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Randomized Clinical Trial Comparing Efficacy of Simo Decoction and Acupuncture or Chewing Gum Alone on Postoperative Ileus in Patients With Hepatocellular Carcinoma After Hepatectomy

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Abstract: To compare the efficacy of simo decoction (SMD) combined with acupuncture at the tsusanli acupoint or chewing gum alone for treating postoperative ileus in patients with hepatocellular carcinoma (HCC) after hepatectomy.

In postoperative ileus, a frequent complication following hepatectomy, bowel function recovery is delayed, which increases length of hospital stay. Studies suggest that chewing gum may reduce postoperative ileus; SMD and acupuncture at the tsusanli acupoint have long been used in China to promote bowel movement.

Patients with primary HCC undergoing hepatectomy between January 2015 and August 2015 were randomized to receive SMD and acupuncture (n = 55) or chewing gum (n = 53) or no intervention (n = 54) starting on postoperative day 1 and continuing for 6 consecutive days or until flatus. Primary endpoints were occurrence of postoperative ileus and length of hospital stay; secondary endpoints were surgical complications.

Groups treated with SMD and acupuncture or with chewing gum experienced significantly shorter time to first peristalsis, flatus, and defecation than the no-intervention group (all $P < 0.05$). Hospital stay was significantly shorter in the combined SMD and acupuncture group

(mean 14.0 d, SD 4.9) than in the no-intervention group (mean 16.5 d, SD 6.8; $P = 0.014$), while length of stay was similar between the chewing gum group (mean 14.7, SD 6.2) and the no-intervention group ($P = 0.147$). Incidence of grades I and II complications was slightly lower in both intervention groups than in the no-intervention group.

The combination of SMD and acupuncture may reduce incidence of postoperative ileus and shorten hospital stay in HCC patients after hepatectomy. Chewing gum may also reduce incidence of ileus but does not appear to affect hospital stay. (Clinicaltrials.gov registration number: NCT02438436.)

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Abbreviations: HCC = hepatocellular carcinoma, SMD = simo decoction.

INTRODUCTION

Hepatectomy is widely used to treat patients with hepatocellular carcinoma (HCC), even those with intermediate and advanced disease.^{1,2} Despite its well-demonstrated clinical safety and efficacy in many patients, it is associated with postoperative morbidity and mortality.^{2,3} One complication after hepatectomy is delayed resumption of gastrointestinal function, known as postoperative ileus. This can decrease patient comfort and increase morbidity and mortality, prolonging hospital stay, and raising healthcare costs.^{4,5} While postoperative ileus usually resolves within approximately 3 days, it can last longer in some cases as a condition termed postoperative paralytic ileus.⁶ Postoperative use of opioid-based analgesics can increase incidence of postoperative ileus.^{7,8}

No drugs or interventions to prevent or treat postoperative ileus have been approved by the China Drug Administration or the US Food and Drug Administration. Studies suggest that postoperative oral administration of simo decoction (SMD)⁹ and acupuncture¹⁰ can accelerate the return of gastrointestinal function following several types of surgery. Several studies also show that chewing gum, a new and simple modality, can accelerate complication-free recovery of gastrointestinal function following gastrointestinal surgery^{5,11} and obstetrical-gynecological surgery.^{12,13} This raises the question whether postoperative SMD, acupuncture, or chewing gum can reduce risk of postoperative ileus following hepatectomy.

To examine this question, we conducted a randomized controlled trial to compare incidence of postoperative ileus and length of hospital stay in HCC patients who received SMD and acupuncture, chewing gum or no intervention following hepatectomy.

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METHODS

The protocol for this trial was approved by the Medical Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University, and was designed in accordance with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT02438436). Data were collected, analyzed, and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

Patients

Patients older than 18 years who underwent open hepatectomy at 1 of the 2 Hepatobiliary Surgery Departments of the Affiliated Tumor Hospital of Guangxi Medical University (Nanning, China) were eligible to participate in the study. Diagnosis of HCC was based on 2 types of clinical imaging, together with a serum level of α -fetoprotein higher than 400 ng/mL; diagnosis was confirmed by histopathological examination of surgical samples. Patients were excluded if they had a history of exploratory laparotomy, laparoscopic surgery, inflammatory bowel disease, abdominal radiation, or substance abuse; if they had psychological or social conditions that might interfere with their participation in the study; if they were allergic to mint; or if they required intensive care more than 24 hours postoperatively or a nasogastric tube beyond the first postoperative morning.

