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Association between Postoperative Adjuvant Vasodilator Therapy and In-Hospital Mortality for Non-Occlusive Mesenteric Ischemia: A Nationwide Observational Study

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Background: Although several clinical guidelines recommend vasodilator therapy for non-occlusive mesenteric ischemia (NOMI) and immediate surgery when bowel necrosis is suspected, these recommendations are based on limited evidence.

Methods: In this retrospective nationwide observational study, we used information from the Japanese Diagnosis Procedure Combination inpatient database from July 2010 to March 2018 to identify patients with NOMI who underwent abdominal surgeries on the day of admission. We compared patients who received postoperative vasodilator therapy (vasodilator group) with those who did not (control group). Vasodilator therapy was defined as venous and/or arterial administration of papaverine and/or prostaglandin E1 within 2 days of admission. The primary outcome was in-hospital mortality. Secondary outcomes included the prevalence of additional abdominal surgery performed ≥3 days after admission and short bowel syndrome.

Results: We identified 928 eligible patients (149 in the vasodilator group and 779 in the control group). One-to-four propensity score matching yielded 149 and 596 patients for the vasodilator and control groups, respectively. There was no significant difference in in-hospital mortality between the groups (control vs. vasodilator, 27.5% vs. 30.9%; risk difference, 3.4%; 95% confidence interval, −4.9 to 11.6; p= 0.42) and no significant difference in the prevalences of abdominal surgery, bowel resection ≥3 days after admission, and short bowel syndrome.

Conclusions: Postoperative vasodilator use was not significantly associated with a reduction in in-hospital mortality or additional abdominal surgery performed ≥3 days after admission in surgically treated NOMI patients. (J Nippon Med Sch 2024; 91: 316–321)

Key words: non-occlusive mesenteric ischemia, surgery, papaverine, prostaglandin, vasodilator

Introduction

Non-occlusive mesenteric ischemia (NOMI) refers to microvascular vasoconstriction without occlusion of mesenteric arteries, which results in splanchnic necrosis[1–5]. NOMI accounts for 20-30% of all cases of acute mesenteric ischemia and has an alarmingly high mortality of

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50-80%[2,3,6].

Several clinical guidelines on mesenteric ischemia recommend vasodilator therapy for NOMI and immediate surgical intervention in cases of suspected bowel necrosis[7–10]; however, there is limited evidence supporting these recommendations[11–13]. A small-scale study conducted in 1977 examined intra-arterial infusion of papaverine to relieve superior mesenteric artery vasoconstriction and reported an improvement in mortality in cases of acute mesenteric ischemia[11]. A study conducted in 2007 showed that the combination of early diagnosis using multidetector row computed tomography and treatment with continuous intravenous prostaglandin E1 (PGE1) might improve mortality in patients with NOMI[12]. Because these studies were small (n = 15-22)[11–13], our team launched the first large-scale nationwide observational study (n = 1,837) in 2020[14]. Our previous study found that vasodilator therapy using papaverine and/or PGE1 was associated with lower in-hospital mortality and lower prevalence of abdominal surgery in patients with NOMI. However, that study excluded patients who underwent abdominal surgery within 2 days of admission because it was designed to assess the direct effect of vasodilator therapy on mortality in the absence of surgical intervention. Although postoperative adjuvant vasodilator therapy may prevent further necrosis of the gut, previous studies of vasodilator therapy for NOMI have not assessed this specific indication[11–13].

The present study used a nationwide inpatient database to evaluate the effectiveness of postoperative adjuvant vasodilator therapy in NOMI patients who underwent emergency abdominal surgery on the day of admission.

Materials and Methods

This study was approved by the Institutional Review Board of the University of Tokyo (approval number, 3501). Because of the anonymous nature of the data, the requirement for informed consent was waived. This study is reported in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE).

Data Source

In this retrospective cohort study, data were extracted from the Japanese Diagnosis Procedure Combination database[15], a national inpatient claims database in Japan. The database contains discharge abstracts and administrative claims data from more than 1,200 acute-care hospitals (approximately 90% of all tertiary-care emergency hospitals in Japan). The database includes individual data on age, sex, comorbidities on admission, level of consciousness on admission, procedures, prescriptions, intensive care unit (ICU) admission, and discharge status (discharge to home, discharge to other facility, or in-hospital death). Diagnoses, comorbidities, and complications were recorded in Japanese by using International Classification of Diseases Tenth Revision (ICD-10) codes. The diagnoses and procedures in this database have been validated. The specificity of diagnoses is greater than 96%, while sensitivity ranged from 50% to 80%. The specificity and sensitivity of procedures both exceeded 90%[16].

