



CLINICAL ARTICLE

Early Intervention of Perioperative Delirium in Older Patients (>60 years) with Hip Fracture: A Randomized Controlled Study

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Objective: To explore the effect of early intervention for perioperative delirium in older (> 60 years) hip fracture patients.

Methods: This prospective study enrolled hip fracture patients aged ≥ 60 years who were admitted into our hospital between July 2011 and August 2019. Hip fractures were classified according to the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification. This study included patients with isolated hip fracture and excluded patients with pathological or peri prosthetic fracture or patients with multiple traumatic injuries and high-energy trauma. They were randomized to receive conventional orthopedic care group ($n = 65$) or comprehensive orthopedic care group including preoperative psychological counseling and preventative risperidone ($n = 63$). Daily assessment was based on patient interview with the CAM-CR, and delirium was diagnosed by the Delirium Rating Scale (DRS-R-98). The rate, severity and duration of perioperative delirium and the length of postoperative stay were analyzed.

Results: Totally 200 patients were screened for eligibility. Twenty patients were excluded due to alcohol abuse and 40 were excluded because of brain lesions on head CT. In addition, 12 patients were excluded because of impaired cognition. Finally 128 patients were enrolled. Their mean age was 75.3 ± 2.2 years for the comprehensive orthopedic care group and 73.5 ± 6.1 years for the conventional orthopedic care group, and 53.9% of the patients were female. Sixty-eight (53.1%) patients had intertrochanteric fracture, 39.8% patients had femoral head fracture, and 7.0% patients had subtrochanteric fracture. In addition, 58.6% patients underwent internal fixation and 41.4% patients received arthroplasty. In this study, 63 patients were randomized to the comprehensive orthopedic care group and 65 patients to the conventional orthopedic care group. The two groups were comparable in demographic and baseline characteristics ($P > 0.05$). The rate of perioperative delirium was significantly lower in the comprehensive care group vs the conventional care group (15.9% vs. 30.8%; $P < 0.05$). The comprehensive care group had significantly reduced length of postoperative hospital stay vs the conventional care group (11.3 ± 2.5 days vs. 14.2 ± 2.2 days, $P < 0.01$). The mean DRS-R-98 score was 7.1 ± 2.7 for the comprehensive care group, and was significantly lower than that of the conventional orthopedic care group (11.2 ± 3.0 ; $P < 0.05$).

Conclusions: Our early intervention may reduce the incidence of perioperative delirium in elderly hip fracture patients (>60 years).

Key words: Delirium; Early intervention; Elderly; Hip fracture; Perioperative

Introduction

Delirium is characterized by disturbed consciousness, altered cognition, or perceptual disturbance and can

occur as a severe neuropsychiatric complication of hip fracture in older persons (aged >60 years).^{1,2} Delirium is a geriatric syndrome of acute onset and has a fluctuating course

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Received 11 June 2020; accepted 18 February 2022

Orthopaedic Surgery 2022;14:885-891 • DOI: 10.1111/os.13244

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and frequently occurs in the perioperative period and is associated with increased risk of postoperative mortality, morbidity, poor functional outcomes, and long hospital stay and increased healthcare costs.³⁻⁵ The incidence of perioperative delirium in elderly (aged ≥ 65 years) hip fracture patients is as high as 15% to 61%.⁶ In China, the incidence of perioperative delirium in elderly hip fracture patients is reported to be 22.3%.⁷ The higher incidence of perioperative delirium in elderly patients with hip fracture, in addition to advanced age, may also be related to the fact that most hip fractures are emergency surgeries, the residential environment and life habits have changed dramatically, and patients often have combined metabolic disorders, malnutrition, and energy intake disorders due to cerebrovascular disease.⁸ However, although the incidence of delirium is high, clinical recognition rate is low and mainly related to the clinical characteristics of delirium. The clinical manifestations of delirium can be divided into: (i) apathy type, patients mainly show drowsiness, weakness, and weak response to things; (ii) restless type, patients mainly show high alertness state, easy agitation, disorientation and delusions; and (iii) mixed type, mind between the two or alternating between apathy type and agitation type symptoms. Most nonpsychiatric specialists recognize and value agitation type delirium easily, whereas recognition of apathy type delirium is difficult, and it is common in older patients, has low recognition rate in general hospitals, can be easily missed or misdiagnosed as anxiety and depression, and leads to the inability to perform effective early intervention. Many studies on perioperative delirium focus on risk analysis and risk reduction such as preoperative assessment of risk factors and active treatment of perioperative hypotension, hypoxemia, and anemia which are known risks of perioperative delirium in elderly hip fracture patients.⁵ A recent meta-analysis showed that comprehensive geriatric care may reduce the incidence of perioperative delirium and also lessen the severity of perioperative delirium as well as shorten the duration of perioperative delirium.⁹

