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Factors Related to Postoperative Delirium in Patients with Lower Limb Ischaemia: A Prospective Cohort Study

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WHAT THIS PAPER ADDS?

- Postoperative delirium (POD) is associated with severe obstacles to effective nursing care, prolonged recovery times, and longer stays in the intensive care unit, resulting in higher morbidity and mortality. Investigations have spanned various surgical fields over the past half-century, but reported risk factors for the development of POD vary, likely because of the heterogeneity of study cohorts. The current prospective cohort study identified five definitive risk factors for POD in patients undergoing bypasses for limb ischaemia. Predicting the candidates for close postoperative monitoring and interventions to prevent or mitigate POD will benefit the nursing staff and clinicians caring for patients.

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ABSTRACT

Objectives: To preoperatively determine candidates at definitive risk of postoperative delirium (POD), we identified relevant factors in patients with arteriosclerosis obliterans who underwent bypass surgery.
Design: A prospective cohort study.
Patients and methods: 299 patients (age ≥60 years) who underwent bypasses in 1995–2006 were enrolled. Cognitive impairment was assessed by the Revised Hasegawa Dementia Scale, the Confusion Assessment Method was also used, and severity was graded as Grade I–III (mild to severe) based on the Delirium Rating Scale. All patients were followed for 3 years.
Results: POD occurred in 88 patients (29%), with a median age of 75 (10) years (IQR). Onset was 2 (1) days postoperatively, and a duration of 2 (2) days was observed. POD was hyperactive in 89% and was Grade I, II, and III in 11%, 68%, and 21% respectively. Multiple logistic regression analysis identified the following risk factors for POD: age ≥72 years (<0.0001), end-stage renal failure (0.001), multiple occlusive lesions (<0.0001), cognitive impairment (0.003), and critical limb ischaemia (0.034). The 3-year survival rate was similar when comparing POD and non-POD patients (84% vs. 88%, NS).
Conclusions: This study identified 5 risk factors for POD in patients undergoing bypasses for limb ischaemia. Long-term outcomes were similar when comparing the patients who experienced POD with those who did not.

Introduction

Delirium is defined as a transient organic mental syndrome of acute onset, which predominantly occurs in elderly patients who are seriously ill. Postoperative delirium (POD) is associated with severe obstacles to effective nursing care, prolonged recovery times, and longer stays in the intensive care unit, resulting in higher morbidity and mortality as well as higher costs of care.

Concern about these negative consequences has led to widespread investigation of the clinical characteristics of POD, the relevant risk factors, and the outcomes of patients with POD.

Investigations have spanned various surgical fields, including orthopaedic surgery,[1–3] cardiac[4–7] and vascular surgery,[8–10] urology,

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and gastrointestinal surgery, over the past half-century. Regardless, the pathophysiological mechanisms surrounding POD remain poorly defined.

Common predisposing factors for POD include old age and cognitive impairment; these factors have been validated within various cohort studies.[1,2,8,10–13] However, the incidence and significance of other risk factors remain unclear, in part because of the heterogeneity of clinical cohorts.[14] In 1994, our group conducted a preliminary study in patients undergoing vascular surgery that demonstrated a higher incidence of POD in elderly patients undergoing arterial bypasses for critical limb ischaemia (CLI) than in patients undergoing other types of procedure (e.g. arterial bypass for claudication, aortic replacement for abdominal aortic aneurysm). As a follow-up to these observations, our group initiated a cohort study in April 1995.

Interim analysis showed that the incidence of POD was high (42%) in patients over 70 years and CLI was identified as a specific risk factor for POD.[8] The goal of the present study was to identify other risk factors for the development of POD in elderly patients undergoing arterial bypass surgery for chronic lower limb ischaemia.

Patients and Methods

Study design

This was a prospective cohort study designed to identify risk factors for the development of POD in elderly patients with chronic lower limb ischaemia due to arteriosclerosis obliterans (ASO) who underwent elective bypass surgery. The preliminary study was initiated in 1994, and this cohort study was initiated in 1995. Enrolment was finished in 2006, and the final three-year follow-up was completed in March 2009. The ethics committee in the Asahikawa Medical University was not formed until 2005, and thus institutional ethical approval for this study protocol was not obtained.