Randomization

The study information was explained to all enrolled patients. After written informed consent was obtained, patients were assigned randomly to groups that would receive SMD combined with acupuncture or chewing gum or no intervention. Randomization was performed the day before hepatectomy using TenAlea software (<http://nl.tenalea.net>). The fundamentally different characteristics of SMD or chewing gum meant that no blinding was used after randomization. Patients were informed that the ability of SMD, acupuncture, or chewing gum to promote recovery of gastrointestinal function after hepatectomy was not known, and that none of these measures was expected to cause obvious side effects.

Interventions

The same surgical team performed all hepatectomies using general anesthesia, the same evidence-based protocol of perioperative management and standardized postoperative care plans.^{3,14,15} An abdominal cavity drainage tube was placed in each patient. The nasogastric drainage tube was removed on the first postoperative morning. Enteral or nasogastric feeding was not provided until after passage of first flatus. All patients were mobilized as soon as possible in the postoperative period. Additional opioid or nonsteroidal analgesia was prescribed for pain when required and their use carefully documented. Then nursing ward staff administered the following interventions to the randomized groups, recording their actions in patient records.

One group of patients received oral SMD decoction (Hansen Co., Ltd, Yiyang, Hunan Province, China, 10 mL/dose) 3 times per day beginning on the first day after hepatectomy. They also received bilateral injections of vitamin B1 (50 mg \times 2) at the tsusanli acupoint 1 time per day after the skin was swabbed with 75% alcohol. This intervention was performed for a total of 6 consecutive days or until flatus.

Another group of patients was instructed to chew commercially available sugarless chewing gum (Extra & Reg, Wm.

Wrigley Jr. Co., Ltd, Shanghai, China) 3 times daily starting on postoperative day 1. They were instructed to chew the piece of gum for 30 minutes. This intervention was performed for a total of 6 consecutive days or until flatus.

A third group did not receive any postoperative intervention, including SMD, acupuncture, chewing gum, or adjuvant drugs that might influence recovery of bowel function.

Outcomes

Primary endpoints were time to first flatus and time to defecation, which were recorded daily by nursing staff. Secondary endpoints were length of hospital stay and postoperative complications such as fever, pneumonia, wound infection, and bleeding. Length of hospital stay was defined as the number of days from hepatectomy to discharge. Criteria for hospital discharge included stability of vital signs with no fever, achievement of flatus or defecation, ability to tolerate solid food without vomiting, control of postoperative pain, absence of other postoperative complications, and ability to function at home independently or with the home care provided. Postoperative complications were classified and graded according to the Clavien–Dindo scheme.¹⁶

Sample Size Calculation

Sample size calculation was based on our previous retrospective study¹⁷ performed in patients with HCC after hepatectomy. Mean time to first flatus was assumed to be 73 and 51 hours between SMD combined with acupuncture and no-intervention group. The minimum detectable difference was 22. Assuming that the common standard deviation is 24 hours, the sample size was calculated to be a total of 171 participants applying statistical power of 90% at a 2-sided significance level of 5%. We recruited an additional 10 subjects to offset potential attrition.

Statistical Analysis

SPSS 19.0 (IBM, USA) was used for all statistical analyses, with the threshold of significance defined as a two-tailed $P < 0.05$. Data for continuous variables were expressed as median (range), while data for categorical variables were expressed as number (percentage). Intergroup differences in continuous variables were assessed for significance using Student t test (if data were normally distributed) or the Mann–Whitney U test (if data were skewed). Intergroup differences in categorical data were assessed using the χ^2 test or Fisher exact tests (2-tailed), as appropriate. Length of hospital stay was calculated using Kaplan–Meier analysis and compared between groups using the log-rank test.