Two recent meta analyses showed that haloperidol or second-generation antipsychotics for the prevention of delirium did not shorten length of stay in hospital and also had no effect on cognitive function and delirium severity.¹⁰ However, studies have shown that perioperative delirium is preventable in 30%–40% of the cases.¹¹ In patients undergoing cardiac surgery, perioperative use of pharmacologic agents has been shown to prevent postoperative delirium development. A prospective study of 263 patients with hip fracture (≥ 65 years) who were cognitively intact at admission showed that a multi-factorial program including intensified pre-hospital and perioperative treatment and care could reduce the incidence of delirium during hospitalization by 35%.¹² In the current prospective randomized controlled study, we investigated the effect of a comprehensive orthopedic care program including psychological counseling and preventative risperidone vs conventional orthopedic care on the rate of perioperative delirium in 128 older hip fracture patients

(≥ 60 years). The purpose of this study was to investigate the effects of early intervention on the incidence, severity, and outcomes of perioperative delirium in elderly (>60 years) hip fracture patients.

Patients and Methods

Patients

This prospective study enrolled hip fracture patients aged ≥ 60 years who were admitted into our hospital between July 2011 and August 2019. Hip fractures were classified according to the Arbeitsgemeinschaft für Osteo-synthesefragen (AO) classification (A1: 91; A2: 28; A3: 9).

Inclusion criteria: (i) patients were over 60 years old; and (ii) with an isolated hip fracture.

Exclusion criteria: (i) patients with pathological or peri-prosthetic hip fracture or patients with multiple traumatic injuries and high-energy trauma; (ii) the presence of cerebral diseases by physical examination and head CT; (iii) severe dementia according to the Reisberg Global Deterioration Scale (GDS); (iv) a history of psychiatric illness; (v) a history of psychologically active drug abuse and alcohol abuse; and (vi) patients who died during the study.

Ethical Statement

The study protocol was approved by the ethics committee of the authors' affiliated institution (No. KY201105). The study was registered at Chinese Clinical Trial Registry (No. ChiCTR2200055446). All study patients provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki.

Therapeutic Interventions

Patients were randomly assigned to the comprehensive orthopedic care group or the conventional orthopedic care group according to a computer generated randomization sequence after informed consent was obtained. An opaque, sealed envelope was opened to determine group assignment after informed consent was obtained. Patients were not informed of their treatment assignment.

The conventional orthopedic care group received routine orthopedic care including preoperative skin traction, analgesia, correction of electrolyte imbalance, postoperative fluid therapy, treatment of hypoxemia, and monitoring vital signs. Patients who showed manifestations of delirium and a CAM-CR score ≥ 20 received risperidone (0.5–3 mL/day).

The comprehensive orthopedic care group received, apart from routine orthopedic care, preoperative psychological counseling and self-hypnosis instruction. Self-hypnosis was carried out according to certain prompts, and on this basis, patients can use their own imagination to achieve a self-hypnotic state. The time for self-hypnosis is generally 10–15 min.

In addition, patients with no signs of delirium and a CAM-CR score <20 were orally given preventative risperidone 0.5–2 mL/day and risperidone dose was adjusted

according to daily CAM-CR scores. For patients who had signs of delirium and a CAM-CR score ≥ 20 , risperidone was increased, and psychiatric consultation was also requested. The primary outcome was the rate of delirium in both groups. Adverse events were reported including wound infection, postoperative thrombosis other medical events (cardiac, urinary, neurological, or pulmonary), or death.

Postoperative Outcome

This study assessed the average length of hospital stay, infection, lower extremity thrombosis, and mortality in both groups.

