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Histamine-2 receptor antagonists (H_2RA) may negatively impact ADL assessment in patients on a convalescent rehabilitation ward

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Background/aim: In the convalescent rehabilitation ward, many elderly patients undergo rehabilitation. Histamine-2 receptor antagonists (H_2RA), which is a one of the acid secretion inhibitors, is frequently prescribed for the patients as a peptic ulcer prevention measure. At present, H_2RA are reported as being associated with factors that reduce cognitive function. However, little is known about the relationship H_2RA and rehabilitation outcome. Therefore, this study examined the relationship between H_2RA use and Functional Independence Measure (FIM) gain, which determines rehabilitation outcomes for patients admitted to the convalescent rehabilitation ward. *Patients and methods:* We retrospectively investigated FIM gain on discharge by both the administration group (H_2RA (+)) (n = 118) and non-administration group (H_2RA (-)) (n = 118). *Results:* The FIM gain scores of Motor FIM total, Cognition FIM total, and Total FIM were significantly lower in H_2RA (+) than in H_2RA (-) (Motor FIM total: 8.0 [4.0-16.0] [Inter-Quartile Range] vs. 12.0 [5.0-19.2], p =0.0217, Cognition FIM total: 3.0 [1.0-6.0] vs. 5.0 [2.0-7.0], p =0.0120, Total FIM: 11.5 [4.8-20.2] vs. 17.0 [8.0-27.0], p =0.0089). *Conclusion:* The administration of H_2RA to elderly patients undergoing rehabilitation may prevent cognitive function maintenance or recovery by rehabilitation.

1. Introduction

In the convalescent rehabilitation ward, intensive rehabilitation is carried out to mitigate the decline in ability to perform activities of daily living (ADL) associated with the sequelae, aiming at home and social reintegration. Diseases that are often targeted for rehabilitation include cerebrovascular diseases and musculoskeletal diseases. In cerebrovascular disease, many administration examples of the acid secretion inhibitors are seen for preventing the reflux of gastric acid by peptic ulcer due to the stress of higher brain dysfunction or dysphagia. There are many pain cases in musculoskeletal disease and nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for pain management, where peptic ulcer development is a concern. Therefore, acid secretion inhibitors are frequently prescribed for patients with convalescent rehabilitation as a peptic ulcer prevention measure. Among the acid secretion inhibitors are histamine-2 receptor antagonists (H_2RA). Cimetidine was marketed as H_2RA in the UK in 1976. Six types of H_2RAs, namely cimetidine, ranitidine hydrochloride, famotidine, roxatidine acetate hydrochloride, nizatidine, and lafutidine, are currently marketed in Japan, and for peptic ulcers H_2RA has been widely used for many years. However, H_2RA has side effects such as granulocytopenia and rhabdomyolysis. Furthermore, despite its low penetration into the central nervous system (CNS), serious CNS side effects such as impaired consciousness, mental confusion, hallucinations, and convulsions have been reported (Murata et al. 2011; Shimokawa et al. 1993), and these are reported as dose-dependent side effects (Tawadrous et al. 2014).

Many elderly patients undergo rehabilitation. Elderly people often have a reduced renal function, and it is possible that the reduction delays their elimination of H_2RA, and adverse events occur. At present, sporadic reports suggest that H_2RA are associated with factors that reduce cognitive function (Boustani at el, 2007; Hanlon et al. 2004). However, little is known about the relationship between H_2RA and rehabilitation outcome. Therefore, this study examined the relationship between H_2RA use and Functional Independence Measure (FIM) gain, which determines rehabilitation outcomes for patients admitted to convalescent rehabilitation wards.

2. Investigations and results

2.1. Patient characteristics

Among the target patients, patients who were taking H_2RA during the hospitalization period were defined as the administration group (H_2RA (+)), and patients not taking it were defined as the non-administration group (H_2RA (-)).

2.2. Adjustment of covariates by propensity score matching (PSM)

Gender, number of stroke and admission fracture patients, age, admission ACB score, admission BMI, admission Alb, admission eGFR, admission γ -GTP, admission Total FIM was chosen as the covariates at the time of propensity score (PS) calculation, based on clinical knowledge. The C-statistic at the time of PS calculation was 0.712. This paper used standardized difference (Std Dif) to measure covariate balance, Std Dif of each covariate was below 0.1 after PSM. Of before PSM H_2RA (+), 53.6 % (n=118) were matched to similar patients of H_2RA (-) (n=118). The balance of selected covariates in the matched cohort was improved. The targeted patients in this study were 236 patients (76 male and 160 female, 118 H_2RA (-) and 118 H_2RA (+)). Tables 1 and 2 show comparison of covariates before and after PMS.

2.3. Comparison of patient information, comorbidities, and laboratory values on admission

Table 3 shows the results of analyzing patient information, comorbidities, and laboratory values on admission in H_2RA (-) and H_2RA (+) by group after PSM.

