Introduction

According to Torre LA et al, it was estimated that 14.1 million new cancer cases occurred, and 8.2 million cancer died from cancer worldwide in 2012. Even today, surgical resection is one of the important methods for treating cancer, and management of postoperative morbidity is essential. However, the rate of postoperative morbidity has been reported to range from 20% to 65%.

Recently, some studies have shown that the development of postoperative complications can reduce a patient’s survival or increase the incidence of recurrence in various malignancies. Among the various postoperative complications, delirium is a common morbidity after surgery. When postoperative delirium occurs, patient management becomes much more difficult, leading to increased costs and severe discomfort for the patient.

Delirium is also associated with increased postoperative mortality and morbidity and with a delayed functional recovery.

However, despite the fact that numerous studies have been performed to investigate postoperative delirium in patients with various types of malignancies, most previous studies have used and evaluated retrospectively collected data with a relatively small sample size. Retrospective studies have many limitations, such as unspecified indications for surgery, heterogeneous patient selection, heterogeneous treatment, and a description bias regarding “delirium”. To overcome the limitations associated with retrospective studies, we focused on cases that were enrolled in randomized clinical trial to evaluate TJ-54 (Yokukansan: a traditional Japanese medicine) for the prevention and/or treatment of postoperative delirium (UMIN000005423). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) was used to diagnose postoperative delirium.

The aim of this study was to evaluate the incidence of postoperative delirium and the predictors of postoperative delirium after surgery for gastrointestinal malignancies using the data from a phase II clinical trial.

Clinical research article

Risk factors for postoperative delirium after gastrointestinal surgery - using randomized Phase II trial data

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Abstract

Background/Aim: Postoperative delirium is a common complication which is associated with increased postoperative mortality and morbidity. The aim of this study was to evaluate the incidence and predictors of postoperative delirium using data from a phase II clinical trial.

Patients and Methods: We analyzed the cases that were enrolled in randomized clinical trial to evaluate TJ-54 (Yokukansan, a traditional Japanese medicine [Kampo]) for the prevention and/or treatment of postoperative delirium (UMIN000005423). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) was used to diagnose postoperative delirium.

Results: A total of 167 patients were registered, delirium was observed in 9% of them. High age over 80 and low MMSE less than 27 were identified as significant independent risk factors.

Conclusion: Surgeon should pay attention to the possible development of postoperative delirium in patients aged over 80 with a low MMSE less than 27 in performing surgery for gastrointestinal malignancies.

Keywords: postoperative delirium, risk factors, gastrointestinal malignancy, MMSE

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Patients and Methods

The patients who underwent a protocol treatment in a randomized phase II trial were examined in this study. This randomized phase II trial had been described in our previous report. Briefly, the key eligibility criteria included patients of ≥70 years of age who had received surgery for gastrointestinal malignancies. All participants were required to have a performance status of ≤2; to undergo a Mini-Mental State Examination (MMSE) before enrollment, and to have adequate hepatic, renal, and bone marrow functions. Eligible patients were randomly assigned at a 1:1 ratio to receive either TJ-54 or control during their perioperative care. The study medication, Yokukansan (Tsumura Yokukansan Extract Granules for Ethical Use; TJ-54 [Tsumura, Japan]), was administered 3 times a day (2.5 g each time, 7.5 g/day). The amount of TJ-54 could be reduced depending on the participant’s condition or adverse reactions. A total sample size of 200 was required to achieve a statistical power of approximately 0.8.

Assessment of postoperative delirium

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) was used to assess patients with suspected postoperative delirium. DSM-IV lists key features that characterize delirium as follows: disturbance of consciousness and a change in cognition or the development of a perceptual disturbance that develops over a short period of time and which tends to fluctuate during the course of the day. When the investigator found evidence that these symptoms were caused by the surgery and its postoperative course, the patient was diagnosed with postoperative delirium.