Outcome Measure

This study retrieved demographic and baseline variables of the study patients from the hospital's record system including age, gender, fractures by location, treatment, anesthesia and concomitant diseases.¹³

Confusion Assessment Method-Chinese Revision (CAM-CR)

All patients were assessed daily after admission by the CAM-CR.¹⁴ The CAM-CR has been validated for use in Chinese subjects.¹⁴ The CAM-CR includes acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbance, psychomotor retardation, psychomotor agitation, and altered sleep-wake cycle. A score ≥ 20 indicated delirium, and a score < 19 excluded delirium.

DRS-R-98

After delirium was diagnosed, the Delirium Rating Scale (DRS-R-98) was used to differentiate dementia and schizophrenia. DRS-R-98 includes three items for diagnosis and 13 items for severity of delirium. Severity items are rated on a scale of 0–3 and diagnostic items are rated on a scale of 0–2 or 0–3. The maximum possible score for severity items is 39, while the maximum total score is 46. Higher scores indicate more severe delirium. DRS-R-98 has been validated for use in the Chinese population.¹⁵ All raters received training in the use of DRS-R-98 and demonstrated consistency with an ICC of 0.81–0.85. Patients were rated at 9:00 p.m. each night and raters gave the score of patients.

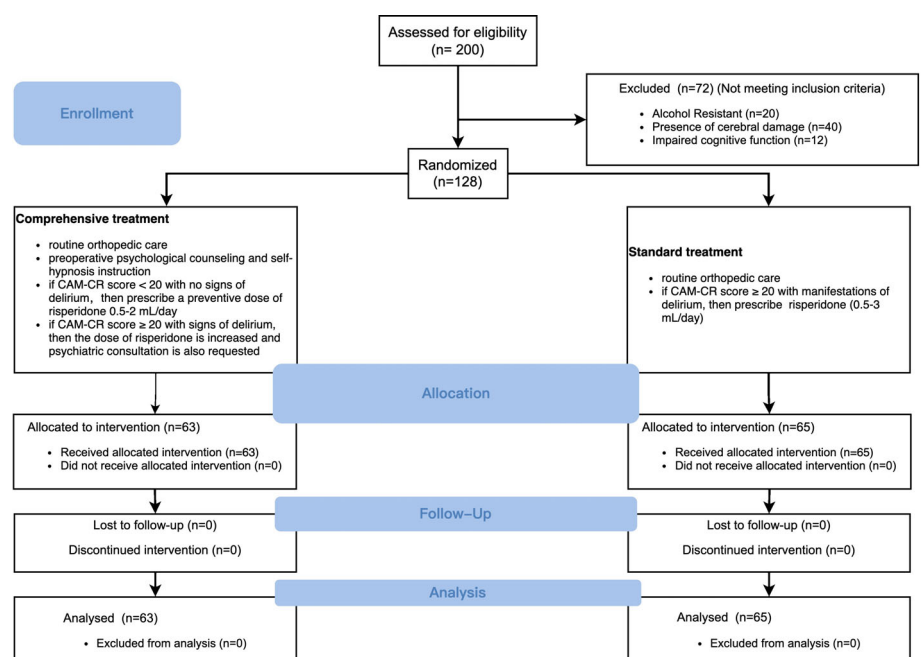
Discharge Standard

The discharge standard for all the patients includes: (i) no pain and other complaints; (ii) no signs of infection in wound; (iii) good functional exercise of affected limbs; and (iv) no abnormalities in mental behavior.

Statistical Analysis

Frequencies and descriptive statistics were used for reporting baseline variables in the study population. Statistical analysis was done using SPSS18.0 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed in mean \pm SD. The incidence of delirium between the two groups and between different ages were compared using χ^2 test and Fisher's exact test. Descriptive data were analyzed using Student's *t* test. $P < 0.05$ indicated statistically significant difference.

Fig. 1 Flow chart of patients with isolated hip fracture. Totally 200 patients were screened for eligibility. Twenty patients were excluded due to alcohol abuse and 40 were excluded because of brain lesions on head CT. In addition, 12 patients were excluded because of impaired cognition. Finally 128 patients were enrolled. They were randomized to receive conventional orthopedic care ($n = 65$) or comprehensive orthopedic care including preoperative psychological counseling and preventative risperidone ($n = 63$).