Table 1: Results of single regression analysis of covariates before propensity score matching

selected covariates	Before PSM					
	n (H_2RA(-))	H_2RA(-)	n (H_2RA(+))	H_2RA(+)	*p value*	Std Dif
		n (ratio%)		n (ratio%)		
gender (M/F)	242	98 (40.5) / 144 (59.5)	220	67 (30.5) / 153 (69.5)	0.0245	0.211
stroke	242	103 (42.6)	220	73 (33.2)	0.0381	0.194
fracture upon admission	242	102 (42.1)	220	132 (60.0)	<0.0001	0.363
		mean ± SD		mean ± SD		
age (year)	242	77.9 ± 7.6	220	79.6 ± 7.8	0.0310	0.212
admission ACB score	242	0.7 ± 1.1	220	1.1 ± 1.4	<.0001	0.346
admission Alb (g/dL)	236	3.7 ± 0.6	220	3.8 ± 0.5	0.1348	0.146
admission BMI (kg/m^2)	210	22.0 ± 4.0	213	22.8 ± 4.6	0.0623	0.184
admission eGFR (mL/min/1.73m^2)	236	75.4 ± 26.2	219	70.8 ± 23.9	0.1400	0.183
admission γ-GTP (IU/L)	182	35.0 ± 85.8	213	33.3 ± 56.8	0.2642	0.024
admission Total FIM	242	79.8 ± 23.6	220	79.1 ± 26.0	0.8044	0.029

Student's test, Wilcoxon rank sum test, χ^2-test
PSM denotes propensity score matching, and Std Dif standardized difference.

Table 2: Results of single regression analysis of covariates after propensity score matching

selected covariates	After PSM					
	n (H_2RA(-))	H_2RA(-)	n (H_2RA(+))	H_2RA(+)	*p value*	Std Dif
		n (ratio%)		n (ratio%)		
gender (M/F)	118	40 (33.9) / 78 (66.1)	118	36 (30.5) / 82 (69.5)	0.5774	0.072
stroke	118	47 (39.8)	118	44 (37.3)	0.6883	0.052
fracture upon admission	118	54 (45.8)	118	58 (49.2)	0.6021	0.068
		mean ± SD		mean ± SD		
age (year)	118	78.3 ± 8.0	118	78.7 ± 7.6	0.7154	0.053
admission ACB score	118	0.9 ± 1.3	118	0.8 ± 1.2	0.8821	0.062
admission Alb (g/dL)	118	3.8 ± 0.5	118	3.8 ± 0.5	0.6247	0.078
admission BMI (kg/m^2)	118	22.4 ± 4.4	118	22.0 ± 3.8	0.9377	0.099
admission eGFR (mL/min/1.73m^2)	118	74.1 ± 25.9	118	74.0 ± 23.2	0.7007	0.005
admission γ-GTP (IU/L)	118	28.8 ± 30.5	118	28.8 ± 35.2	0.7718	0.002
admission Total FIM	118	79.9 ± 23.3	118	78.7 ± 26.1	0.6644	0.047

Student's test, Wilcoxon rank sum test, χ^2-test
PSM denotes propensity score matching, and Std Dif standardized difference.

Age, gender, height, weight, BMI, ACB score, GNRI, GNRI>92 (number of patients), comorbidity (stroke, cerebral infarction, cerebral infarction (excluding cardiogenic cerebral embolism), fracture upon admission, type-2 diabetes), ALT, AST, γ-GTP, BUN, BUN abnormality (number of patients), Cre, Cre abnormality (number of patients), eGFR, eGFR<60 (number of patients), eGFR<30 (number of patients), CRP, CRP abnormality (number of patients), Alb, TP, Hb, WBC were not significantly different between the two groups.

Table 3: Patient information, comorbidities, laboratory values on discharge in H_2RA (-) and H_2RA (+) after PSM

On admission	H_2RA(-)	H_2RA(+)	
	n=118	n=118	*p* value
Gender (M/F)	40 (33.9) / 78 (66.1)	36 (30.5) / 82 (69.5)	0.5774
Age (year)	78.0 [71.8-84.0]	77.0 [72.0-85.0]	0.7154
Height (cm)	152.2±9.3	152.3±9.0	0.9779
Weight (kg)	50.6 [43.6-59.2]	52.6 [43.2-58.2]	0.9924
BMI (kg/m^2)	21.7 [19.3-24.7]	22.3 [19.5-24.7]	0.9377
GNRI	95.4 [90.0-102.7]	96.8 [89.7-101.8]	0.7880
GNRI<92	37 (31.4)	39 (33.0)	0.7805
ACB score	0 [0-1]	1 [0-1]	0.8821
ALT (IU/L)	16.5 [11.8-23.2]	17 [14.0-22.0]	0.4919

