Introduction

Postoperative bowel dysfunction (PDD) frequently occurs after abdominal surgery and is characterized by the transient impairment of bowel motility, which frustrates patients and surgeons\(^1\). In PDD, bowel motility commonly recovers at 24–48 h postoperatively in the small intestine and at 48–72 h postoperatively in the large intestine\(^2,3\). Decreased intestinal motor function (intestinal hypomotility) following open abdominal surgery is categorized as a physiological event if the motor function recovers within 3 days of surgery and does not correspond to prolonged intestinal hypomotility (i.e., postoperative ileus [POI] in the narrow sense), which is subject to treatment. Prolonged PDD after various abdominal surgeries has become a major cause of morbidity, increased length of stay, and increased hospital costs\(^1,4,5\). Flatus and/or evacuation (bowel movements) could indicate the end of PDD. Different mechanisms, including a neurogenic pathway\(^6\), have been proposed to explain the pathogenesis of PDD. Sympathetic overactivity appears to play an important role in this pathway, and the operative time has been reported to be associated with this pathway\(^1,4,5\).

Although several advances in medical therapy have been made to reduce the incidence and severity of PDD, the incidence of prolonged PDD and POI remains high\(^1\).

One of the latest approaches for reducing POI involves the use of a traditional Japanese prescribed herbal medication called daikenchuto (DKT)\(^7\). Three exploratory controlled studies, which were supported by the Japanese...
Foundation for Multidisciplinary Treatment of Cancer (JFMC), have been published on this subject\textsuperscript{8-10}. The results of one of these studies indicated a significant decrease in the time to first passage of stool\textsuperscript{10}. The remaining two studies demonstrated no significant difference but indicated a slight tendency toward a reduction in POI\textsuperscript{8,9}.

The present study performed a pooled analysis to determine the role of DKT in accelerating gastrointestinal recovery after open abdominal surgery. This pooled analysis included data from more than 800 patients; therefore, it provides a more reliable assessment of the effect of DKT on PDD compared with any of the previous individual studies. This study maintained a special focus on the time from the end of surgery (tracheal tube extubation) to the first bowel movement.

**Ethics**

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the internal review boards of all participating institutions. This pooled analysis study was approved by the internal review board of the JFMC and has been registered in the University Hospital Medical Information Network Clinical Trials Registry as UMIN000026292.

**Clinical trials and patients**

The data of 862 patients from three clinical trials (JFMC project numbers 39–0902, 40–1001, and 42–1002) were pooled\textsuperscript{8-10}. These exploratory trials were performed to evaluate the clinical benefits of DKT with regard to PDD after open abdominal surgery for cancer (colon, stomach, or liver).

**Data preparation and statistical analysis**

The primary end-point, which was the time from the end of surgery (tracheal tube extubation) to the first bowel movement, was analyzed using Kaplan-Meier method, organ-stratified log-rank test, and Cox proportional hazard regression analysis. Distributions of the background factors were evaluated using the Cochran-Mantel-Haenszel test, which was employed for the stratification of organs to identify adjustment factors of interest for the study outcomes. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). A P-value of < 0.05 was considered statistically significant.

The primary end-point was identical to that of the previous three studies. One purpose of this study was to confirm the reproducibility of the findings of the previous studies. However, the analysis was performed using stratification methods, because the pooled-data comprised different numbers of subjects in whom different organs were operated. The details of the findings and interpretations are in preparation.

**Results**

The data of 740 eligible patients were collected and analyzed. The results of one of these studies indicated a significant decrease in the time to first passage of stool\textsuperscript{10}. The remaining two studies demonstrated no significant difference but indicated a slight tendency toward a reduction in POI\textsuperscript{8,9}.

**Acknowledgment (Disclosure Statement)**

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**Conflict of interest statement**

Toru Kono and Mitsuo Shimada received the research grant by TSUMURA & CO. (Tokyo, Japan). Junichi Sakamoto received honorariums for lectures in academic meetings from Tsumura & Co. The other authors declare that they have no conflict of interest.

**References**

1) Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. (2015) Postoperative ileus: Recent developments in pathophysiology and management. Clin Nutr. 34: 367-376. doi: 10.1016/j.clinu.2015.01.016
2) Luckey A, Livingston E, Tache Y. (2003) Mechanisms and treatment of postoperative ileus. Arch Surg. 138: 206-214. doi: 10.1001/archsurg.138.2.206
3) Livingston EH, Passaro EP, Jr. (1990) Postoperative ileus. Dig Dis Sci. 35: 121-132.
4) Kehlet H. (2008) Postoperative ileus--an update on preventive techniques. Nat Clin Pract Gastroenterol Hepatol. 5: 552-558. doi: 10.1038/ncpgasthep1230
5) Baig MK, Wexner SD. (2004) Postoperative ileus: a review. Dis Colon Rectum. 47: 516-526. doi: 10.1007/s10350-003-0067-9
6) Bauer AJ, Boecxxtsuen G. (2004) Mechanisms of postoperative ileus. Neurogastroenterol Motil. 16 Suppl 2: 54-60. doi: 10.1111/j.1743-3150.2004.00558.x
7) Kono T, Shimada M, Yamamoto M, Kaneko A, Oomiya Y, Kubota K, Kase Y, Lee K, Uezono Y. (2015) Complementary and synergetic therapeutic effects of compounds found in Kampo medicine: analysis of daikenchuto. Front Pharmacol. 6: 159. doi: 10.3389/fphar.2015.00159
8) Katsuno H, Maeda K, Kaibo T, Kunieda K, Funahashi K, Sakamoto J, Kono T, Hasegawa H, Furukawa Y, Imazu Y, Morita S, Watanabe M. (2015) Clinical efficacy of Daikenchuto for gastrointestinal dysfunction following colon surgery: a randomized, double-blind, multi-center, placebo-controlled study (JFMC39-0902). Jpn J Clin Oncol. 45: 650-656. doi: 10.1093/jjco/hvy056.
9) Yoshikawa K, Shimada M, Wakabayashi G, Ishida K, Kaibo T, Kitagawa Y, Sakamoto J, Shiraishi N, Koeda K, Mochiki E, Saikawa Y, Yamaguchi K, Watanabe M, Morita S, Kitanou S, Saji S, Kanematsu T, Kitajima M. (2015) The effect of DKT, a traditional Japanese herbal medicine, after total gastrectomy for gastric cancer: a multi-center, randomized, double-blind, placebo-controlled phase II trial (JFMC42-1002). J Am Coll Surg. 2: 571-578. doi: 10.1016/j.jamcollsurg.2015.03.004
10) Shimada M, Morine Y, Nagano H, Hatano E, Kaiho T, Miyazaki M, Kono T, Kamiyama T, Morita S, Sakamoto J, Kusano M, Suji S, Kanematsu T, Kitajima M. (2015) Effect of TU-100, a traditional Japanese medicine, administered after hepatic resection in patients with liver cancer: a multi-center, phase III trial (JFMC40-1001). Int J Clin Oncol. 20: 95-104. doi: 10.1007/s10147-014-0678-2