Results

General Results

The study flowchart is shown in Fig. 1. Sixty-five patients were classified in receive conventional orthopedic care group and 63 patients were classified in comprehensive orthopedic care group including preoperative psychological counseling and preventative risperidone. Their mean age was 75.3 ± 2.2 years for the comprehensive orthopedic care group and 73.5 ± 6.1 years for the conventional orthopedic care group and 53.9% of the patients were female. Sixty-eight (53.1%) patients had intertrochanteric fracture, 39.8% patients had femoral head fracture, and 7.0% patients had subtrochanteric fracture. In addition, 58.6% patients underwent internal fixation and 41.4% patients received arthroplasty. Sixty-three patients were randomized to the comprehensive orthopedic care group and 65 patients to the conventional orthopedic care group. The two groups were comparable in demographic and baseline characteristics ($P > 0.05$; Table 1). The mean dose of risperidone was 0.83 ± 0.17 mL/day for the comprehensive orthopedic care group and 1.04 ± 0.21 mL/day for the conventional orthopedic care group. The mean treatment duration was 3.8 ± 1.2 days for the comprehensive orthopedic care group and 3.6 ± 0.3 days for the conventional orthopedic care group.

Outcomes of Delirium

The mean baseline DRS-R-98 score was 18.3 ± 3.4 for the comprehensive orthopedic care group, and was only 86% of the conventional orthopedic care group (21.3 ± 3.6 ; $P < 0.05$). The incidence of delirium in the comprehensive orthopedic care group ($n = 10$, 15.9%) was 51% of the conventional orthopedic care group (30.8%; $\chi^2 = 3.96$, $P < 0.05$). The duration of delirium in the comprehensive orthopedic care group (2.1 ± 1.0 days) was 62% of that in the conventional orthopedic care group (3.4 ± 1.6 days, $P < 0.05$). Meanwhile, the mean DRS-R-98 score at the end of intervention was 7.1 ± 2.7 for the comprehensive orthopedic care group, and was only 63% of the conventional orthopedic care group (11.2 ± 3.0 ; $P < 0.05$) (Table 2). No patient died while delirious.

We further determined the rate of delirium in our patients according to age. In patients aged between 60 and 75 years, the rate of delirium was 8.9% for the comprehensive orthopedic care group and 48% for the conventional orthopedic care group (18.6%, $P < 0.05$). Moreover, patients aged above 75 years, the rate of delirium was 33.3% for the comprehensive orthopedic care group, 61% for the conventional orthopedic care group (54.5%, $P < 0.05$). In the comprehensive orthopedic care group, the rate of delirium was significantly lower in patients aged between 60 and 75 years vs those aged above 75 years ($\chi^2 = 4.07$, $P < 0.05$) (Table 3). Furthermore, in the conventional orthopedic care group, the rate of delirium was lower in patients aged between 60 and 75 years vs those aged above 75 years ($\chi^2 = 8.82$, $P > 0.05$).

Table 1 Demographic and baseline characteristics of the study population

Groups	Fractures by location, n (%)				Treatment, n (%)		Anesthesia, n (%)				Concomitant diseases, n (%)				
	Female gender, n (%)	Age, years	N	Femoral head fracture	Intertrochanteric fracture	Subtrochanteric fracture	Internal fixation	Arthroplasty	Regional	General	Respiratory diseases	Cardiovascular diseases	Endocrine diseases	Diseases of the gastrointestinal tract	Diseases of the urinary tract
The comprehensive orthopedic care group	35 (55.6)	75.3 (2.2)	63	24 (38.1)	33 (52.4)	6 (9.5)	38 (60.3)	25 (39.7)	45 (71.4)	18 (28.6)	21 (33.3)	14 (22.2)	16 (25.3)	6 (9.52)	0 (0)
The conventional orthopedic care group	34 (52.3)	73.5 (6.1)	65	27 (41.5)	35 (53.9)	3 (4.6)	37 (56.9)	28 (43.1)	49 (75.4)	16 (24.6)	18 (27.6)	17 (26.1)	14 (21.5)	7 (10.7)	3 (4.61)
<i>P</i> Value	0.71	-	-	0.69	0.86	0.27	0.69	0.69	0.61	0.02	0.48	0.6	0.99	0.81	0.08

The data were expressed as Mean (SD)