ASO patients

Between April 1995 and March 2006, 490 consecutive ASO patients underwent bypasses at Asahikawa Medical University Hospital and were screened for participation in the study. Inclusion criteria were as follows: age $\geq$60 years, symptomatic ASO manifesting as disabling claudication, rest pain or ischaemic tissue loss, and suitability for elective bypass surgery. Of 490 patients, 95 were excluded because of the unavailability of a preoperative interview as a result of a profound mental disorder, critical illnesses, or a simultaneous operation for associated diseases. The remaining 395 patients were invited to participate in the study, and 299 patients ultimately consented to participate and were enrolled. The procedures for 299 patients included 259 conventional bypasses, 27 extra-anatomic bypasses, and 13 hybrid operations consisting of simultaneous infrainguinal bypass and balloon angioplasty for iliac artery lesions. Seventeen underwent revision surgery in the early postoperative phase for vein graft thrombosis.

Assessment for preoperative cognitive status

After enrolment and before surgery, cognitive status was assessed in all patients using the Revised Hasegawa Dementia Scale (HDS-R), which is comparable to the Mini-Mental State Examination. The method for assessment by HDS-R has been previously described;[8] the HDS-R consists of nine questionnaires with a scale of 0–30. A score of 20 or less indicates mild cognitive impairment.

Assessment for POD

All patients were admitted to the intensive care unit or high care unit after surgery, and postoperative status was carefully screened by nursing staff and documented in daily nursing records. The Confusion Assessment Method (CAM)[15] was applied to borderline patients to determine whether delirium was present. In addition, delirious patients were classified into three subtypes: hyperactive, hypoactive, and mixed type. The severity of POD was assessed by modified assessment criteria based on the Delirium Rating Scale (DRS)[16] and classified as Grade I–III (mild, moderate, and severe) (Table 1).

Relevant factors for POD

Patient characteristics were recorded (Table 2). Specific factors related to bypass surgery included severity of ischaemia, extent of arterial occlusion, and bypass procedures. Severity of limb ischaemia was dichotomised between claudication, rest pain, and gangrene/ulcer, and between claudication and CLI (including rest pain with ankle pressure $<$50 mmHg and tissue loss with $<$70 mmHg in TASC-II criteria[17]).

Patients with incompressible arterial calcification were sorted according to their clinical manifestations. Other parameters included methods of anaesthesia, intraoperative transfusion, operative time, early reoperation because of graft thrombosis, and results from routine preoperative laboratory tests (Table 3).

Follow-up for outcome

All patients underwent follow-up for 3 years after surgery (at 3-month intervals for the first 2 years and every 6 months thereafter) to assess bypass graft patency and outcomes. Cognitive status was also serially assessed in patients who rated lower than 21 in preoperative HDS-R testing. These patients underwent repeat HDS-R testing every 6 months for 3 years or until their scores improved to reach the normal range.

Statistical methods

All statistical analyses were performed using the statistical software package SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Estimation of continuous and categorical variables was performed using medians (interquartile rage: IQR), and percentages.

Age and operative time were dichotomised by constructing receiver-operating characteristic curves at 72 years and 376 min, respectively, whereas the other variables were dichotomised by their respective standards or normal values. All variables were

Table 1
Categories and respective criteria for severity of delirium.

Grade	I (Mild)	II (Moderate)	III (Severe)
Awareness of own medical state	Yes	No	No
Cognitive deficits	No–Yes	Yes	Yes
Lability of mood	No–Yes	Yes	Yes
Altered speech and/or behaviour[a]	1–2 times	Several	Frequent
Management			
Nursing care level	Careful	Very careful	Intensive
Coaxing	Often	More often	Repeatedly
Restraints	No	No	Use
Medication	No	No	Rarely

[a] When abnormal speech and/or dangerous behaviours due to perceptual disturbances, illusions, hallucination, and/or delusions are recognised; Coaxing, persuading the patient to stop dangerous behaviours, such as pulling out intravenous lines or gastric tube, or leaving bed; Restraints, physical restraints to prevent dangerous behaviour; Medication, haloperidol was used.

