceutical Factory, Tokushima, Japan) (Fig. 1). The composition of each test solution is shown in Table 1. Participants were asked to drink 500 mL either OS-1® (ORS group) or Arginaid Water® (ONS group) on 2 separate occasions >5 days apart. Participants were instructed to abstain from alcohol, caffeine, medications, and strenuous exercise after 9:00 PM of the day before examination. They were asked to avoid food after 8:00 AM (>10 hours before ingestion) and beverages after 12 noon on the day of examination (>6 hours before ingestion). The time to ingest test drinks was set at approximately 6:00 PM. Before ingestion, participants' height, weight, and blood glucose levels were measured, followed by MRI scanning. Participants then consumed either beverage poured in paper cups in a sitting position within 3 minutes. MRI scans were done at 30, 60, 90, and 120 minutes after ingestion. Blood glucose levels were measured with the finger-prick method using Medisafe-mini® (Terumo Corporation, Tokyo, Japan) at 30, 60, and 120 minutes after ingestion.

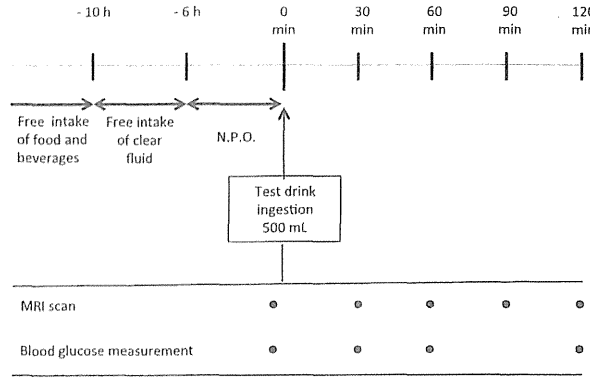

Figure 1. Schematic illustration of the experimental procedures. Closed circles indicate measurement or sampling. All participants in the present study started ingestion of beverages (0 minutes in the schematic) at approximately 6:00 PM.

Table 1. Composition of Each Test Fluid

	ONS-oral nutritional supplement, (Nestle Health Science Company, Arginaid Water®)	ORS-oral rehydration solution, (Otsuka Pharmaceutical Factory, OS-1®)
Energy (kcal/mL)	0.8	0.1
Carbohydrate (%)	18	2.5
Glucose (%)		1.8
Sodium (mEq/L)	0	50
Potassium (mEq/L)	—	20
Magnesium (mEq/L)	—	2
Lactate (mEq/L)	—	31
Chloride (mEq/L)	—	50
Phosphorus (mEq/L)	0.18	2
Zinc (%)	0.008	—
Copper (%)	0.0008	—
L-Arginine (%)	2	—
Osmolality (mOsm/L)	545	270

MRI Studies

All MRI scans were performed on 1.5-Tesla unit (MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany) at the University of Tokyo Hospital by a single professional operator who did not know which beverage was ingested. Each participant was positioned supine in the unit, and a coarse scout scan was taken to locate the position of the abdominal organs. Then, the half-Fourier acquisition single-short turbo spin echo (HASTE) sequence was used to acquire T2-weighed transverse images of the stomach with the following conditions: TE 83 milliseconds, field of view 350 mm, slice width 5 mm, gap width 1.5 mm, image matrix 205 × 256. Twenty-eight slices

were taken at each time point under a single breath-hold for 19.6 seconds.

All images were transferred to a personal computer in DICOM format and viewed to locate the gastric lumen and GFV. An example of a series of images throughout the abdomen from 1 participant is shown in Figure 2. The liquid content in the stomach in each slice was manually outlined as the area of interest using Osirix imaging software (Pixmeo SARL, Bernex, Switzerland) (Version 4.0, downloaded from: http://www.osirix-viewer.com) by 1 investigator blinded to the ingested beverages. The volume of gastric content was obtained by summing the volumes calculated from each slice; the area of interest in each slice was multiplied by the thickness of each slice.

End Points and Sample Size

The primary end point of the study was the remaining GFV at 60 minutes after oral ingestion measured on MRI. Secondary end points included blood glucose at each time point.