TABLE 2 Rate and duration of delirium of the study population

Groups	Delirium, n (%)	Duration of delirium, days	DRS-R-98 scores	
			Initial	Final
The comprehensive orthopedic care group	10 (15.9)	2.06 ± 1.03	18.3 ± 3.4	7.1 ± 2.7
The conventional orthopedic care group	20 (30.8)	3.42 ± 1.57	21.3 ± 3.6	11.2 ± 3.0
t	-	5.76	4.80	8.26
P	-	<0.05	<0.05	<0.05

The data were expressed as Mean (SD)

Table 3 The rate of postoperative delirium by age

Group	Age, years	
	60–75	76–92
The comprehensive orthopedic care group	4/45 (8.9)	6/18 (33.3)*
The conventional orthopedic care group	8/43 (18.6)	12/22 (54.5) ^b
χ^2	1.03	1.04
P	>0.05	>0.05

* P > 0.05 vs the intervention group in the same age range; ^b P < 0.05 vs the standard treatment group.

Hospitalization Time

The mean hospital stay was 11.3 ± 2.5 days for the comprehensive orthopedic care group and was only 80% of the conventional orthopedic care group (14.2 ± 2.2 days) ($t = 6.79$; $P < 0.01$).

Complications

No infection and thrombosis of the lower extremities were observed in both groups. No patients died during hospitalization. All patients were discharged from the hospital.

Discussion

Importance of Recognition and Management of Perioperative Delirium

Perioperative delirium is associated with increased risk of postoperative mortality, a rise in the rate of postoperative complications such as lung infections and prolonged postoperative hospital stay and elevated healthcare costs.¹⁶ Preoperative assessment of risk factors and active management of known risks of perioperative delirium such as perioperative hypotension help reduce the rate of perioperative delirium.¹² Nie *et al.* show that pain and cognitive impairment are risks of perioperative delirium in older hip fracture patients.¹⁷ Our current prospective randomized controlled study on the effect of a comprehensive orthopedic care program including psychological counseling and preventative risperidone in

older Chinese hip fracture patients demonstrated that our comprehensive orthopedic care program significantly reduced the rate of perioperative delirium vs conventional orthopedic care (15.9% vs. 30.8%). This is also accompanied by significantly shortened duration of perioperative delirium and markedly reduced length of postoperative stay. Björkelund *et al.* showed that a multi-factorial program including intensified pre-hospital and perioperative treatment and care significantly reduced the rate of delirium as well as shortened duration of delirium.¹² Our study and the study by Björkelund *et al.* show that an integrated approach combining psychological counseling, environmental and pharmacological strategies is effective in reducing the incidence of perioperative delirium, shortening the duration of delirium and decreasing hospitalization costs.

Quantitative Assessment and Intervention Modalities of Controllable Risk Factors for Delirium

Many investigators have pointed out that prevention is more important and effective in reducing the occurrence of perioperative delirium than treatment in older hip fracture patients.^{1,2} Active preoperative assessment and control of risk factors of perioperative delirium could reduce the incidence of perioperative delirium and severity of the first episode of perioperative delirium and lessen neurological impairment, thus facilitating functional recovery of the patients.¹¹ Many studies¹⁸ have shown that uncontrollable risk factors of perioperative delirium include advance age, a history of psychiatric illness, underlying diseases such as dementia, diseases of the urinary system, and lung and heart diseases, type of surgery (orthopedic surgery, and cardiovascular surgery), and controllable risk factors include infection, fever, postoperative pain, sleep disorder, electrolyte disorder and hematological abnormalities. Prevention and therapeutic intervention in perioperative delirium is a rather challenging task given the presence of numerous risk factors of perioperative delirium and the myriad manifestations of delirium. Currently, diagnosis and treatment of perioperative delirium in older hip fracture patients are mostly empirical and do not have consensus guidelines for diagnosis and tailored treatment. As a result, missed or delayed diagnosis, delayed or unnecessary treatment occurs. Our comprehensive

orthopedic care program provides early intervention in the perioperative period targeting controllable risk factors with a focus on perioperative psychological counseling and preventative risperidone therapy, showing that perioperative psychological counseling and preventative risperidone therapy offer an effective approach for managing perioperative psychological counseling and preventative risperidone therapy of delirium. In our study, both CAM-CR and DRS-R-98 scores were used to diagnose perioperative delirium and quantify delirium severity in older hip fracture patients, which provides guidance in our early intervention efforts for preventing and controlling perioperative delirium.

