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Incidence and Risk Factors of Acute Postoperative Delirium in Geriatric Neurosurgical Patients

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Objective : Postoperative delirium (POD) is characterized by an acute change in cognitive function and can result in longer hospital stays, higher morbidity rates, and more frequent discharges to long-term care facilities. In this study, we investigated the incidence and risk factors of POD in 224 patients older than 70 years of age, who had undergone a neurosurgical operation in the last two years.

Methods : Data related to preoperative factors (male gender, >70 years, previous dementia or delirium, alcohol abuse, serum levels of sodium, potassium and glucose, and co-morbidities), perioperative factors (type of surgery and anesthesia, and duration of surgery) and postoperative data (length of stay in recovery room, severity of pain and use of opioid analgesics) were retrospectively collected and statistically analyzed.

Results : POD appeared in 48 patients (21.4%) by postoperative day 3. When we excluded 26 patients with previous dementia or delirium, 17 spontaneously recovered by postoperative day 14, while 5 patients recovered by postoperative 2 months with medication, among 22 patients with newly developed POD. The univariate risk factors for POD included previously dementic or delirious patients, abnormal preoperative serum glucose level, pre-existent diabetes, the use of local anesthesia for the operation, longer operation time (>3.2 hr) or recovery room stay (>90 min), and severe pain (VAS>6.8) requiring opioid treatment ($p<0.05$). Backward regression analysis revealed that previously dementic patients with diabetes, the operation being performed under local anesthesia, and severe postoperative pain treated with opioids were independent risk factors for POD.

Conclusion : Our study shows that control of blood glucose levels and management of pain during local anesthesia and in the immediate postoperative period can reduce unexpected POD and help preventing unexpected medicolegal problems and economic burdens.

KEY WORDS : Anesthesia · Diabetes · Geriatric · Pain · Postoperative delirium.

INTRODUCTION

Delirium is an acute confusional state characterized by fluctuating symptoms such as inattention, disturbances of consciousness, or disorganized thinking. Other important hallmarks of this syndrome include disorientation, memory impairment, perceptual disturbances, altered psychomotor activity, and disturbed sleep-wake cycles[12)]. Postoperative delirium (POD), one of the most unexpected and perplexing complications encountered in the perioperative period, is relatively well reported and investigated in the field of cardiac and major non-cardiac orthopedic surgery. According to these reports, POD is associated with greater cost, longer length of hospital stays or institutionalization, more frequent discharge to long-term care facilities, additional complications aside from POD, poor recovery, and mortality[8,19,26)]. Although reversible in nature, POD precedes with some cognitive deficits remaining for up to months after surgery, particularly in the elderly[4,21)]. The main differences between POD and dementia are the potential for reversibility, length of morbidity, and presence of an initiating event. For this reason, clinicians sometimes encounter unexpectedly intriguing situations, if uninformed or unprepared prior to the surgical intervention. Therefore, prevention and early cognition of POD are most important.

However, it is little known about the incidence of POD and risk factors in populations with neurosurgical illness, regardless of the specific disease category including brain, spine or peripheral nervous system. Moreover, as the population becomes older as a whole, the incidence of POD is also likely to increase accordingly, as proven by previous literature[1,4)]. In this study, we investigated the real incidence and risk factors of POD in elderly neurosurgical patients.

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MATERIALS AND METHODS

Study population

In this retrospective study, we collected pertinent demographic and laboratory data of patients who had been admitted to the neurosurgical department for operative procedures during 2 consecutive years between November 2004 and October 2006. During the study period, a total of 1762 consecutive patients were admitted and underwent surgical procedures. Among these, 292 patients were older than 70 years at the time of surgery, and 68 patients were excluded for the following reasons : moribund state or decreased consciousness upon admission or surgery not amenable to command order; incomplete data gathering due to in-hospital death, and lost follow-up due to discharge to recuperating facilities. In total, 224 patients were enrolled in this study.