Study Population

We identified patients with NOMI who underwent abdominal surgeries on the day of admission from July 2010 to March 2018. The diagnosis of NOMI is included in the ICD-10 category K550 in the Japanese text[14]. Patients were excluded from the present study if they i) were younger than 18 years of age, ii) had documented readmission for NOMI, iii) had died or were discharged within 2 days of admission (to avoid immortal time bias), or iv) were diagnosed with NOMI as a complication after admission (i.e., NOMI diagnosed after cardiac surgery).

We compared patients who received postoperative vasodilator therapy (vasodilator group) with those who did not (control group). We defined vasodilator therapy as venous and/or arterial administration of papaverine and/or PGE1 within 2 days of admission.

Outcomes and Covariates

The primary outcome was in-hospital mortality. The secondary outcomes included prevalence of additional abdominal surgery, bowel resection performed ≥3 days after admission, and incident short bowel syndrome. The list of abdominal surgeries as outcomes included exploratory laparotomy, damage control surgery, laparoscopic exploratory laparotomy, laparoscopic exploratory excision, surgery for secondary peritonitis, laparoscopic surgery for secondary peritonitis, enterectomy, small bowel resection, laparoscopic small bowel resection, colectomy, laparoscopic colectomy, enteroanastomosis, colostomy, laparoscopic colostomy, proctostomy, rectal excision, and laparoscopic rectal excision. The list of bowel resections as outcomes included laparoscopic exploratory excision, enterectomy, small bowel resection, laparoscopic small bowel resection, colectomy, laparoscopic colectomy, rectal excision, and laparoscopic rectal excision. Short bowel syndrome was defined as the placement of central ve-

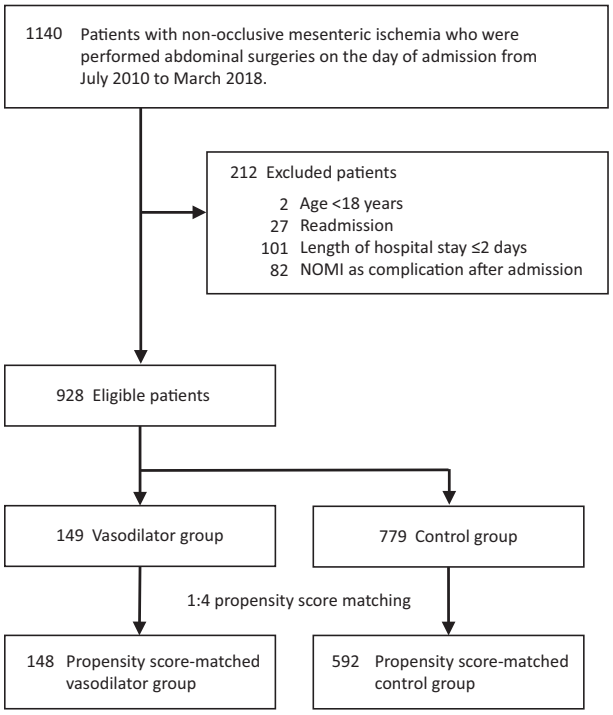

Fig. 1 Flow of patient selection
NOMI, Non-occlusive mesenteric ischemia

nous port systems and/or diagnosis of short bowel syndrome entered into the claims database in Japanese text.

The covariates included in the study were age, sex, ambulance use, Charlson Comorbidity Index, Japan Coma Scale at admission, abdominal surgery with bowel resection on the day of admission, procedures performed within 2 days of admission (mechanical ventilation, renal replacement therapy and invasive arterial monitoring), use of vasopressors (dopamine, dobutamine, adrenaline, noradrenaline, and vasopressin), antibiotic use (carbapenem, anti-methicillin-resistant *Staphylococcus aureus* agents, and others), use of sodium bicarbonate solution, blood transfusions (fresh frozen plasma, red blood cells, and platelets), albumin, hydroxyethyl starch, and unfractionated heparin within 2 days of admission, amount of crystalloid used within 2 days of admission, type of hospital (teaching or non-teaching), and ICU admission within 2 days of hospital admission.

Charlson Comorbidity Index scores were calculated from comorbidities on admission and categorized into four groups: 0, 1, 2, and ≥3[17]. The Japan Coma Scale score was categorized into four groups as 0 (alert), 1-3 (delirium), 10-30 (somnolence), and 100-300 (coma)[18]. The Japan Coma Scale correlates well with the Glasgow Coma Scale[18].