Based on the previous report by Lobo et al.,[10] the mean difference in GFV 60 minutes after oral ingestion was anticipated to be 80 mL, with a standard deviation (SD) of 50 mL, between groups ONS and ORS. Assuming an α error of 0.05 and a power of 90%, the sample size was calculated to be 10 per beverage.

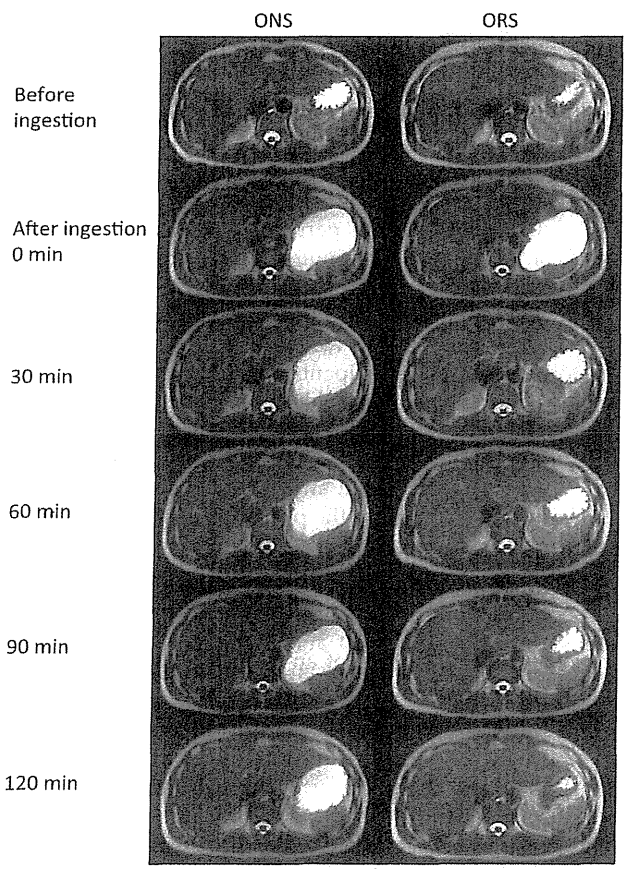

Figure 2. Sequential axial magnetic resonance imaging scans in 1 participant before and after ingestion of the drink. ONS = oral nutritional supplement (Arginaid Water ®); ORS = oral rehydration solution (OS-1®).

Statistical Analysis

All results are expressed as medians (interquartile range; IQR) except where noted. The Wilcoxon rank-sum test was used to compare differences of GFV at 60 minutes after ingestion between groups and blood glucose at each time point. Two-tailed *P*-value of 0.05 indicated significance for GFV at 60 minutes. Corrected *P*-value of 0.0125 was applied to indicate statistical significance for blood glucose at each time point to avoid a type I error for multiple comparisons between groups. The time course differences in blood glucose levels were compared using Dunn test with the pre-ingestion value as the control. Statistical analysis was done with JMP Pro v 9 for Macintosh (SAS Institute Inc., Cary, NC).

RESULTS

All volunteers were men. The median (IQR) age, weight, height, and body mass index of the 10 volunteers were 31.5 (27.8–34.3) years, 64.5 (61–70) kg, 169.5 (166.8–174.5) cm, and 21.9 (21.1–24.9) kg/m^2, respectively. No participant had underlying medical problems known to delay gastric emptying. All participants completed serial studies with 2 beverages, and no side effects were observed.

The fasting period and residual gastric volume before entering the study did not differ significantly between the groups: 6.5 (6.50–6.54) hours vs 6.5 (6.4–7.0) hours (P = 0.587), and 15 (8.3–38.2) mL vs 10.4 (6.1–23.3) mL (P = 0.4055) in the ORS and ONS group, respectively.