For patients with acute postoperative cognitive impairment, detected either by caregivers or medical personnel, we immediately obtained radiographic images of the brain, either by computed tomogram (CT) or magnetic resonance imaging (MRI), to exclude the possibility of an organic lesion. For the patients without an organic brain lesion, resident physicians and attending nurses measured the cognitive status using the mini-mental status examination (Korean version (MMSE))[6] and the confusion assessment method (CAM) score[12] on postoperative day 1, 2, and 3. Each interviewer had previously been trained on the interview contents and had a uniform structural written checklist. The interviewers conducted daily interviews with the patients and completed the checklist form as well as medical records denoting the mental state as "agitated", "confused", "disoriented", "delirious", "unable to sleep", or "looks something weird". POD was confirmed when the recorded MMSE score was less than 23 points or relevant features were eminent in the CAM score (1. acute onset and fluctuating course of cognitive and behavioral impairment, 2. inattention or distractibility, 3. disorganized thinking, 4. altered level of consciousness; the test was positive if both of the first two features were present or if 1 and either 3 or 4 were present).

Assessment of risk factors

We selected various known risk factors to verify their applicability to our cohort. Preoperative factors included male, older age (>65 years), patients already suffering dementia or delirium regardless of underlying conditions, history of alcohol abuse (>10 yr), abnormal serum level of sodium (<130 or >150 mmol/L), potassium (<3.0 or >6.0 mmol/L), and glucose (fasting <60 or postprandial 2hr >300 mg/dL), and co-morbidities of more than 2 diseases with or without diabetes[7,19,22]. Operative factors included location of surgery (brain, spine, or peripheral nervous system), type of surgery (emergency vs. elective), type of anesthesia (general vs. local, neuroleptic or regional) and duration of surgical procedures. Types of brain surgery were further subdivided by traumatic, cerebrovascular, neoplastic, and others. Those of spine surgery were categorized by degenerative, traumatic, and others. Types of surgery were divided according whether they were performed at working time (8 A.M. to 6 P.M.) or not. The types of anesthesia were divided as followings : general endotracheal endocircle semiclosed anesthesia attended by anesthesiologists; local infiltration of lidocaine conducted by neurosurgeons aided by midazolam, benzodiazepine and other parenteral analgesics injection; neuroleptic anesthesia with intravenous propofol, midazolam and fentanyl conducted by anesthesiologists, and regional nerve blockade conducted by anesthesiologists[2,20]. Postoperative factors were mainly related to pain and its management such as the time spent in the recovery room, postoperative pain measured by a 10-cm visual analogue scale (VAS), and narcotic usage to control pain[18,23].

Statistical analysis

Univariate comparisons for categorical variables and continuous variables were performed using χ^2-tests and Student's t-tests, respectively. Continuous variables were also dichotomized according to their respective mean values; pre-existent co-morbidities (2.4), duration of surgery (3.2 hr), recovery room stay (90 min), VAS score (6.8). Multivariate association was conducted using the backward regression method with factors having univariate significance. In doing so, we analyzed the association between potential risk factors and the emergence of POD. Finally, we assessed the relative risk (odds ratio : OR) and corresponding 95% confidence interval (CI) for each risk factor. We also assessed the discriminative power of the last multivariate test using the area under the curve for the respective receiver operating characteristic curve[10]. An area under the curve generally ranges from 0.5 (no discriminative power) to 1.0 (perfect prediction). Statistical significance was considered if the p value was less than 0.05.

RESULTS

For the patients included in our study, the mean age (SD) was 70.5±4.26 years (range 65 to 89 years) and 55.5% were male (n=123). Among 224 patients, 48 showed evidence of POD (21.4%) by postoperative day 3 (Table 1). POD appeared on postoperative day 1 in 35 patients (72.9%), on postoperative day 2 in 11 patients, and on postoperative day

Table 1. Clinical summary of elderly patients undergoing neurosurgical operation (n=224)*