On admission	$H_2RA(-)$ n=118	$H_2RA(+)$ n=118	*p* value
AST (IU/L)	22 [18.0-27.2]	22 [19.0-28.0]	0.7039
γ-GTP (IU/L)	18.5 [12.0-33.2]	18.0 [12.0-31.5]	0.7718
BUN (mg/dL)	15.2 [12.6-19.4]	16.4 [12.9-20.5]	0.3845
BUN abnormality	25 (21.2)	27 (22.9)	0.7534
Cre (mg/dl)	0.7 [0.5-0.8]	0.6 [0.5-0.8]	0.5336
Cre abnormality	9 (7.6)	7 (5.9)	0.6046
eGFR (mL/min/1.73m^2)	71.0 [59.5-87.0]	73.0 [59.0-87.0]	0.7007
eGFR<60	29 (24.6)	30 (25.4)	0.8805
eGFR<30	3 (2.5)	2 (1.7)	0.6512
CRP (mg/L)	0.2 [0.1-1.8]	0.3 [0.1-2.2]	0.5340
CRP abnormality	53 (44.9)	58 (49.2)	0.5143
Alb (g/dL)	3.8 [3.5-4.2]	3.8 [3.4-4.1]	0.6247
TP (g/dL)	6.8±0.7	6.8±0.6	0.9066
Hb (g/dL)	12.3±1.9	12.0±1.9	0.3012
WBC(×10^3/μL)	64.0 [48.0-85.0]	64.0 [52.0-92.2]	0.2466
stroke	47 (39.8)	44 (37.3)	0.6883
Cerebral infarction	30 (25.4)	37 (31.4)	0.3122
Cerebral infarction (excluding cardiogenic cerebral embolism)	25 (21.2)	26 (22)	0.8743
Fracture upon admission	54 (45.8)	58 (49.2)	0.6021
Type-2 diabetes	29 (24.6)	30 (25.4)	0.8805

Student's test (Mean±Standard Deviation), Wilcoxon rank sum test (Median [Inter-Quartile Range]), χ^2-test (Number (Ratio%))
There were no significant differences (p <0.05) between the two groups.

2.4. Comparison of patient information, comorbidities, and laboratory values on discharge

Table 4 shows the results of analyzing patient information, comorbidities, and laboratory values on discharge in H_2RA (-) and H_2RA (+) by group after PSM.

Weight, BMI, duration of hospitalization (days), ACB score, GNRI, GNRI amount-of-change, GNRI decrease (number of patients), comorbidities (falls, reflux esophagitis, aspiration pneumonia), ALT, AST, γ-GTP, BUN, BUN abnormality (number of patients), Cre, Cre abnormality (number of patients), eGFR, eGFR<60 (number of patients), eGFR<30 (number of patients), CRP, CRP abnormality (number of patients), Alb, TP, Hb were not significantly different between the two groups. GNRI reduction (number of patients) was significantly more number in H_2RA (+) than in H_2RA (-). WBC was significantly higher in H_2RA (-) than in H_2RA (+).

Table 4: Patient information, comorbidities, laboratory values on discharge in H_2RA (-) and H_2RA (+) after PSM.

On discharge	$H_2RA(-)$ n=118	$H_2RA(+)$ n=118	p value
Weight (kg)	48.2 [42.1-54.9]	47.8 [41.0-54.2]	0.6881
BMI (kg/m^2)	21.2±3.7	20.9±3.5	0.5250
GNRI *	87.8±10.2	86.5±10.6	0.3999
GNRI<92 *	55 (67.1)	69 (63.9)	0.6480
GNRI amount-of-change *	-6.1±9.1	-7.6±8.2	0.2293
GNRI decrease *	58 (70.7)	90 (83.3)	0.0381
Duration of hospitalization (day)	93.1±33.1	87.6±36.6	0.2246
ACB score	1 [0-2]	1 [0-2]	0.1088
ALT (IU/L) *	14.0 [9.0-21.0]	13.0 [9.0-25.0]	0.7240
AST (IU/L) *	18.0 [15.0-24.0]	18.0 [15.0-22.0]	0.6363
γ-GTP (IU/L) *	20.0 [12.0-33.5]	18.0 [12.0-31.5]	0.7314
BUN (mg/dL) *	15.8 [12.9-20.0]	14.4 [12.0-18.6]	0.1212
BUN abnormality *	17 (20.7)	20 (18.3)	0.6800
Cre (mg/L) *	0.7 [0.5-0.8]	0.6 [0.5-0.8]	0.0931