The GFV

After ingestion of the test drinks, the ORS group showed an immediate decrease in GFV, with less intersubject variation (Fig. 3A). GFV of all participants reached <1 mL/kg at 90 minutes (Fig. 4). In contrast, the ONS group showed varied patterns in decreasing GFV among participants (Fig. 3B). GFV did not reach <1 mL/kg at 120 minutes after ingestion in any participant (Fig. 4). The remaining GFV at 60 minutes was significantly higher (P = 0.0002) in the ONS group

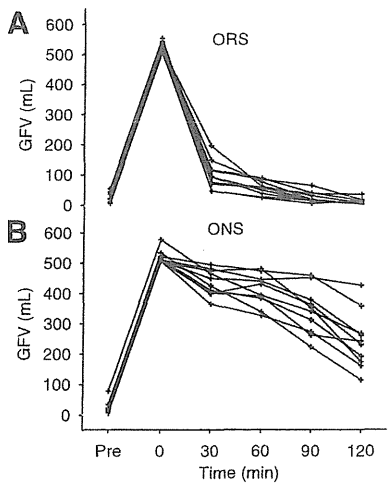

Figure 3. Individual residual gastric fluid volumes before and after ingestion (0, 30, 60, 90, and 120 minutes). A: ORS = oral rehydration solution. B: ONS = oral nutritional supplement. Individual gastric fluid volume kinetics is shown with symbols connected with solid lines. Volume at 0 minutes is the sum of the ingested volume (500 mL) and gastric fluid volume before ingestion. The gray line indicates gastric fluid volume as 0 mL. GFV = gastric fluid volume.

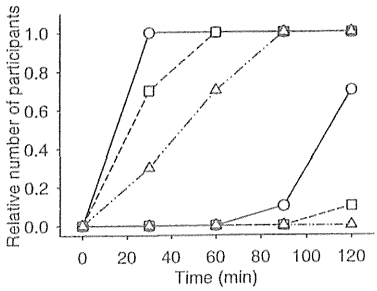

Figure 4. Cumulative fraction of participants (*n*/10) with body weight-corrected gastric fluid volume (GFVw) at each time point after oral fluid ingestion. Open symbols = oral nutritional supplement (Artinaid Water®); Gray symbols = oral rehydration solution (OS-1®); Circles = GFVw <50% of corresponding maximum GFVw after ingestion; Squares = GFVw <2 mL/kg; Triangles = GFVw <1 mL/kg. The gray dotted line indicates fraction 1.0.

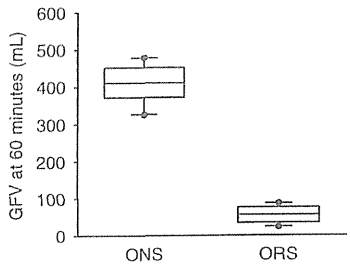

Figure 5. Residual gastric fluid volume (GFV) at 60 minutes after oral ingestion. Box plot of gastric residual volume for either oral nutritional supplement (ONS; Arginaid Water®) or oral rehydration solution (ORS; OS-1®) at 60 minutes after oral ingestion. Each vertical box with error bars represents 10th, 25th median and 75th and 90th percentile of GFV in each group. Closed dots indicate maximum and minimum GFV.

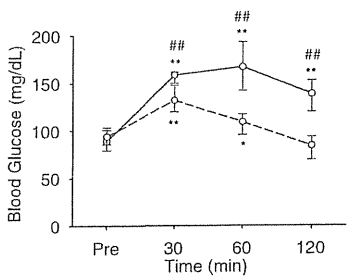

Figure 6. Blood glucose levels in the 2 groups. Open circles = oral nutritional supplement; Gray circles = oral rehydration solution. **P* = 0.01 to baseline, ***P* < 0.0001 to baseline (i.e. before ingestion), ##*P* < 0.001 between 2 groups at the same timepoint (*P* = 0.0009, 0.0003, and 0.0002, at 30, 60, and 120 minutes, respectively).

(410.9, 371.2–451.6 mL, 95% confidence intervals (CIs) of means (95% CI, 371.4–447.0 mL) than in the ORS group (55.3, 34.1–76.6 mL, 95% CI, 39.0–70.9 mL) (Fig. 5).