Statistical Analysis

Propensity score matching analyses were performed to account for differences in the characteristics between the vasodilator and control groups. Propensity scores were calculated using a multivariable logistic regression model for receiving vasodilator therapy within 2 days of admission. All covariates mentioned above were included as covariates in the propensity score calculations. We conducted one-to-four matching with replacement using the nearest neighbor matching within 20% of the standard deviation of the estimated propensity scores on the logit scale[19]. Using the standardized difference, we assessed the characteristics of NOMI patients between the two groups before and after propensity score matching[20]. An absolute standardized difference of <10% was regarded as balanced[21]. For comparisons of the primary and secondary outcomes, we used the chi-square test to calculate risk differences with 95% confidence intervals (CI) between the two groups in the propensity-matched cohort. Continuous variables were presented as median and interquartile range (IQR) and categorical variables as numbers and percentages.

A two-sided p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using Stata MP 15 software (Stata Corp., College Station, TX, USA).

Results

A total of 928 eligible patients from 390 facilities were identified during the study period. Patients were divided into the vasodilator (n=149) and control group (n=779). One-to-four propensity score matching yielded 149 and 596 patients for the vasodilator and control groups, respectively (**Fig. 1**).

Table 1 shows the baseline characteristics of the two groups before and after propensity score matching. Patients were more likely to receive vasodilator therapy if they received vasopressors, blood transfusions, and unfractionated heparin before propensity score matching. Abdominal surgery with bowel resection on the day of admission was more likely to be performed in the control group before propensity score matching. After propensity score matching, most of the baseline patient characteristics were well-balanced between the two groups. The C-statistic for the propensity score model was 0.76.

Table 2 shows patient outcomes after propensity score matching. There was no significant difference in mortality between the control and vasodilator groups (control vs. vasodilator, 27.5% vs. 30.9%; risk difference, 3.4%; 95% CI, −4.9 to 11.6; p=0.42) and no significant difference in the prevalences of additional abdominal surgery,

Table 1 Characteristics of patients in the control and vasodilator groups before and after propensity score matching

Variables	Before propensity score matching			After propensity score matching		
	Control group (n=779)	Vasodilator group (n=149)	ASD (%)	Control group (n=596)	Vasodilator group (n=149)	ASD (%)
Age, years, median (IQR)	79 (71, 85)	80 (73, 85)	0.7	78 (69, 84)	80 (73, 85)	7.5
Male	424 (54.4)	79 (53.0)	2.8	317 (53.2)	79 (53.0)	0.3
Ambulance use	581 (74.6)	103 (69.1)	12.1	394 (66.1)	103 (69.1)	6.4
Charlson Comorbidity Index						
0	315 (40.4)	58 (38.9)	3.1	219 (36.7)	58 (38.9)	4.5
1	178 (22.8)	35 (23.5)	1.5	144 (24.2)	35 (23.5)	1.6
2	158 (20.3)	31 (20.8)	1.3	125 (21.0)	31 (20.8)	0.4
3	128 (16.4)	25 (16.8)	0.9	108 (18.1)	25 (16.8)	3.5
Japan Coma Scale						
0 (alert)	459 (58.9)	88 (59.1)	0.3	373 (62.6)	88 (59.1)	7.2
1-3 (delirium)	207 (26.6)	42 (28.2)	3.6	142 (23.8)	42 (28.2)	10.0
10-30 (somnolence)	50 (6.4)	8 (5.4)	4.5	27 (4.5)	8 (5.4)	3.9
100-300 (coma)	63 (8.1)	11 (7.4)	2.6	54 (9.1)	11 (7.4)	6.1
Abdominal surgery with bowel resection on the day of admission	641 (82.3)	108 (72.5)	23.5	425 (71.3)	108 (72.5)	2.6
Procedures within 2 days of admission						
Mechanical ventilation	471 (60.5)	87 (58.4)	4.2	352 (59.1)	87 (58.4)	1.4
Renal replacement therapy	219 (28.1)	48 (32.2)	8.9	197 (33.1)	48 (32.2)	1.8
Invasive arterial monitoring	585 (75.1)	120 (80.5)	13.1	474 (79.5)	120 (80.5)	2.5
Vasopressor use						
Dopamine	265 (34.0)	66 (44.3)	21.1	255 (42.8)	66 (44.3)	3.0
Dobutamine	57 (7.3)	9 (6.0)	5.1	27 (4.5)	9 (6.0)	6.7
Adrenaline	66 (8.5)	12 (8.1)	1.5	47 (7.9)	12 (8.1)	0.6
Noradrenaline	462 (59.3)	87 (58.4)	1.9	348 (58.4)	87 (58.4)	<0.1
Vasopressin	63 (8.1)	16 (10.7)	9.1	50 (8.4)	16 (10.7)	8.0
Antibiotic use						
Carbapenem	418 (53.7)	90 (60.4)	13.6	353 (59.2)	90 (60.4)	2.4
Anti-MRSA agent	22 (2.8)	4 (2.7)	0.9	21 (3.5)	4 (2.7)	4.8
Others	488 (62.6)	90 (60.4)	4.6	377 (63.3)	90 (60.4)	5.9
Transfusions						
Fresh frozen plasma	283 (36.3)	69 (46.3)	20.3	251 (42.1)	69 (46.3)	8.4
Red blood cells	331 (42.5)	82 (55.0)	25.2	321 (53.9)	82 (55.0)	2.4
Platelet	72 (9.2)	22 (14.8)	17.0	79 (13.3)	22 (14.8)	4.3
Albumin use	457 (58.7)	94 (63.1)	9.1	383 (64.3)	94 (63.1)	2.4
Hydroxyethyl starch use	359 (46.1)	77 (51.7)	11.2	332 (55.7)	77 (51.7)	8.1
Crystalloid, mL (IQR)	11,500 (8,000, 17,500)	11,500 (8,000, 17,500)	4.5	11,000 (7,500, 16,000)	11,500 (8,000, 17,500)	12.8
Unfractionated heparin use	228 (29.3)	78 (52.3)	48.2	319 (53.5)	78 (52.3)	2.3
Sodium bicarbonate solution use	262 (33.6)	44 (29.5)	8.8	161 (27.0)	44 (29.5)	5.6
Admission site						
Teaching hospital	723 (92.8)	137 (91.9)	3.3	541 (90.8)	137 (91.9)	4.2
Intensive care unit admission	501 (64.3)	103 (69.1)	10.2	398 (66.8)	103 (69.1)	5.0