On discharge	$H_2RA(-)$ n=118	$H_2RA(+)$ n=118	p value
Cre abnormality *	6 (7.2)	6 (5.5)	0.6249
eGFR (mL/min/1.73m^2) *	70.0 [56.0-87.0]	75.0 [63.0-91.0]	0.0875
eGFR<60 *	27 (32.5)	23 (21.1)	0.0738
eGFR<30 *	3 (3.6)	1 (0.9)	0.1949
CRP (mg/L) *	0.4 [0.1-0.8]	0.2 [0.1-0.7]	0.2234
CRP abnormality *	43 (55.8)	48 (44.4)	0.1263
Alb (g/dL) *	3.4±0.5	3.3±0.6	0.3469
Tp (g/dL) *	6.4 [6.1-6.8]	6.3 [5.9-6.8]	0.4616
Hb (g/dL) *	11.3±1.5	11.0±1.7	0.2163
WBC(x10^3/μL) * **	59.9±19.0	53.7±18.9	0.0249
Falls	23 (19.5)	13 (11)	0.0702
Refluxesophagitis	0 (0)	0 (0)	-
Aspiration pneumonia	1 (0.8)	6 (5.1)	0.0550

Student's test (Mean±Standard Deviation), Wilcoxon rank sum test (Median [Inter-Quartile Range]), χ^2 -test (Number (Ratio%))
* Only patients with data on discharge were noted.
** There were no significant differences (p <0.05) between the two groups except for WBC (x10^3/μL) (p = 3.0249).

2.5. Comparison of FIM scores

Tables 5-7 show the results of FIM scores (each item scores of FIM on admission and discharge, and FIM gain) in H_2RA (-) and H_2RA (+) by group after PSM.

Each item scores of FIM on admission were not significantly different between the two groups (Table 5). In item of FIM on discharge, Eating, Bed/chair/wheelchair transfer were significantly lower in H_2RA (+) than in H_2RA (-) (Table 6). In item of FIM gain, Motor FIM: Eating, Upper dressing, and Motor FIM total, Cognition FIM: Expression (voice/non-voice), Problem solving, and Cognition FIM total, and Total FIM were significantly lower in H_2RA (+) than in H_2RA (-) (Table 7).

Table 5: FIM scores on admission in H_2RA (-) and H_2RA (+) after PSM

FIM on admission	$H_2RA(-)$ n=118	$H_2RA(+)$ n=118	*p* value
Eating	7.0 [5.0-7.0]	6.0 [5.0-7.0]	0.3801
Grooming	5.0 [5.0-7.0]	5.0 [5.0-7.0]	0.7541
Bathing/showering	3.0 [2.0-4.0]	3.0 [1.0-4.0]	0.9658
Upper dressing	5.0 [3.0-7.0]	5.0 [3.0-7.0]	0.4665
Lower dressing	4.0 [2.0-6.0]	4.0 [2.0-7.0]	0.7914
Toileting	5.0 [2.0-6.0]	5.0 [2.0-6.0]	0.8487
Bladder management	7.0 [4.0-7.0]	6.0 [3.0-7.0]	0.2395
Bowel management	6.0 [5.0-7.0]	6.0 [4.0-7.0]	0.6766
Bed/chair/wheelchair transfer	5.0 [4.0-5.0]	5.0 [4.0-5.0]	0.4837
Toilet transfer	5.0 [4.0-6.0]	5.0 [4.0-6.0]	0.9229
Tub/shower transfer	3.0 [1.0-5.0]	3.0 [1.0-4.0]	0.6946
Walk or wheelchair	2.5 [1.0-5.0]	4.0 [1.0-5.0]	0.2879
Stairs	1.0 [1.0-1.0]	1.0 [1.0-1.0]	0.2678
Comprehension	6.0 [4.0-6.0]	5.0 [4.0-7.0]	0.7853
Expression (voice/non-voice)	6.0 [4.0-7.0]	6.0 [4.0-7.0]	0.7761
Social interaction	6.0 [5.0-7.0]	6.0 [4.0-7.0]	0.6612
Problem solving	5.0 [3.0-5.2]	5.0 [2.8-6.0]	0.8084
Memory	5.0 [3.0-6.0]	5.0 [3.0-7.0]	0.9391
Motor FIM total	58.0 [42.8-68.0]	54.0 [41.0-71.0]	0.7953
Cognition FIM total	27.0 [19.0-31.2]	25.0 [16.8-32.2]	0.9111
Total FIM	82.0 [64.8-96.2]	77.5 [58.5-104.2]	0.6644

Wilcoxon rank sum test Median (Inter-Quartile Range)
There were no significant differences (p <0.05) between the two groups.