Blood Glucose Levels

Baseline blood glucose levels before drink ingestion were 94 (85.8–103.5) mg/dL in the ORS group and 89 (79.3–100.8) in the ONS group, with no significant difference between groups ($P = 0.7618$). At 30 minutes after ingestion, blood glucose levels increased significantly in both groups compared with baseline ($P < 0.0001$). Blood glucose levels in the ORS group subsequently decreased and returned to baseline by 120 minutes ($P = 0.205$), whereas they remained significantly higher during the observation period in the ONS group ($P < 0.0001$ at 30, 60, 120 minutes). The ONS group showed significantly higher blood glucose levels than the ORS group throughout the observation period ($P = 0.0009$, 0.0003, 0.0002, at 30, 60, 120 minutes, respectively) (Fig. 6).

DISCUSSION

In the present study, precise MRI-based evaluation of remaining gastric fluid contents after oral administration of ORS showed quicker emptying with small variation among participants, while the ONS group showed delayed and variable emptying. Blood glucose levels were significantly increased in both groups, with sustained elevation in the ONS group.

The rate of transfer of fluid-containing nutrients from the stomach to the duodenum is reported to be 1.5–3 kcal/min,[26] and the present results of 1.9 kcal/min for the ONS group were within that range. Vist and Maughan[27] reported a mean ± SE half gastric emptying time of 600 mL (approximately 8 mL/kg) of a beverage with 18.8% glucose as 64 ± 8 minutes with lower osmolality (237 mOsm/kg) and as 130 ± 18 minutes with higher osmolality (1300 mOsm/kg) for healthy men volunteers. In the present study, 6 of 10 participants cleared half of the ingested 500 mL ONS with 18% glucose and an osmolality 545 mOsm/kg between 90 and 120 minutes (Fig. 4), which indicates that the clearance of ONS used in the present study was close to the high osmolar beverage in Vist and Maughan's report. Proteins in the ONS should stimulate intraluminal gastrin release[28] and increase gastric secretion significantly,[29] which may further increase GFV. Seven of 10 participants cleared >250 mL gastric content within 120 minutes, and that coincides with the carbohydrate-containing drink with the same calorie content (200 kcal).[10] Therefore, we anticipated that having patients drink 250 mL ONS would be safe for preoperative use. However, 2 of 10 participants could clear up to only 160 mL ONS, and clinicians should therefore be aware of the individual variation in gastric emptying when giving ONS. There are other beverages categorized as clear fluids that have a carbohydrate content and osmolality that are similar to those of ONS used in the present study.[30] It is recommended that the gastric emptying time of these beverages be individually evaluated to provide safe preoperative use.

In contrast to the ONS group, the ORS group showed faster gastric clearance. Vist and Maughan[27] reported the time required to clear half of an isotonic (230 mOsm/kg) glucose solution (4%) as 17 ± 1 minutes, and ORS in the present study showed similar results. Minimal individual variation between groups supports the notion that ORS might be suitable for quick passage from the stomach to the duodenum and ileum.

In Nygren's[5] report, blood glucose increased to 162 ± 7.2 mg/dL 40 minutes after ingestion of 400 mL carbohydrate-rich drink (285 mOsm/kg, 12.0% carbohydrate = 48 g, 0.46 mg/mL sodium). The 48 g carbohydrates led to an increase in insulin sufficient to fully depress hepatic glucose

production.[31] In the present study, 8 of 10 volunteers in the ONS group had blood glucose levels similar to those of the carbohydrate-rich drink group in Nygren's report. Therefore, ONS ingestion may be effective for reversing participants' metabolic status to the fed state.

Limitations of the Present Study

In the present study, the participants were healthy, relatively young (33 ± 7.6 years), Japanese men. Although the present results duplicate those of previous reports from Western countries, applying the present results to women,[10,32,33] children, older patients, and other ethnic groups should be done with caution. Special care should also be taken with patients with other comorbidities related to delayed gastric motility.