Table 2
Univariate analysis of the relationship between postoperative delirium and patient characteristics, specific factors of bypass surgery, and operative factors.

	Total $N = 299$	Delirium $n = 88$ (29%)	Non-delirium $n = 211$ (71%)	*P*-value
Patients' characteristics:				
Age (Me [IQR])	72 (10)	75 (10)	70(11)	<0.0001
60 to 71[a] years	147	24 (16%)	123 (84%)	
≥72[a] years	152	64 (42%)	88 (58%)	<0.0001
Sex				
Female	38	11 (29%)	27 (71%)	
Male	261	77 (30%)	184 (70%)	0.9441
BMI (Me [IQR])	22 (4)	22 (4)	21 (4)	0.6371
≥18.5 kg/m^2	256	72 (28%)	184 (72%)	
<18.5 kg/m^2	43	16 (37%)	27 (63%)	0.2265
Prevalent operative risk factors				
Hypertension	218	68 (31%)	150 (69%)	0.2730
Diabetes mellitus (type II)	125	35 (28%)	90 (72%)	0.6453
CNS disease	60	19 (32%)	41 (68%)	0.6709
Cardiac disease	102	32 (31%)	70 (69%)	0.5961
End stage renal failure	30	14 (47%)	16 (53%)	0.0290
HDS-R score (Me [IQR])	26 (6)	24 (8)	27(5)	<0.0001
21–30	243	58 (24%)	185 (76%)	
≤20	56	30 (54%)	26 (46%)	<0.0001
Specific factors in bypass surgery:				
Severity of ischaemia				
Fontaine II	173	34 (20%)	139 (80%)	
Fontaine III	48	20 (42%)	28 (58%)	
Fontaine IV	78	34 (44%)	44 (56%)	<0.0001
Preoperative AP (mmHg; Me [IQR])	62 (46)	56 (74)	68 (38)	0.0005
TASC-II				
Claudication	204	45 (22%)	159 (78%)	
CLI	95	43 (45%)	52 (55%)	<0.0001
Type of occlusion				
Single segment	137	29 (21%)	108 (79%)	
Multiple segments	162	59 (36%)	103 (64%)	0.0039
Bypass procedures				
Aorto-femoral bypass	109	30 (28%)	79 (72%)	
Femoro-popliteal/ crural bypass	85	25 (29%)	60 (71%)	
Aorto-femoro-popliteal/ crural bypass	65	24 (37%)	41 (63%)	
Extra-anatomical bypass	27	6 (22%)	21 (78%)	
Hybrid bypass	13	3 (23%)	10 (77%)	0.5788
Operation related factors:				
Method of anaesthesia				
General	122	31 (25%)	91 (75%)	
Combination	177	57 (32%)	120 (68%)	0.2052
Operative time (Me [IQR])	352 (195)	390 (205)	343 (195)	0.0359
<375 min[a]	165	39 (24%)	126 (76%)	
≥376 min[a]	134	49 (37%)	85 (63%)	0.0147
Intraoperative blood transfusion				
Yes	126	51 (40%)	75 (60%)	
No	173	37 (21%)	136 (79%)	0.0004
Early reoperation				
Yes	17	2 (12%)	15 (88%)	
No	282	86 (30%)	196 (70%)	0.0998

[a] Dichotomised by ROC curve; BMI, body mass index; Me, median; IQR, interquartile range; CNS, central nervous system; HDS-R, Hasegawa's dementia scale-revised version; AP, ankle pressure; TASC-II, see text; claudication, AP≥50mmHg; CLI, critical limb ischaemia, including rest pain with AP<50mmHg and tissue loss with AP<70mmHg; Hybrid, percutaneous transluminal balloon angioplasty w/ stent + femoro-popliteal/crural artery bypass.

compared between delirious and non-delirious groups using the Mann–Whitney *U*-test or the chi-squared test, as appropriate. Variables exhibiting significance levels ≤0.1 according to univariate analyses were assessed by multiple logistic regression analysis to determine the strength of the association for the variables by odds ratios (ORs) with 95% confidence intervals (CIs). Furthermore, estimated incidences were obtained using a forward stepwise regression procedure. Survival rates were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. *P*-values less than 0.05 were considered significant.