Statistical analysis

In this study, comparisons between the two groups were analyzed by a chi-squared test. Uni and multivariate logistic regression analyses were performed to identify risk factors for delirium. Backward elimination was used to select a model. All statistical tests were two-sided, and P values of <0.05 were considered to indicate statistical significance. The SPSS software program (v11.0 J Win, SPSS, Chicago, IL) was used for all of the statistical analyses.

Ethical review

The present phase II trial and the exploratory analysis were conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Yokohama City University Research Ethics Committee. The consent of the study was fully explained with written consent form, and voluntary written consent was obtained from all patients before participating.

Results

Patient characteristics

A total of 186 patients (male, n=105; female, n=62) were registered in the TJ-54 trial between October 2009 and July 2011. Among them, 167 patients received surgery for gastrointestinal malignancy and were eligible for inclusion in the present study, while remaining 19 patients received surgery for lung malignancy and were excluded. The median age was 77 years (range, 70–89 years). The median MMSE score was 29.0 (range, 9–30). The diagnoses of the patients were as follows: gastric cancer (n=87), colorectal cancer (n=72), and other gastrointestinal cancer (n=8). The backgrounds of the 167 patients are shown in Table 1.

Incidence of postoperative delirium

The incidence of postoperative delirium was 9.0% (n=15) and delirium was the most common postoperative complication in the present study (Table 1). The comparison of the characteristics of the patients with and without postoperative delirium revealed significant differences in age (p=0.004) and MMSE score (p=0.027) (Table 2). The median age and MMSE score were 81 years (range, 71 to 88 years) and 26 (range, 20 to 30), respectively, in the patients who developed postoperative delirium, and 76 years (range, 70 to 89 years) and 29 (range, 9 to 30) in the patients who did not.

Risk factors for postoperative delirium

The risk factors for postoperative delirium were analyzed by uni and multivariate analyses using clinical factors that were assessed before enrollment and perioperative period. The results are summarized in Table 3. Among these, a high age over 80 and a low MMSE less than 27 were identified as significant risk factors for postoperative delirium (odds ratio, 3.90; 95% CI, 1.25–12.16; p=0.013 and odds ratio, 0.24; 95% CI, 0.08–0.73; p=0.013, respectively). Gender, BMI, ECOG-PS, type of malignancy, comorbidities (hypertension, diabetes mellitus, respiratory dysfunction, heart disease, cerebrovascular disorder), type of surgery, duration of operation, amount of blood loss and surgical complications were not associated with the risk of postoperative delirium in this study. In the original paper, since TJ-54 did not demonstrate the contribution to prevention of occurring postoperative delirium as a whole, it was not described in Table 3 of this paper.

Discussion

This study evaluated the incidence and predictors of postoperative delirium in elderly patients undergoing surgery for gastrointestinal malignancies using prospectively
### Table 1. The patient characteristics of all cases (n=167)

| Factors                                | n(%)          |
|----------------------------------------|---------------|
| **Sex**                                |               |
| Male                                   | 105(62.9%)    |
| Female                                 | 62(37.1%)     |
| **Age**                                | 77.0(70.0 – 89.0) |
| **BMI**                                | 22.3(14.6 – 35.6) |
| **PS**                                 |               |
| 0 – 1                                  | 149(89.2%)    |
| 2                                      | 18(10.8%)     |
| **Type of malignancy**                 |               |
| Gastric                                | 87(52.1%)     |
| Colorectal                             | 72(43.1%)     |
| Other                                  | 8(4.8%)       |
| **MMSE score, Median(Range)**          | 29.0(9.0 – 30.0) |
| **Comorbidity**                        |               |
| Hypertension                           | 92(55.1%)     |
| Diabetes mellitus                      | 38(22.8%)     |
| Respiratory dysfunction                | 14(8.4%)      |
| Heart disease                          | 36(21.6%)     |
| Cerebrovascular disorder               | 10(6.0%)      |
| **Approach**                           |               |
| Open                                   | 80(47.9%)     |
| Laparoscopic                           | 87(52.1%)     |
| **Operation time, Median(Range)**      | 245.0(83.0 – 594.0) |
| **Blood loss, Median(Range)**          | 120.0(5.0 – 3100.0) |
| **Surgical complication**              | 43(25.7%)     |
| **First oral intake, Median(Range)**   | 4.0(2.0 – 81.0) |
| **Length of hospital stay, Median(Range)** | 16.0(9.0 – 267.0) |