It is important to note that one cannot simply extrapolate the present data to patients before surgery, since patients have a certain degree of anxiety that may disturb rapid fluid clearance from the stomach, although that may not affect gastric emptying time.[5]

Effects of circadian rhythm should also be considered since the present study was done in the evening, whereas most preoperative patients undergo anesthesia in the morning. Although gastric fluid clearance rate is reported to be unchanged between morning and evening,[34] the insulin response to orally administered glucose is generally slower and delayed in the evening.[35]

Conclusions

In conclusion, glucose-supplemented ORS showed faster gastric emptying, which may make it suitable for preoperative administration without increasing the risk of GFV. In contrast, ONS supplemented with arginine with a relatively low osmolality was associated with a longer time for gastric emptying although it showed a sustained increase in blood glucose level that may reverse patients' metabolic status to the fed state. The use of preoperative oral fluids supplemented with glucose and protein should be tailored to each patient's specific needs and based on the safety profile in that patient population.

DISCLOSURES

Name: Makoto Nakamura, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Makoto Nakamura has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Kanji Uchida, MD, PhD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Kanji Uchida has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Masaaki Akahane, MD, PhD.
Contribution: This author helped design and conduct the study and write the manuscript.
Attestation: Masaaki Akahane has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Yasushi Watanabe.
Contribution: This author helped design and conduct the study.
Attestation: Yasushi Watanabe has seen the original study data and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
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Contribution: This author helped design the study and write the manuscript.
Attestation: Kuni Ohtomo has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Yoshitsugu Yamada has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Research paper

A standardized blood test for the routine clinical diagnosis of impaired GM-CSF signaling using flow cytometry

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ABSTRACT

Impaired signaling by granulocyte/macrophage-colony stimulating factor (GM-CSF) drives the pathogenesis of two diseases (autoimmune and hereditary pulmonary alveolar proteinosis (PAP)) representing over ninety percent of patients who develop PAP syndrome but not a broad spectrum of diseases that cause PAP by other mechanisms. We previously exploited the ability of GM-CSF to rapidly increase cell-surface CD11b levels on neutrophils ($CD11b_{Surface}$) to establish the CD11b stimulation index (CD11b-SI), a test enabling the clinical research diagnosis of impaired GM-CSF signaling based on measuring $CD11b_{Surface}$ by flow cytometry using fresh, heparinized blood. (CD11b-SI is defined as GM-CSF-stimulated- $CD11b_{Surface}$ minus unstimulated $CD11b_{Surface}$ divided by unstimulated $CD11b_{Surface}$ multiplied by 100.) Notwithstanding important and unique diagnostic utility, the test is sensitive to experimental conditions that can affect test performance. The present study was undertaken to optimize and standardize CD11b-SI test for detecting impaired GM-CSF signaling in heparinized human blood specimens from PAP patients. Results demonstrated the test was sensitive to choice of anticoagulant, pretesting incubation on ice, a delay between phlebotomy and test performance of more than one hour, and the concentration GM-CSF used to stimulate blood. The standardized CD11b-SI test reliably distinguished blood specimens from autoimmune PAP patients with impaired GM-CSF signaling from those of health people with normal signaling. Intra-subject differences were smaller than inter-subject differences in repeated measures. Receiver operating characteristic curve analysis identified a CD11b-SI test result of 112 as the optimal cut off threshold for diagnosis of impaired GM-CSF signaling in autoimmune PAP for which the sensitivity and specificity were both 100%. These results support the use of this standardized CD11b-SI for routine clinical identification of impaired GM-CSF signaling in patients with autoimmune PAP. The CD11b-SI may also have utility in clinical trials of novel therapeutic strategies targeting reduction in GM-CSF bioactivity now under evaluation for multiple common autoimmune and inflammatory disorders.

1. Introduction

Granulocyte/macrophage-colony-stimulating factor (GM-CSF) is a cytokine with pleiotropic effects on myeloid cells including stimulation of the survival, proliferation, and differentiation myeloid progenitors, as well as augmentation ("priming") of host defense functions of mature macrophages and neutrophils (Lieschke and Burgess, 1992; Condliffe et al., 1998).

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