Table 3
Univariate analysis of the relationship between postoperative delirium and laboratory test results.

	No. of patients with abnormal values	No. of patients with delirium (%)	*P*-value
WBC >9.8 × 10^3/mm^3	34	11 (32)	0.7015
RBC <4.25 × 10^6/mm^3	143	48 (34)	0.1424
Hb <13.4 g/dl	167	53 (32)	0.3458
Ht <39.6%	149	46 (31)	0.6650
TP <6.0 g/dl	32	12(38)	0.2955
Alb <3.8 g/dl	104	39 (38)	0.0272
A/G <1.31	101	45 (45)	<0.0001
BUN >20 mg/dl	104	41 (39)	0.0067
Na <135 or >150 mEq/l	18	6 (33)	0.7092
Cl <96 or >110 mEq/l	11	5 (45)	0.3102

WBC, white blood count; RBC, red blood count; Hb, haemoglobin; Ht, haematocrit; TP, serum total protein; Alb, serum albumin; A/G, serum albumin-globulin ratio; BUN, blood urea nitrogen; Na, serum sodium; Cl, serum chloride.

Results

Incidence and characteristics of POD

The clinical characteristics of patients who developed POD are summarised in Table 4. POD occurred in 88 patients (29%) with a median age of 75 years old (range, 61–91 years). The highest incidence of POD (54%) was among patients with cognitive impairment. The onset of POD ranged from day 2 to day 5, the duration ranged from 24 h to 7 days, and all patients recovered within 7 days. ICU time for POD patients was significantly longer than for non-POD patients. The most common type of POD was hyperactive POD, which occurred in 89%, followed by Grade II, which occurred in 68%. There was no significant relationship between the type and number of risk factors and the severity of POD.

Significant risk factors

Univariate analyses identified the following 8 significant risk factors for the development of POD: advanced age, low preoperative HDS-R score, end-stage renal failure, CLI, multiple occlusive lesions, prolonged operative time, intraoperative blood transfusion, and early reoperation for graft thrombosis (Table 2). No significant correlations were recognised between POD and bypass procedures, including aortic surgery. Analysis of preoperative laboratory testing

Table 4
Incidence and characteristics of postoperative delirium.

No. of patients	299	
No. of delirious patients	88	(29%)
Age (years)	61 to 91	75.4 (9.8)[a]
Onset (days after surgery)	2 to 5	2 (1)[a]
Duration (days)	1 to 7	2 (2)[a]
ICU stay (days)		
POD group	1 to 15	5 (4)[a,b]
Non-POD group	1 to 15	3 (3)[a,b]
Types of delirium		
Hyperactive state	78	(89%)
Hypoactive state	5	(6%)
Mixed state	5	(6%)
Severity of delirium		
Grade I (mild)	10	(11%)
Grade II (moderate)	60	(68%)
Grade III (severe)	18	(21%)

[a] Median (IQR).
[b] $P < 0.0001$.

Table 5
Multiple logistic regression analysis using forward selection procedure for post-operative delirium.

Variable	Odds ratio	(95% CI)	*P*-value
Age ≥72 years	5.5	(2.8–10.7)	<0.0001
End stage renal failure	5.0	(1.9–13.0)	0.001
Multiple segments	2.9	(1.6–5.3)	<0.0001
HDS-R score ≤20	2.8	(1.4–5.6)	0.003
CLI	2.0	(1.1–3.6)	0.034

HDS-R, Revised Hasegawa Dementia Scale; CLI, critical limb ischaemia by TASC-II (see text).

results suggested that low albumin, low albumin/globulin (A/G) ratio, and high blood urea nitrogen (BUN) might be significant risk factors for POD (Table 3). Thus, multiple logistic regression analysis was performed using these 11 candidate risk factors, and identified the following 5 independent risk factors for the development of POD (in order of strength of association): age ≥72 years, end-stage renal failure, multiple occlusive lesions, cognitive impairment, and CLI (Table 5). Expected incidences in the logistic regression model and actual incidences increased with the number of factors with higher association strength, and reached 78–91% and 93%, respectively, when patients had 4 or 5 risk factors (Table 6).