PS: Performance status
MMSE: Mini-Mental State Examination

### Table 2. Comparison of the patients with and without postoperative delirium

| Delirium | p-value |
|----------|---------|
| **Sex**  |         |
| Male     | 95(62.5%) | 10(66.7%) | 1.000 |
| Female   | 57(37.5%) | 5(33.3%)  |
| **Age**  | 76.0(70.0 – 89.0) | 81.0(71.0 – 88.0) | 0.004 |
| **BMI**  | 22.3(14.6 – 35.6) | 22.4(17.0 – 29.0) | 0.812 |
| **PS**   | 134(88.2%) | 15(100.0%) | 0.375 |
| 0 – 1    | 18(11.8%) | 0(0.0%)   |
| 2        | 79(52.0%) | 8(53.3%)  |
| **Type of malignancy**                 | 66(43.4%) | 6(40.0%)  |
| Gastric | 9(5.9%) | 1(6.7%) |
| Colorectal | 143(94.1%) | 14(93.3%) |
| Other   | 7(4.6%) | 1(6.7%) |
| **MMSE score Median(Range)**           | 29.0(9.0 – 30.0) | 26.0(20.0 – 30.0) | 0.027 |
| **Hypertension**                       | 84(55.3%) | 8(53.3%) | 1.000 |
| Yes     | 68(44.7%) | 7(46.7%) |
| No      | 34(22.4%) | 4(26.7%) |
| **Diabetes mellitus**                  | 118(77.6%) | 11(73.3%) | 0.748 |
| Yes     | 139(91.4%) | 14(93.3%) |
| No      | 30(19.7%) | 6(40.0%) |
| **Respiratory dysfunction**            | 122(80.3%) | 9(60.0%) |
| Yes     | 9(5.9%) | 1(6.7%) |
| No      | 143(94.1%) | 14(93.3%) |
| **Heart disease**                      | 72(47.4%) | 8(53.3%) | 0.788 |
| Yes     | 80(52.6%) | 7(46.7%) |
| No      | 118(77.6%) | 11(73.3%) |
| **Cerebrovascular disorder**           | 119(70.0 – 300.0) | 120.0(5.0 – 1481.0) | 0.373 |
| Yes     | 112(70.0 – 300.0) | 120.0(5.0 – 1481.0) | 0.223 |
| No      | 43(25.7%) | 12(80.0%) |
| **Approach**                           | 124(74.3%) | 3(20.0%) |
| Open   | 80(52.6%) | 7(46.7%) |
| Laparoscopic                           | 119(70.0 – 300.0) | 120.0(5.0 – 1481.0) | 0.373 |
| **Operation time, Median(Range)**      | 244.0(83.0 – 496.0) | 284.0(83.0 – 594.0) | 0.095 |
| **Blood loss, Median(Range)**          | 119(70.0 – 300.0) | 120.0(5.0 – 1481.0) | 0.373 |
| **Surgical complication**              | 43(25.7%) | 12(80.0%) |
| Yes    | 124(74.3%) | 3(20.0%) |
| No     | 4.0(2.0 – 81.0) | 5(3.0 – 11.0) | 0.907 |
| **First oral intake, Median(Range)**   | 15.5(9.0 – 267.0) | 16.0(10.0 – 101.0) | 0.384 |
| **Length of hospital stay, Median(Range)** | 15.5(9.0 – 267.0) | 16.0(10.0 – 101.0) | 0.384 |
collected clinical trial data. The incidence of postoperative delirium was 9.0% (n=15) and delirium was the most common postoperative complication. The major finding was that a high patient age and a low MMSE score were significant independent risk factors for postoperative delirium. When surgeons perform surgery for gastrointestinal malignancies, careful attention is required to detect the development of postoperative delirium in patients aged over 80 with low MMSE less than 27.