Variable	POD (−) (n=176)	POD (+) (n=48)	Total
Preoperative factor			
>70 years	60	22	82
Male	92	31	123
Dementia/delirium	2	26	28
Alcohol abuse (+)	56	21	77
Abnormal serum sodium	43	18	61
Abnormal serum potassium	52	20	72
Abnormal serum glucose	58	39	97
Pre−existent co−morbidities (≥2.4)	87	44	131
Operative factor			
Brain/spine/PNS surgery	61/117/2	14/30/0	75/147/2
Cerebrovascular/Tumor/Trauma	25/18/16	5/3/5	30/21/21
Emergency/elective surgery	48/138	10/28	58/166
General/local anesthesia	130/44	29/21	159/65
Duration of surgery (≥3.2 hr)	43	19	62
Postoperative factor			
Recovery room stay (≥90 min)	34	18	52
VAS score (>6.8)	57	31	88
Analgesic usage	7	22	49

*POD : postoperative delirium, abnormal serum sodium : Na<130 or >150 mmol/L, abnormal serum potassium, : K<3.0 or >6.0 mmol/L, abnormal serum glucose : fasting blood sugar <60 or blood sugar 2 hr postprandial >300 mg/dL, PNS : peripheral nervous system, VAS : 10−cm visual analogue scale, analgesic usage : narcotic usage to control postoperative pain

3 in 2 patients. Except 26 patients with preoperative dementia or delirium, all 22 POD patients showed recovery until the 8th postoperative week; 17 patients (77.3%) recovered either spontaneously (n=12) or with conventional haloperidol/gabapentin medication (n=5) until postoperative day 14. Donepezil HCl (Aricept; Eisai Co, Japan) was empirically prescribed (5 mg to 10 mg), once a day, to 5 patients who showed POD beyond postoperative day 14[25]. Of the 5 patients with persistent POD, 2 recovered by postoperative day 28, and 3 patients recovered by post-operative day 56. Of twenty-six patients with preoperative dementia or delirium, postoperative recovery was found only in 6 patients during hospitalization, ranges from 25 days to 251 days.

Univariate analyses showed that postoperative occurrence of POD correlated with factors such as previous dementia or delirium ($p<0.0001$), abnormal serum glucose level (p=0.020), pre-existent diabetes (p=0.017), operation performed under a local or regional anesthesia (p=0.012), longer operation time (>3.2 hr) (p=0.021), severe pain score (VAS>6.8) (p=0.005), postoperative usage of narcotic analgesics (p=0.040), and longer stay in the recovery room (>90 min) (p=0.035; Table 2).

Multivariate analyses using the backward regression method revealed that previous dementia or delirium (95% CI OR, 289.2-852.4), pre-existent diabetes (95% CI OR, 1.17-2.45), the type of operation being performed under local anesthesia (95% CI OR, 1.34-3.47), and severe postoperative pain requiring opioid analgesics (95% CI OR, 1.45-4.16, and 1.06-2.14, respectively) were independent risk factors of POD, irrespective of the patients' neurosurgical diagnoses (Table 3). The area under the curve was 0.72 (OR, 0.64-0.81).

Table 2. Results of univariate risk factors for POD*

Variable	p−value	Odds ratio (95% CI)
Preoperative factor		
>70 years	0.073	0.86 (0.73−1.54)
Male	0.136	0.46 (0.29−1.06)
Dementia/delirium	<0.0001†	784.2 (392−1520)
Alcohol abuse (+)	0.125	0.52 (0.16−1.04)
Abnormal serum sodium	0.062	0.76 (0.41−1.21)
Abnormal serum potassium	0.090	0.55 (0.21−0.97)
Abnormal serum glucose	0.020†	1.88 (1.13−3.07)
Pre−existent co−morbidities (≥2.4)	0.085	0.35 (0.16−0.82)
Pre−existent diabetes (+)	0.017†	2.01 (1.28−3.86)
Operative factor		
Brain surgery	0.062	0.90 (0.41−2.25)
Traumatic brain injury	0.751	0.51 (0.28−0.81)
Emergency surgery	0.070	0.95 (0.52−1.99)
Local anesthesia	0.012†	1.96 (1.37−5.28)
Duration of surgery (≥3.2 hr)	0.021†	1.32 (1.18−1.86)
Postoperative factor		
Recovery room stay (≥90 min)	0.035†	1.28 (1.07−1.83)
VAS score (>6.8)	0.005†	2.61 (1.57−3.52)
Analgesic usage (+)	0.040†	1.41 (1.15−2.28)