RESULTS

Patient Characteristics

From January 1, 2015 to August 31, 2015, 245 patients with HCC were assessed for eligibility. Of these, 43 were excluded because they did not meet the inclusion criteria, 16 refused to participate, 3 were unwilling to receive SMD and 2 were unwilling to receive chewing gum. The remaining 181 patients were randomly assigned to receive SMD with acupuncture ($n = 62$), chewing gum ($n = 60$), or no intervention ($n = 59$). After randomization, 7 patients diagnosed with cholangiocellular carcinoma were excluded. Another 5 patients were excluded because they had a prolonged stay in the intensive care unit and so could not receive SMD or chewing

gum. Four patients discontinued the study and three received the incorrect intervention, so these 7 were excluded from the final analysis. In the end, 162 patients completed the study, comprising 55 in the SMD with acupuncture group, 53 in the chewing gum group, and 54 in the control group (Fig. 1).

Patients in all 3 groups had similar hepatectomy characteristics, including major or minor hepatectomy, mean duration of surgery and blood loss (Table 1). No intervention-related adverse events more severe than grade I were recorded in any of the groups, based on the Common Terminology Criteria for Adverse Events 3.0.¹⁸

Postoperative Ileus

Time to first peristalsis, first flatus, and first defecation was significantly shorter in the 2 intervention groups than in the no-intervention group (all $P < 0.05$). All 3 time intervals were slightly shorter in the groups receiving SMD with acupuncture than in the group receiving chewing gum (all $P > 0.05$) (Table 2).

Length of Hospital Stay

Hospital stay lasted a mean of 14.0 d (SD 4.9, median 13) for patients receiving SMD with acupuncture, 14.7 d (SD 6.2, median 13) for patients receiving chewing gum, and 16.5 (SD 6.8, median 15) for no-intervention controls (Table 2). Kaplan–Meier analysis showed that length of stay was significantly shorter for SMD with acupuncture than for no intervention ($P = 0.014$) (Fig. 2). In contrast, length of stay was slightly shorter for the group receiving SMD with acupuncture than the

group receiving chewing gum ($P = 0.295$), and it was slightly shorter for the group receiving chewing gum than for the group receiving no intervention ($P = 0.147$).

Complications

The frequency of complications was significantly higher in the no-intervention group than in the groups receiving SMD with acupuncture or receiving chewing gum ($P < 0.001$). Most complications were grade I or II and included wound pain, abdominal distension, fever, and hydrothorax. One patient in the chewing gum group required second surgery because of liver bleeding. One patient in the SMD with acupuncture group and 1 patient in the no-intervention group died within 30 d after hepatectomy because of liver failure (Table 3).

DISCUSSION

Although most hepatectomies do not involve gastrointestinal surgery, transient impairment of gastrointestinal motility known as postoperative ileus occurs in a substantial proportion of patients. This increases healthcare costs and resource utilization.¹⁹ Various strategies have been developed to reduce the incidence of postoperative ileus, including fast-track care, minimally invasive surgery, and epidural anesthesia, but none of these methods is entirely satisfactory.²⁰ Our results suggest that the combination of SMD and acupuncture may reduce incidence of postoperative ileus and shorten hospital stay in HCC patients after hepatectomy. Chewing gum may also reduce incidence of ileus but does not appear to significantly affect hospital stay.