Previous studies have shown that the incidence of delirium after gastrointestinal surgery ranged from 10–30%\(^{16-20}\). The incidence of postoperative delirium in the present study was lower in comparison to previous reports. The previously reported risk factors for postoperative delirium include increased blood loss and an increased operative time\(^{21, 22}\). Furthermore, 50% of the patients received laparoscopic surgery. Generally, the surgical stress of laparoscopic surgery is lower in comparison to conventional procedures\(^{23, 24}\). These differences might have affected for the results.

In the present study, we found that the high age over 80 was a significant independent risk factor for postoperative delirium. Previous studies demonstrated similar results. For example, Van der Sluis et al evaluated 436 patients who underwent colorectal cancer surgery and reported that age was a risk factor for postoperative delirium (odds ratio, 4.01; 95% CI, 1.55–10.37; \(p=0.004\))\(^{19}\). A systematic review by Scholz, which included 11 studies (1427 patients), assessed the incidence of delirium after gastrointestinal surgery and found a statistically significant association between age and postoperative delirium (odds ratio, 4.83; 95% CI, 3.14–6.52; \(p<0.001\))\(^{18}\). Various mechanisms have been suggested to contribute to delirium, including neurotransmitters, inflammation, physiological stressors, metabolic disorders, electrolyte disorders, and genetic factors\(^{9, 25, 26}\). In elderly patients in

| Characteristics               | Number(%)   | Univariate analysis | Multivariate analysis |
|-------------------------------|-------------|---------------------|-----------------------|
|                               |             | odds    | 95% CI    | P value | odds   | 95% CI    | P value |
| Sex                           |             |         |           |         |        |           |         |
| Male                          | 105(62.9)   | 1.20    | 0.39 – 3.69 | 0.750   | 1.20    | 0.39 – 3.69 | 0.750   |
| Female                        | 62(37.1%)   | 1.20    | 0.39 – 3.69 | 0.750   | 1.20    | 0.39 – 3.69 | 0.750   |
| Age                           |             |         |           |         |        |           |         |
| < 80 years                    | 48(28.7%)   | 4.35    | 1.45 – 12.99 | 0.009   | 4.47    | 1.38 – 14.45 | 0.013   |
| ≥ 80 years                    | 119(71.3%)  | 4.35    | 1.45 – 12.99 | 0.009   | 4.47    | 1.38 – 14.45 | 0.013   |
| Type of malignancy            |             |         |           |         |        |           |         |
| Gastric                       | 87(52.1%)   | 0.71    | 0.08 – 6.51 | 0.863   |        |           |         |
| Colorectal                    | 72(43.1%)   | 0.64    | 0.07 – 6.07 | 0.693   | 0.64    | 0.07 – 6.07 | 0.693   |
| Other                         | 8(4.8%)     | 0.64    | 0.07 – 6.07 | 0.693   | 0.64    | 0.07 – 6.07 | 0.693   |
| MMSE score                    |             |         |           |         |        |           |         |
| ≥ 27                          | 103(71.0%)  | 0.23    | 0.08 – 0.69 | 0.009   | 0.23    | 0.07 – 0.73 | 0.013   |
| < 27                          | 42(29.0%)   | 0.23    | 0.08 – 0.69 | 0.009   | 0.23    | 0.07 – 0.73 | 0.013   |
| Heart Disease                 |             |         |           |         |        |           |         |
| Yes                           | 36(21.6%)   | 2.71    | 0.90 – 8.21 | 0.078   |        |           |         |
| No                            | 131(78.4%)  | 2.71    | 0.90 – 8.21 | 0.078   |        |           |         |
| Operation time                |             |         |           |         |        |           |         |
| ≥ median(245)                 | 85(50.9%)   | 1.50    | 0.51 – 4.42 | 0.462   |        |           |         |
| < median(245)                 | 82(49.1%)   | 1.50    | 0.51 – 4.42 | 0.462   |        |           |         |
| Blood loss                    |             |         |           |         |        |           |         |
| ≥ median(120)                 | 84(50.3%)   | 1.14    | 0.39 – 3.31 | 0.806   |        |           |         |
| < median(120)                 | 83(49.7%)   | 1.14    | 0.39 – 3.31 | 0.806   |        |           |         |
| Type of approach              |             |         |           |         |        |           |         |
| Open                          | 80(47.9%)   | 1.27    | 0.44 – 3.68 | 0.660   |        |           |         |
| Laparoscopic                  | 87(52.1%)   | 1.27    | 0.44 – 3.68 | 0.660   |        |           |         |
| First oral intake             |             |         |           |         |        |           |         |
| ≥ median(4)                   | 105(62.9%)  | 4.24    | 0.92 – 19.46 | 0.063   |        |           |         |
| < median(4)                   | 62(37.1%)   | 4.24    | 0.92 – 19.46 | 0.063   |        |           |         |
| Surgical complications        |             |         |           |         |        |           |         |
| Yes                           | 43(25.7%)   | 2.82    | 0.96 – 8.31 | 0.060   |        |           |         |
| No                            | 124(74.3%)  | 2.82    | 0.96 – 8.31 | 0.060   |        |           |         |
particular, the high risk of age-related organ dysfunction and comorbidities after major surgery are considered to influence the incidence of postoperative delirium. Another study mentioned that elderly patients have both a reduced ability to respond to stress and to adapt to an abnormal metabolism, a dysfunctional state that is accompanied by the loss of central cholinergic neurons. In the presence of acute stressors such as gastrointestinal malignancy and surgical procedures, disturbances to a wide variety of neurotransmitter systems appear to make elderly individuals more prone to postoperative delirium. However, this point has not been sufficiently evaluated.