*POD : postoperative delirium, CI : confidence interval, abnormal serum sodium : Na<130 or >150 mmol/L, abnormal serum potassium : K<3.0 or >6.0 mmol/L, abnormal serum glucose : fasting blood sugar <60 or blood sugar 2 hr postprandial>300 mg/dL, VAS : 10−cm visual analogue scale, analgesic usage : narcotic usage to control postoperative pain. †Statistically significant, by χ^2 tests and Student' s t−tests

DISCUSSION

Because the presentation of POD varies and can often be vague and multifaceted in a majority of cases, only a high

Table 3. Results of multivariate risk factors for POD*

Variable	Odds ratio	95% CI	p−value
Previous dementia/delirium	630.4	289.2−852.4	<0.0001
Abnormal preoperative serum glucose (+)	0.82	0.52−1.51	>0.05
Pre−existent diabetes (+)	1.47†	1.17−2.45	0.012
Local or regional anesthesia (+)	2.21†	1.34−3.47	<0.001
Duration of surgery (≥3.2 hr)	0.60	0.35−1.42	>0.05
Recovery room stay (≥90 min) (+)	0.51	0.38−1.41	>0.05
VAS score (> 6.8) (+)	1.99†	1.45−4.16	<0.001
Analgesics usage (+)	1.38†	1.06−2.14	0.038

*POD : postoperative delirium, CI : confidence interval, abnormal serum glucose : fasting blood sugar <60 or blood sugar 2hr postprandial >300 mg/dL, VAS : 10−cm visual analogue scale, analgesic usage : narcotic usage to control postoperative pain. †Statistically significant, by multivariate analysis using backward regression method index of suspicion makes the patient approach, diagnosis, and ongoing management amenable. If patients already have dementia or delirium preoperatively, occurrence of POD is very likely and moreover, recovery from POD is also very unlikely to happen irrespective of treatment provided. Once POD is strongly suspected, swift initial action should be attempted either by close patient interview with psychiatric tools (MMSE, CAM, etc), radiographic images (CT, MRI), or by any other method to confirm POD or to rule out the presence of an organic brain lesion. One major finding in this study was that we were able to reduce the incidence of POD by identifying at-risk patients earlier in the preoperative period and by managing blood sugar levels, pain, and anxiety during the perioperative period, albeit only to limited extent. Effective control of postoperative pain plays the most crucial role in reducing POD, and this finding is compatible with that of previous reports, although we did not provide details on the methods of analgesia[9,18)].

Incidence and risk factors of POD

The incidence of POD varies between 5.1% and 52.5% in elderly patients undergoing major surgery, and certain procedures such as hip fracture or aortic surgery having higher risk of POD[4,5,7,8,21,22,27)]. Because there has been practically no neurosurgical literature on the incidence of POD, we could not compare the 21.4% incidence in our study with that from similar studies. We could only assume that the incidence was not much higher than expected. Several contributing factors such as exclusion of a certain percentage of decreased consciousness due to brain lesions and in-hospital mortality could result in a lower incidence. Unless these factors had been excluded, the incidence would have been increased further more. For patients with preoperative delirium or dementia, the assessment of new onset POD was not easy and straightforward, but the literature strongly supported this association[4,19,21,27)]. Persistence, alteration or aggravation of prior symptoms might be culprits to suspect POD. With strong suspicion, close attention and cautious patient monitoring, prompt detection can be achieved.

With regard to length of time for POD emergence, the findings of our study are comparable with those of previous reports. In our cohort, 72.9% of patients exhibited POD on postoperative day 1, 22.9% on postoperative day 2, and the remainder on postoperative day 3. POD usually occurs by the third postoperative day and becomes worse at night[4,18,23)]. This fact suggests that intensive postoperative management of pain, blood sugar levels, and patient discomfort should be conducted as soon as the patient leaves the operating room and should be sustained until at least postoperative day 3. The factors associated with the development of POD in our study were similar to those identified in previous reports[1-4,7,13-18,27)]. Surprisingly, we could not obtain any significant relationship between brain surgery and POD, regardless of disease category or surgery, such as performed on microscope or by naked-eye. The incidence of POD was not different between patients who underwent surgery on the brain and spine diseases. Our findings reaffirm the predominant role of systemic, extracerebral factors on the occurrence of POD.