Our comprehensive orthopedic care program led to a significant reduction in the controllable risk factors of perioperative delirium vs conventional orthopedic care (15.9% vs. 30.8%) and a marked decrease in the length of postoperative hospital stay. Management of risk factors of delirium such as correction of electrolyte imbalance, postoperative fluid therapy, and treatment of hypoxemia was undertaken in both the conventional orthopedic care group and the comprehensive care group, which helps prevent and control of perioperative delirium. In addition, our comprehensive care program provided preoperative psychological counseling to the patients and used CAM-CR scores to promptly diagnose delirium. Patients in the conventional orthopedic care program were treated with risperidone when they showed signs of delirium and their CAM-CR score was ≥ 20 . By contrast, patients in our comprehensive care program were given risperidone preventatively when their CAM-CR score was < 20 and the patients did not exhibit any signs of delirium. This proactive approach minimizes the chance of missing or delaying diagnosis of delirium and effectively reduces the incidence of perioperative delirium and shortens hospital stay.

In addition, DRS-R-98 scores were used to assist assessment of severity of delirium after the diagnosis was made. DRS-R-98 could be used to dynamically monitor changes in the severity of delirium and help adjust doses of therapeutic drugs after consultation with psychiatric specialists. Our study showed that patients in the comprehensive orthopedic care group had markedly reduced severity of delirium and greatly shortened duration of delirium vs the conventional orthopedic care group. These findings indicate that early intervention in the perioperative period should be carried out with the use of a quantitative instrument such as DRS-R-98 as guidance for adjusting therapy, which avoids unnecessary pharmacotherapy. Together with active management of risk factors of delirium and treatment of delirium, our comprehensive care program greatly reduced severity and duration of delirium.

Management of Uncontrollable Risk Factors for Delirium

It has been shown that advanced age is an independent risk of perioperative period delirium;¹⁹ the incidence of perioperative delirium is increased in patients aged

≥ 65 years, and becomes further elevated in patients aged ≥ 75 years. This may be due to reduced stress coping ability and impaired hepatic detoxification and renal clearance in elderly patients as well as the presence of many concomitant somatic diseases and neurodegenerative diseases. We also found that the rate of perioperative delirium increased with age in our patients, suggesting that the more advanced patients are, the more vigilant the orthopedic care team should be in preventing, diagnosing and treating perioperative delirium so that early intervention can be instituted.

Pharmacologic Prevention and Treatment of Delirium

The study used CAM-CR scores to assess psychiatric symptoms of patients that did not yet meet the diagnosis of delirium; however and guide early intervention for preventing delirium by oral risperidone. This helped reduce the incidence of perioperative delirium. Haloperidol is considered first line drug for delirium, but it causes extrapyramidal symptoms and QT prolongation and other side effects. Risperidone is an antagonist of dopamine and 5-hydroxytryptamine receptor and has fewer side effects and has proven efficacy and can be given orally. The drug has recently been used widely clinically. Wu *et al.*²⁰ showed that risperidone was similar in efficacy to haloperidol but safer for postoperative delirium in hip fracture patients. Other investigators¹² have also shown that together with active management of risks of perioperative delirium, anti-psychiatric medications at low doses can be prescribed to prevent and reduce the risk of perioperative delirium, which is consistent with our study. However, our results may not be generalizable to hip fracture patients who present with delirium or when the onset of delirium occurs beyond the perioperative period. In addition, the size of the study population is still relative small and future trials with a larger patient population should be conducted to confirm our findings. Furthermore, the study was undertaken at a tertiary care setting and the findings may not be applicable to secondary or primary care settings.

Conclusion

In conclusion, for early intervention for perioperative delirium in older hip fracture patients, early diagnosis by using instruments such as CAM-CR for patient evaluation and quantified treatment should be carried out first. In addition, early management of risk factors of perioperative delirium and dynamic monitoring of delirium and correction of risk factors should be undertaken. For patients with worsening psychiatric symptoms, consultation with psychiatric specialists should be carried out. For patients with more advanced age, vigilance and early screening of risk factors can be done. In addition, low dose atypical antipsychotic drugs can be provided. Our comprehensive orthopedic care program effectively reduces the incidence of perioperative delirium, lessens the severity of delirium

and shortens duration of severity and length of hospital stay.

Conflict of Interest

The authors declare there is no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher's web-site:

TABLE S1 The specific course of treatment for each patient

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