We found that a low MMSE score was one of the factors associated with postoperative delirium (hazard ratio, 0.67; 95% CI, 0.50–0.89; p=0.002). Saczynski et al. used the MMSE score to investigate the cognitive trajectories after postoperative delirium among 225 patients who underwent cardiovascular surgery. The preoperative MMSE scores of the patients who developed postoperative delirium were lower than the scores of those who did not (median: 26 and 28, p<0.001). It is not yet known why a low MMSE score contributes to postoperative delirium. Price et al. focused on the 5 domains of the MMSE (delayed recall, working memory, orientation, language and visuoconstruction) and found that delayed recall and working memory were significantly impaired in patients who developed postoperative delirium. The working memory functions are commonly associated with the frontal cortex and subcortical nuclei. These neuroanatomical areas and cognitive domains, as well as memory and executive domains, are considered to be critical areas for the development of postoperative cognitive dysfunction.

The present study is associated with several potential limitations; thus special attention is required when interpreting our results. First, the sample size was relatively small, despite the fact that patient data were prospectively collected at multiple institutions. Second, the cutoff levels of the age and MMSE score for predicting postoperative delirium have not been sufficiently evaluated. The cutoff ages differ between studies, and the traditional cutoff MMSE score for diagnosing dementia is 24 (27 is considered more accurate for college-educated individuals); thus, further investigation is necessary. Third, we could not deny the possibility that the elderly people in the present study might have been selected and fit for surgery. Moreover, the surgical operations were heterogeneous.

The major finding of this study was that a high patient age and a low MMSE score were significant independent risk factors for postoperative delirium. When surgeons perform surgery for gastrointestinal malignancies, careful attention is required to detect the development of postoperative delirium in patients aged over 80 with low MMSE score less than 27.

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Consent to Publish
Not applicable.

Competing interests
The authors declare no competing interests in association with the present study.

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Authors’ Contributions
MK and TA: collected all references and wrote the draft. MK, TA, JM, YM, SA, SS, MN, MT, HT, NS, TS, HM, NY, TO, MM and YR: collected all data of the clinical. MK and TA: offered the conception and design, revised and discussed the meaning of the manuscript. All authors read and approved the final manuscript.

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