Pathophysiology and treatment of POD

As for the pathophysiology of POD, reversible neuronal dysfunction is likely the cause, following toxic or metabolic disturbances. Systemic inflammatory response and adhesion, activation and degranulation of some vasoactive substances and the consequent development of perivascular edema, result from the interaction between leukocytes and endothelial cells. This reversible edema presents as a conduction disability of the nerve and decreased cerebral perfusion in certain brain areas. Acetylcholine also seems to play a crucial role in the development of POD due to its various roles in the regulation of cerebral functions, including motor activity, rapid eye movement (REM) sleep, mood, attention, and memory. Thus, the lack of acetylcholine or relative excess of dopaminergic transmission seems to be connected to the development of POD. The age-dependent decrease of acetylcholine transmission is a physiologic process, and reduced "cholinergic reserve" may be responsible for the significantly higher incidence of POD among geriatric patients[8,11,16)]. These findings normally do not appear on conventional radiographic images as organic brain lesions, since only sophisticated targeted images can display such tiny chemical abnormalities.

The primary treatment of delirium involves focusing on the underlying cause and factors, but severe behavioral, environmental, and psychiatric symptoms also require treatment. If non-pharmacological interventions are ineffective, psychotropic medication may be needed. Neuroleptics such as haloperidol or droperidol, and benzodiazepine are generally employed to control symptoms like agitation, restlessness, and altered perception. Vitamins may be useful for alcoholics and melatonin has been suggested to prevent and treat delirium by normalizing alterations in the sleep-wake cycle. Physostigmine and metrifonate are also considered breakthrough pharmaceuticals for treating behavioral problems associated with POD by ameliorating cholinesterase activity[4,9)]. Successful use of donepezil, an effective regimen against dementia that lowers serum anticholinergic activity, has been recently reported in a delirious patient[19)]. Most POD patients improve spontaneously or with medical treatment by 3 months[9], it is still debatable whether these patients simply follow their natural course or specifically respond to the drug treatment.

Limitations and future directions

Some crucial limitations of this study should be acknowledged. First, because this study was conducted by the retrospective review of patients at a single institution, collection bias was likely to occur, although we think that we gathered all such cohorts. This might act on omission of possible delirious patients at that time point. A multicenter, prospectively designed study with refined criteria is mandated to eliminate such a bias. Second, we are not sure that selected 224 patients enrolled in this study stood for a real proportion of POD. In other words, of the 68 patients excluded, patients who died during hospitalization, who were severely moribund or unresponsive to command probably had significant delirium prior to death. This can add further skewing in interpretation of retrieved raw data. Third, with regard to the anesthesia, we are still not confident why patients who had undergone local and regional anesthesia had a higher incidence. This was likely due to their overall risks being higher, thus precluding them from undergoing general anesthesia. From a view point of pain and anxiety, we think that local or regional itself is a definite risk factor, but we also suspect this just identified a higher risk patient population. Finally, most importantly, because we did not know the precise natural course and fundamental pathophysiologic processes of POD, a critical reappraisal of risk factors, disease-modifying variables, and appropriate management should be conducted. Differentiating delirium from dementia is generally relied upon their time course, instead of severity or associated conditions and therefore, our report lacks in some end-point assessment.

CONCLUSION

In summary, our study highlights the importance of strict control of blood sugar levels and postoperative pain during local anesthesia and in the immediate postoperative period for the prevention or treatment of POD. When dealing with high-risk patients prior to a surgical procedure, it might be helpful to include the probable incidence of POD with informed consent and to counsel the immediate family members or surrogates in order to avoid unexpected economic burdens and unnecessary medicolegal problems.

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