Table 6: FIM scores on discharge in H_2RA (-) and H_2RA (+) after PSM

FIM on discharge	H_2RA(-) n=118	H_2RA(+) n=118	*p* value
Eating *	7.0 [6.0-7.0]	7.0 [6.0-7.0]	0.0238
Grooming	7.0 [5.0-7.0]	7.0 [5.0-7.0]	0.1385
Bathing/showering	4.0 [3.0-5.0]	4.0 [3.0-5.0]	0.2751
Upper dressing	7.0 [5.0-7.0]	7.0 [4.8-7.0]	0.2013
Lower dressing	7.0 [5.0-7.0]	7.0 [3.0-7.0]	0.2290
Toileting	6.0 [5.0-7.0]	6.0 [4.0-7.0]	0.2424
Bladder management	7.0 [5.8-7.0]	7.0 [4.0-7.0]	0.1196
Bowel management	6.0 [6.0-7.0]	6.0 [5.0-7.0]	0.5702
Bed/chair/wheelchair transfer *	6.0 [5.0-7.0]	5.0 [4.8-7.0]	0.0487
Toilet transfer	6.0 [5.0-7.0]	5.5 [5.0-7.0]	0.1256
Tub/shower transfer	5.0 [3.8-5.0]	4.0 [3.0-5.0]	0.1271
Walk or wheelchair	6.0 [5.0-7.0]	5.5 [4.0-7.0]	0.1340
Stairs	4.0 [2.0-5.0]	3.0 [1.0-5.0]	0.0738
Comprehension	6.0 [5.0-7.0]	6.0 [4.0-7.0]	0.5629
Expression (voice/non-voice)	7.0 [5.0-7.0]	7.0 [4.0-7.0]	0.8427
Social interaction	7.0 [5.0-7.0]	7.0 [5.0-7.0]	0.8988
Problem solving	5.0 [3.0-6.0]	5.0 [3.0-6.0]	0.8664
Memory	5.5 [4.0-7.0]	5.0 [3.0-7.0]	0.9627
Motor FIM total	78.0 [63.5-83.0]	74.0 [52.8-83.0]	0.1694
Cognition FIM total	30.0 [22.0-33.0]	30.5 [20.8-33.0]	0.9329
Total FIM	108.0 [85.8-116.0]	102.0 [74.0-116.0]	0.2591

Wilcoxon rank sum test Median (Inter-Quartile Range)
* Eating (p =0.0238), Bed/chair/wheelchair transfer (p =0.0487) were significantly lower (p <0.05) in H_2RA (+) than in H_2RA (-).

Table 7: Each item scores of FIM gain on discharge in H_2RA (-) and H_2RA (+) after PSM

FIM gain	H_2RA(-) n=118	H_2RA(+) n=118	*p* value
Eating *	1.0 [0-2.0]	1.0 [0-1.0]	0.0254
Grooming	1.0 [0-2.0]	1.0 [0-2.0]	0.0526
Bathing/showering	1.0 [0-2.0]	1.0 [0-1.0]	0.0557
Upper dressing *	2.0 [0-4.0]	1.0 [0-4.0]	0.0213
Lower dressing	0 [0-1.0]	0 [0-1.0]	0.6475
Toileting	1.0 [0-3.0]	0 [0-2.0]	0.1370
Bladder management	0.5 [0-2.0]	0 [0-2.0]	0.4209
Bowel management	0 [0-1.0]	0 [0-1.0]	0.7946
Bed/chair/wheelchair transfer	0 [0-1.0]	0 [0-1.0]	0.1869
Toilet transfer	0 [0-2.0]	0 [0-2.0]	0.1423
Tub/shower transfer	1.0 [0-2.0]	0.5 [0-2.0]	0.0563
Walk or wheelchair	0 [0-1.0]	0 [0-1.0]	0.4689
Stairs	0 [0-1.0]	0 [0-1.0]	0.6641
Comprehens ion	0 [0-1.0]	0 [0-1.0]	0.9563
Expression (voice/non-voice) **	2.0 [0-4.0]	1.0 [0-3.0]	0.0070
Social interaction	0 [0-1.0]	0 [0-1.0]	0.8118
Problem solving **	1.0 [0-2.0]	0 [0-1.2]	0.0330
Memory	0 [0-1.0]	0 [0-1.0]	0.4250
Motor FIM total *	12.0 [5.0-19.2]	8.0 [4.0-16.0]	0.0217

FIM gain	$H_2RA(-)$ n=118	$H_2RA(+)$ n=118	*p* value
Cognition FIM total **	5.0 [2.0-7.0]	3.0 [1.0-6.0]	0.0120
Total FIM ***	17.0 [8.0-27.0]	11.5 [4.8-20.2]	0.0089

Wilcoxon rank sum test Median (Inter-Quartile Range)
* Motor FIM: Eating (p =0.0254), Upper dressing (p =0.0213), and Motor FIM total (p =0.0217) were significantly lower (p <0.05) in H_2RA (+) than in H_2RA (-)
** Cognition FIM: Expression (voice/non-voice) (p =0.0070), Problem solving (p =0.0330), and Cognition FIM total (p =0.0120) were lower (p <0.05) in H_2RA (+) than H_2RA (-).
*** Total FIM (p =0.0089) were significantly lower in H_2RA (+) than in H_2RA (-).

3. Discussion

The most important finding obtained from this study is the fact that the administration of H_2RA to elderly patients undergoing rehabilitation may prevent cognitive function maintenance or recovery by rehabilitation. There was a negative association between H_2RA administration and improving cognitive function. Cognitive FIM gain was significantly lower in H_2RA (+) compared with H_2RA (-). The Motor FIM gain was also significantly lower in H_2RA (+) than in H_2RA (-). Imada et al. reported that there is a correlation between Cognitive FIM on admission and Motor FIM gain (Imada et al. 2014). On the other hand, Cognitive FIM on admission was not significantly different between the two groups in our study, it is possible that not only Cognitive FIM on admission but also Cognitive FIM gain affects Motor FIM gain.