Outcomes of delirious patients

There were no significant differences between the POD and non-POD groups in the preoperative incidence of life-threatening diseases (e.g., cardiac disease and central nervous system disease), and the cumulative 3-year survival rates were similar between patients who experienced POD and those who did not (Fig. 1).

Of the 56 patients with cognitive impairment, 47 patients survived to 3 years, and 27 (57%) experienced recovery of the HDS-R score to the normal range (≥21). POD tended to occur more often in patients who experienced HDS-R recovery than those who did not experience HDS-R recovery (59% (16/27) vs. 45% (9/20), NS).

Discussion

Varying incidences of POD have been reported in different studies. The overall incidence of POD is 37%, with a wide range of 0–74%,[18] and the incidence of POD among clinical studies in specific surgical fields remains widely variable: 6%[7]–34%[5] after cardiac surgery, 24%[3]–40%[2] after orthopaedic surgery, and 20%[19]–39%[10] after vascular surgery.

The type and severity of POD represent practical concerns for postoperative management. Liptzin et al.[20] reported that incidences of hyperactive, hypoactive, and mixed types according to the DMS-III criteria were 15%, 19%, and 52%, respectively, and more recent studies reported that 66%[12]–71%[2] of POD is classified as hypoactive. In contrast, the present study observed that 89% of POD was classified as moderate to severe hyperactive delirium. Further investigation will be necessary to clarify actual incidences of the different types and severities of POD. Another study reported that the proportion of delirium that was classified as severe following orthopaedic surgery was 49%,[3] and Marcantonio et al. reported that 51% of POD cases were classified as severe.[2] We modified the DRS to suite the assessment of early postoperative patients, and 21% of POD cases were classified as severe. Differences in the type and severity of POD among studies may be due to differences in diagnostic tools and disagreement in the categorisation criteria for borderline cases.

Table 6
Actual and expected incidences of postoperative delirium with a logistic regression model using five factors in order of association strength (advanced age, haemodialysis, multiple occlusive lesions, cognitive impairment, and critical limb ischaemia).

Combination of five factors		Range of expected incidences	Averaged actual incidences	Actual no. of patients with combination
No. of factors	No. of combinations			Delirium/total patients
5–4[a]	5	91–78%	93%	13/14
3[b]	8	78–41%	57%	30/53
2[c]	8	41–19%	32%	28/87
1[d]	5	19–8%	12%	13/106
0	1	4%	10%	4/39

[a] 5 combinations include advanced age and one 5-factor-combination.
[b] Including one 4-factor-combination in 8 combinations.
[c] Including two 3-factor-combination in 8 combinations.
[d] Including one 2-factor-combination in 5 combinations.

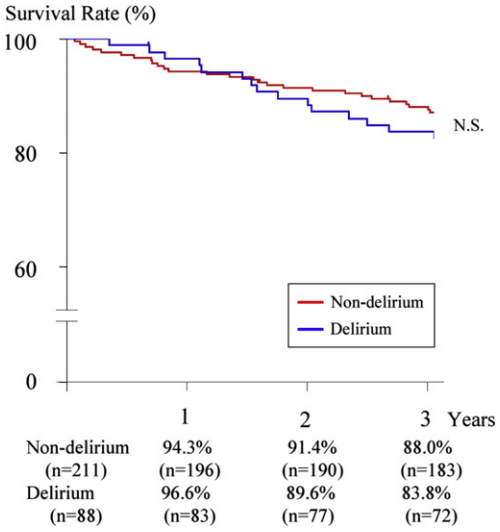

Figure 1. Survival rates of delirious and non-delirious patients after bypass surgery, showing no statistical difference (Kaplan–Meier method and log-rank test).