ASD, absolute standardized difference; IQR, interquartile range; MRSA, Methicillin-resistant *Staphylococcus aureus*

bowel resection ≥3 days after admission, and short bowel syndrome.

Discussion

This nationwide cohort study examined the potential

Table 2 Outcomes after propensity score matching

Outcomes	Control group	Vasodilator group	Risk difference (95%CI)	p-value
Primary outcome				
In-hospital mortality	27.5% (164/596)	30.9% (46/149)	3.4% (–4.9% to 11.6%)	0.42
Secondary outcomes				
Abdominal surgery ≥3 days after admission	13.8% (82/596)	14.8% (22/149)	1.0% (–5.3 to 7.3)	0.75
Bowel resection ≥3 days after admission	8.4% (50/596)	5.4% (8/149)	–3.0% (–7.3 to 1.2)	0.22
Short bowel syndrome	7.6% (45/596)	5.4% (8/149)	–2.2% (–6.4 to 2.0)	0.35

CI, confidence interval

benefits of postoperative adjuvant vasodilator therapy in patients who received abdominal surgery for NOMI in the acute phase. After using propensity score matching to adjust for numerous confounders, no significant difference was noted in mortality or additional abdominal surgery ≥3 days after admission between the control and vasodilator groups.

Although we previously found that vasodilator therapy was associated with reduced mortality for NOMI[14], no significant differences were noted in the present study. A possible reason for this discrepancy is differences in the inclusion criteria for the two studies, i.e., whether abdominal surgery was performed during the early phases of NOMI. The present patients underwent surgery on the day of admission, presumably because of the possibility of intestinal necrosis. Disease severity was thus likely worse in the present study. Similarly, the present patients in the vasodilator group were more likely to receive mechanical ventilation, renal replacement therapy, vasopressors, and blood transfusions than were those in the previous study.

During initial laparotomy on the day of admission, necrotic bowels are often resected. In the present study, most patients underwent abdominal surgery with bowel resection on the day of admission. Vasodilator therapy might not have reduced mortality in the present study because most regions affected by NOMI were necrotic and resected during the laparotomy. Therefore, vasodilators may rescue regions affected by NOMI that have not yet developed transmural bowel necrosis in abdominal surgeries on the day of admission.

This study has several limitations that warrant mention. First, it was a retrospective cohort study without randomization. Although propensity score matching was used to adjust for differences in baseline characteristics and disease severity, there could be residual unmeasured confounders. Second, the present administrative claims database has no information on the reason for selecting additional abdominal surgery ≥3 days after admission. Third, the protocol adopted for use of vasodilator therapy in our cohort was not standardized. Therefore, the dosage and timing of vasodilator administration were determined by clinicians using their own criteria. Fourth, patients who underwent a planned "second look" surgery ≥3 days after admission may have been inadvertently included in the secondary outcome because the current DPC database does not distinguish scheduled from unscheduled surgeries.

Conclusions

To examine the effectiveness of postoperative adjuvant vasodilator therapy with papaverine and/or PGE1, we performed propensity score matching analyses of patients with NOMI who received abdominal surgery. There was no significant difference in mortality or the rate of additional abdominal surgery ≥3 days after admission between the control and vasodilator groups.

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Conflict of Interest: The authors declare no conflict of interest in association with this study.

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