Patients undergoing rehabilitation often receive intensive secondary preventative drug therapy to improve lifestyle-related disease. It is necessary to determine whether these secondary preventative drugs and countermeasures against adverse effects are significant or beneficial for their rehabilitation.

Cerebral infarction is the most frequent disease targeted for rehabilitation. According to the Annual Health, Labour and Welfare Report 2017, cerebrovascular disease (stroke) is the fourth leading cause of death in Japan, of which about 75% is cerebral infarction (Ministry of Health, Labour and Welfare 2017). In addition, it is the second cause disease that requires care (Ministry of Health, Labour and Welfare 2016). Even if patients survive the cerebral infarction by appropriate treatment after onset, some neurological disorder sequelae such as speech disorder or motor dysfunction, and higher cortical dysfunction such as aphasia or memory impairment may remain. Patients, who have higher cortical dysfunction, often suffer from reflux esophagitis due to the decline in swallowing function, or peptic ulcers due to stress. Acid secretion inhibitors are often prescribed for suppressing aggressive factors. However, considering the results of this study, in the convalescent rehabilitation ward, it may be necessary to refrain from prescribing unnecessary H_2RA that may have implications for FIM, which is an indicator of ADL improvement.

On the other hand, diseases requiring rehabilitation include musculoskeletal diseases for elderly patients such as femur fracture, and the causes include osteoporosis. They are susceptible to osteoporosis due to environmental factors such as lack of exercise and malnutrition, especially postmenopausal women are more susceptible to it due to decreased estrogen (Japan Osteoporosis Society 2015). As a result, they can fracture their femur easily by falling. According to the Ministry of Health, Labour and Welfare (MHLW), it is estimated that the number of patients with femoral fractures will reach about 260.000 people in 2030 (The Japanese Orthopaedic Association 2011). In femoral fractures, the outcome of surgical treatment is superior to that of conservative treatment in terms of both life and functional prognosis, and surgical treatment is selected in most cases (Noda and Ozaki 2010). In addition, NSAIDs are frequently prescribed for pain management. NSAID usage is listed as a significant factor for onset of peptic ulcers (The Japanese Society of Gastroenterology 2015; Sakamoto et al. 2006), and acid secretion inhibitors are often prescribed along with NSAIDs. As the results of this study suggest that H_2RA administration may affect the outcome of rehabilitation for the elderly, the pharmacist assesses the risks and benefits provided by the administration of acid secretion inhibitors for each patient, and in some cases, the pharmacist should suggest to the doctor to change the prescription. On the other hand, proton-pump inhibitors (PPI) are other acid secretion inhibitors, however it was reported that their use decreases bone density and increases the risk of fractures (Arj et al. 2016; Lin et al. 2018; Nassar and Richter 2018). Therefore, further consideration will be needed to determine whether PPI are appropriate as an alternative to H_2RA. So far, there are many reports that H_2RA reduce cognitive function when comparing H_2RA and PPI (Fujii et al. 2012). However, similar to H_2RA, PPI were also reported to reduce cognitive function. Administration of PPI may cause hyponatremia and hypomagnesemia, these may cause delirium, and it is possible that delirium reduces cognitive function (Bebarta et al. 2008). Even if H_2RA is changed to PPI, it is considered necessary to pay attention to the onset of delirium, cognitive decline, and reduced bone density. The subject drug of this study was a H_2RA only. In the future, further considerations have to be made about the relationship of rehabilitation outcome of cognitive function and use of PPI.

In addition, when delirium develops, it is thought that cognitive function declines, however it is difficult to distinguish between delirium and cognitive decline, as various studies have reported (Jackson et al. 2004). Generally, the elderly tend to lifestyle-related diseases and geriatric syndromes, and they are more likely to make simultaneous use of several drugs (Ministry of Health, Labour and Welfare 2018). Geriatric syndrome is a complex disease due to hypofunction of various organs due to aging, including delirium. In the MHLW Guidance of Appropriate Medication for elderly patients, H_2RA are listed as a major cause of drug-induced geriatric syndromes (Ministry of Health, Labour and Welfare 2018). In the elderly there is an increased risk of delirium and cognitive decline, therefore the guideline recommends that they refrain from use as much as possible (Ministry of Health, Labour and Welfare 2018). It is thought that manipulating the central histaminergic system by blocking the histamine receptors can potentially modify delirium symptom induction and maintenance through manipulating levels of histamine (HIS) through autoreceptors, acetylcholine and noradrenalin, through heteroreceptors binding to histamine receptors, acetylcholine receptor and adrenergic receptors (Chazot et al. 2019). Histamine 2 receptors are present in most of the cerebral cortex, in the corpus striatum putamen, in the nucleus accumbens septi, and in the hippocampus. The cerebral cortex is involved in visual and auditory senses, the hippocampus is involved in short-term memory. From this, it is said that the blockade of histamine 2 receptors is likely to be involved in mental confusion, such as hallucination, disorientation to time and place, and delirium (Ruat et al. 1990).