The present study identified the following five independent risk factors for the development of POD (in order of strength of association): age ≥72 years, end-stage renal failure, multiple occlusive lesions, cognitive impairment, and CLI. When elective surgery is planned for patients with these risk factors, it is important to raise the awareness of nursing staff and clinicians, and interventions such as proactive geriatric consultation[21] and haloperidol use might be useful to prevent POD. Advanced age has been identified as a strong risk factor for POD; one study reported that the incidence of POD was only 22% under 60 and increased to 42%, 72%, and 92% for every additional decade of age.[12] The present study limited the age of participants to ≥60 years in order to be able to focus on a cohort of older patients. Gustafson et al. reported that the best predictor of POD was advanced age, followed by cognitive impairment,[3] which is consistent with findings from other studies.[4,6,12,14] HDS-R is used to screen for mild cognitive impairment, including impairments seen with dementia, depression, or pseudodementia with depression. In the present study, POD occurred in 54% of the 56 patients with mild cognitive impairment, and these results suggest that mild cognitive impairment is associated with the development of POD. The present study demonstrated that CLI and multiple occlusive lesions were independent risk factors for the development of POD. Limb ischaemia is commonly accompanied by disability of physical function, which is an important risk factor for POD.[12,13] Furthermore, multiple arterial occlusive lesions imply latent systemic atherosclerosis, including cerebrovascular lesions, which has been speculated to affect frontal lobe control processes that contribute to the pathogenesis of delirium.[11]

Low serum albumin,[3,12] high BUN,[5] electrolyte disturbances,[10] low haematocrit, and hypoxaemia have previously been reported as significant risk factors for POD. However, none of these factors demonstrated significant differences in the present study. Similarly, a prior history of POD, the methods of anaesthesia, bypass procedures, blood transfusion, operative time, early reoperation, and late redo operation were not risk factors for the development of POD. In contrast, recent studies in vascular surgery have reported that aortic surgery is an important risk factor for POD,[10,22,23] whereas our results demonstrated no significant correlations. Interestingly, end-stage renal failure was an independent risk factor for POD, suggesting that delirium seen in patients with a high BUN may result from the general metabolic disturbance associated with renal insufficiency rather than a high BUN alone.

Smoking history was a probable factor, but we could not assess smoking because of many variations in histories and much missing data. In the literature, Benoit et al. demonstrated that heavy smoking was the most statistically significant predictor of POD in patients with abdominal aneurysm,[22] but other studies have reported no significant correlation.[10]

The combination of multiple risk factors results in additive or synergistic risk. Using a multiple logistic regression model, Rudolph et al. developed a preoperative prediction rule,[24] which identified 4 variables, i.e. prior stroke, mental test score, serum albumin, and depression score, and assigned points from 0 to $\geq$3; the cumulative incidences of POD were 19%, 47%, 63%, and 86%, respectively. In the present study, the expected incidences obtained from the number and combination of risk factors coincided with the actual incidences of POD (Table 6).

Some studies have reported increased mortality, increased readmission rates, and worse outcomes in patients who developed severe POD.[2,12,25] In the present study, there was no significant difference in outcomes between POD and non-POD groups or between mild and severe POD groups at the 3-year follow-up time point.

Limitations

This study has three notable limitations. First, because 20% of consecutive patients were excluded as candidates due to the strict inclusion and exclusion criteria, and 19% of the screened patients were not enrolled in this study due to a failure to obtain informed consent, enrolment was non-consecutive. This is suboptimal for a cohort study, as there may be a risk of selection bias and of failure to identify some predictive factors. Second, the present study did not assess the effect of smoking, drugs, and anaesthetic drugs on POD. Third, the present study focused strictly on cases of POD that resulted in obstacles to nursing care; thus, the CAM was not administered to patients who did not pose problems to nursing care, and patients with less disruptive POD may have gone undetected.

Conclusion

POD occurred in about 30% of elderly patients with lower-limb ischaemia undergoing bypass surgery. These cases were primarily composed of hyperactive delirium, which required extra nursing care. Risk factors for POD included age $\geq$72 years, end-stage renal failure, multiple occlusive lesions, cognitive impairment, and CLI. The expected and actual incidences of POD reached 78%–91% and 93%, respectively, when 4–5 factors were present. The outcomes of patients with POD were not poor in the early phase.

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Conflict of Interest

None.

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