On the other hand, the use of anticholinergics is considered as a cause of delirium (Han et al. 2001). Anticholinergics is a general term for drugs that inhibit the binding of the neurotransmitter acetylcholine to the muscarinic acetylcholine receptors, and includes antidepressants, antipsychotics, antiparkinsonian drugs, anticonvulsants, antiallergics, antiemetics and drugs for overactive bladder treatment, etc. These are prescribed for various symptoms such as bowel motility disorder, overactive bladder and chronic obstructive pulmonary disease. Among them, tricyclic antidepressants, first generation antihistamines, antiparkinsonian drugs and the like have strong anticholinergic effects. As aging progresses, of cholinergic neuron in the basal forebrain, degeneration of dendritic processes, synapses and axons, and decrease in the number of acetylcholine receptors gradually reduce their functions. Hence, as

they get older, it is possible that the sensitivity of anticholinergic effects is increased, and they are more susceptible to anticholinergics. Studies in elderly patients suggest, even if anticholinergic effects are low, that anticholinergics cause various impairments in cognitive function (Mulsant et al. 2003), and the use of anticholinergics is an important predictor of a common daily activity, mild cognitive impairment, and delirium. H_2RAs have anticholinergic activity and are also reported to be associated with cognitive decline (Chew et al. 2008). Therefore, it is desirable to consider the effects of ACB scores on rehabilitation outcome as well. In this study, ACB scores on admission and discharge were not significantly different between the two groups, the anticholinergic effects of other drugs on outcome was adjusted.

One of the most reliable scales used to diagnose delirium is the Delirium Rating Scale, Revised 98 (DRS-R98), and the reliability of the Japanese version is also considered. The evaluation score is based on a severity score of 3 items and a diagnosis score of 3 items. The cutoff value for diagnosis of delirium is 10 points for severity score and 14.5 points for the total score. Although it may be complicated as a scale used on a daily basis, items necessary for delirium evaluation are covered, and it can be a highly reliable assessment method (Kato et al. 2010). When comparing H_2RA and PPI using DRS-R98, it was reported that administration of PPI showed a significantly lower incidence of delirium and that the incidence of delirium was significantly increased by discontinuing administration of H_2RA (Fujii et al. 2012). It was also reported that patients who develop delirium show lower scores of FIM than patients who do not develop delirium (Heyman et al. 2015), and it is considered that delirium and reduction of FIM gain are related. The primary outcome in this study was FIM gain as indicators of rehabilitation outcome, and cognitive function was not assessed by DRS-R98. Further consideration will be needed to yield any findings about the relationship between H_2RA and delirium assessed by DRS-R98, and the effect of drug-induced delirium on cognitive function and on rehabilitation outcome, in the convalescent rehabilitation ward.

Most H_2RAs commonly used are renally excreted drugs, and in elderly people, the reduction in renal function causes an accumulation of the drug, which is likely to cause concentration-dependent adverse events due to an increase in blood concentration. It was reported that the use of H_2RA in elderly patients with renal dysfunction likely causes central nervous system side effects (disorientation, delirium, hallucinations, changes in mental status, etc.), and this may be related to cognitive decline (Cantú and Korek 1991; Shimokawa et al. 1993; Slugg et al. 1992). In this study, two groups with no significant difference in laboratory values of renal function at admission were compared, and no significant difference was found in the proportion of patients with abnormal renal function. Moreover, comparing Cre, eGFR, and BUN in H_2RA (+) and H_2RA (-) on discharge, no significant difference of rehabilitation outcome was observed. In the future, it is considered necessary to investigate the relationship with renal dysfunction and rehabilitation outcome. Moreover, the differences between each H_2RA were not examined in this study, it is considered necessary to compare each ingredient, such as the blood-brain barrier transit due to the difference in the lipid solubility of the ingredients, in the future (Murata et al. 2011).

In clinical practice, H_2RA are reported to be predisposed to cause a decline in the cognitive function of patients due to long-term administration. It is thought that the pharmacist needs to suggest to the doctor strategies such as discontinuation or changing the drug to an alternative, in order to prevent cognitive decline. Furthermore, the onset of delirium is reported to be dependent on the dose of H_2RA, it is considered necessary to consider appropriate dose and administration methods (Tawadrous et al. 2014).

From examining the findings, it is suggested that H_2RA affects the outcome of rehabilitation. Therefore, for improving the outcome of rehabilitation for the elderly in convalescent rehabilitation wards, it is necessary to conduct comprehensive drug monitoring from a pharmaceutical point of view, to determine whether the prescription of H_2RA is appropriate and not automatically choose long-term administration.

Finally, there are some study limitations. First, as this study is a single-center retrospective study, care needs to be taken in interpreting the results. Second, no consideration was given to the dose and the administration period. Finally, although the effects of the drugs are being considered, the severity of the disease was not considered. Therefore, it cannot be denied that these factors may affect the results obtained this time. Further studies will be needed to consider the use of H_2RA for patients undergoing rehabilitation.

4. Experimental

4.1. Patients

Out of 978 patients discharged from Hitachi, Ltd. Hitachinaka General Hospital Convalescent Rehabilitation Ward from July 2010 to March 2015, 759 patients aged 65 and older were targeted. 462 patients were included in the survey, excluding 297 patients who had dementia, also were with no FIM on admission or discharge available, or who took proton-pump inhibitors (PPIs) during the hospitalization period. This paper excluded patients with dementia from the target patients as they are already experiencing cognitive decline and may be receiving treatment.

4.2. Outcome evaluation criteria

In this study, FIM, which is widely used as an objective index in the field of rehabilitation, was used as an evaluation method for ADL. FIM consists of 18 items including 13 items of ADL of exercise (Motor FIM) and 5 items of ADL of Cognition (Cognition FIM). The Motor FIM includes self-care (eating, grooming, bathing, upper dressing, lower dressing and toileting), sphincter control (bladder and bowel management), mobility (bed/chair/wheelchair transfer, toilet transfer and tub/shower transfer) and locomotion (walking/wheelchair and stairs). The Cognition FIM comprises communication (comprehension and expression.) and social cognition (social interaction, problem solving and memory). In each item, it is evaluated in seven steps from total assistance (1 point) to complete independence (7 points). The total score (Total FIM) is a maximum of 126 points and a minimum of 18 points. This paper used FIM gain as an outcome indicator. FIM gain can be determined by subtracting FIM on admission from FIM on discharge. In other words, FIM gain is an indicator of ADL improvement during hospitalization. The team consisting of specialist physicians in convalescent wards, nurses with a long work history in the ward, and rehabilitation staff (physical, occupational, and speech-hearing therapists) discussed and scored FIM.

4.3. Survey items

The following items were retrospectively surveyed in medical records: basic information (gender, age, height), comorbidities (stroke, cerebral infarction, cerebral infarction [excluding cardiogenic cerebral embolism]), type-2 diabetes, and fracture upon admission, and falls, reflux esophagitis, and aspiration pneumonia during the hospital stay), patient information on admission and discharge (weight, body mass index (BMI), anticholinergic burden score (ACB score), Geriatric Nutritional Risk Index (GNRI), GNRI amount-of-change, and duration of hospitalization), laboratory values on admission and discharge (alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (γ-GTP), urea-nitrogen (Blood Urea Nitrogen : BUN), serum creatinine (Cre), estimated glomerular filtration rate (eGFR), total protein (TP), serum albumin (Alb), hemoglobin (Hb), C-reactive protein (CRP), and white blood cell count (WBC)), FIM scores (each item scores of FIM on admission and discharge, and FIM gain).

4.4. Statistical processing

Analysis of this study was performed using JMP® Pro 14 (SAS Institute Inc., Cary, NC, USA). Patient characteristics, laboratory test values, and FIM scores were compared between the two groups of H_2RA (+) and H_2RA (-). Before comparison, PSM was used to adjust factors affecting FIM gain and H_2RA administration so that the background of the two groups had the same conditions. The PS was calculated by fitting the chosen covariates to a logistic regression model. The appropriateness of PS calculation was confirmed using C-statistic. In general, the C-statistic is desirably 0.7 or more. Based on the calculated PS, a matching was performed on the two groups, and the covariates were adjusted. As a matching method, nearest neighbor matching was used, and a caliper indicating the distance of PS to be matched was set to 0.2 × SD (standard deviation of logit conversion value of PS). Matching balance was evaluated based on whether the standardized difference (Std Dif) was less than 0.1 (Table 1). Generally, when Std Dif is less than 0.1, it can be determined that appropriate matching has been performed. Shapiro-Wilk's W test was performed to confirm the normality of the quantitative variable after PSM. The test of homogeneity of variance was performed by two-sided F test. Student's t-test and Welch's t test as a parametric test, and Wilcoxon rank sum test as a non-parametric test was performed to compare the quantitative variable of between the two groups. $\chi 2$ test was performed to compare qualitative variables of between the two groups after PSM. Data were reported with mean value ± standard deviation, median value [quartile range], or number of people (proportion %), and the statistical significance level of each test was $p < 0.05$.

4.5. Ethical considerations

This study was approved by the Hitachinaka General Hospital Ethics Committee and the Nihon University School of Pharmacy Ethics Committee. All procedures

performed in studies involving human participants were in accordance with the "Ethical guidelines for medical and health research involving human subjects" and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study is a retrospective observational study with electronic medical records, and there is no disadvantage for individuals.

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