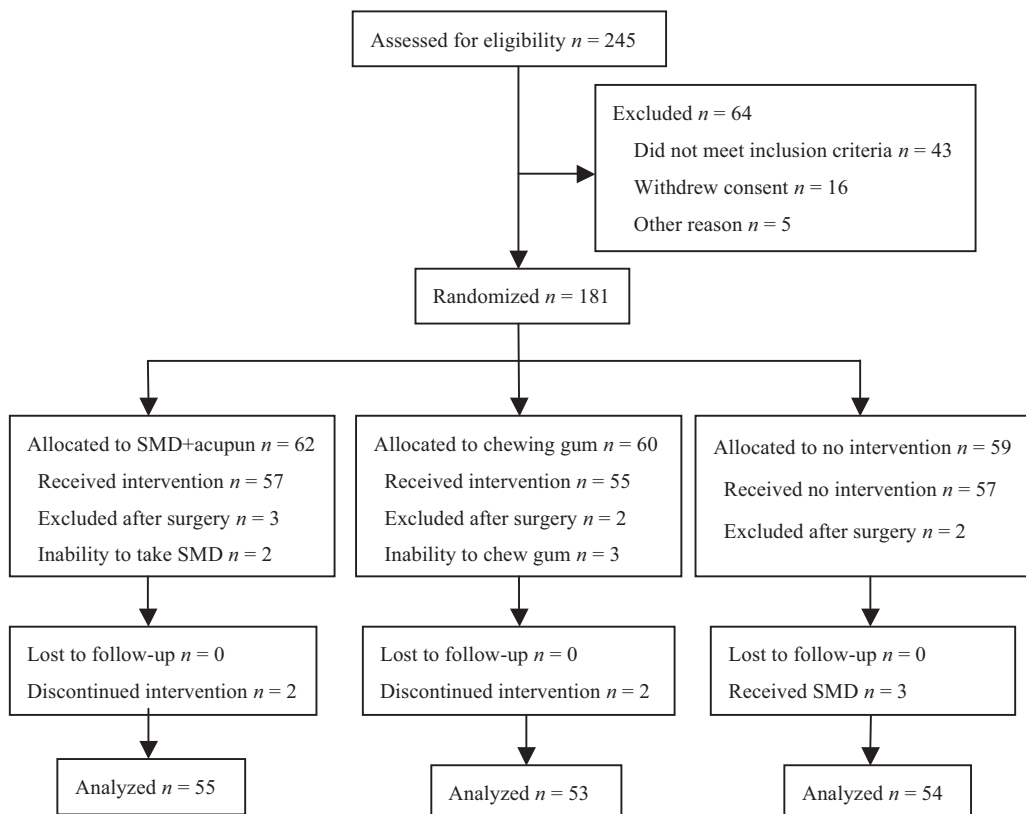


FIGURE 1. CONSORT diagram for the study. SMD + acupun, simo decoction with acupuncture.

TABLE 1. Clinicopathological Data of Patients With Hepatocellular Carcinoma Treated With Simo Decoction + Acupuncture, Chewing Gum, or No Intervention

Variable	Simo Decoction + Acupuncture (n = 55)	Chewing Gum (n = 53)	No Intervention (n = 54)	P
Age, y	48 (28–71)	53 (29–75)	51 (28–69)	0.270
Male	45 (82)	46 (87)	44 (81)	0.711
BMI	22.6 (19.3–28.0)	22.2 (16.3–29.9)	22.5 (17.3–30.1)	0.655
Diabetes mellitus	11 (20)	11 (21)	9 (17)	0.848
Smoking	7 (13)	9 (17)	8 (15)	0.824
Alcohol use	25 (45)	20 (38)	19 (35)	0.521
Major hepatectomy	26 (47)	29 (55)	28 (52)	0.840
Surgical time, min	181 (100–382)	215 (110–424)	192 (100–371)	0.427
Blood loss, mL	515 (100–2750)	450 (80–2550)	525 (50–3400)	0.317
Opioid analgesia use	21 (38)	23 (43)	32 (59)	0.072

Values shown are median (range) or n (%). BMI = body mass index.

TABLE 2. Outcomes of Postoperative Simo Decoction + Acupuncture or Chewing Gum in Patients With Hepatocellular Carcinoma

Variable	Simo Decoction + Acupuncture (n = 55)	Chewing Gum (n = 53)	No Intervention (n = 54)	P
Time to first peristalsis, h	19.6 (8.5–46.2)	25.2 (12.0–52.5)	29.6 (16.5–69.4)	0.127*, 0.014†, 0.035‡
Time to first flatus, h	51.4 (22.5–82.1)	55.9 (28.4–110.5)	70.6 (46.8–127.3)	0.353*, 0.012†, 0.013‡
Time to first defecation, d	2.5 (0.8–4.6)	3.3 (1.5–9.4)	4.7 (4.2–8.7)	0.158*, 0.003†, 0.035‡
Length of postoperative hospital stay, d	13.1 (7.0–28.1)	13.2 (6.4–34.1)	15.3 (7.4–41.2)	0.295*, 0.014†, 0.147‡

Values shown are median (range).

*Simo decoction + acupuncture versus chewing gum.

†Simo decoction + acupuncture versus no intervention.

‡Chewing gum versus no intervention.

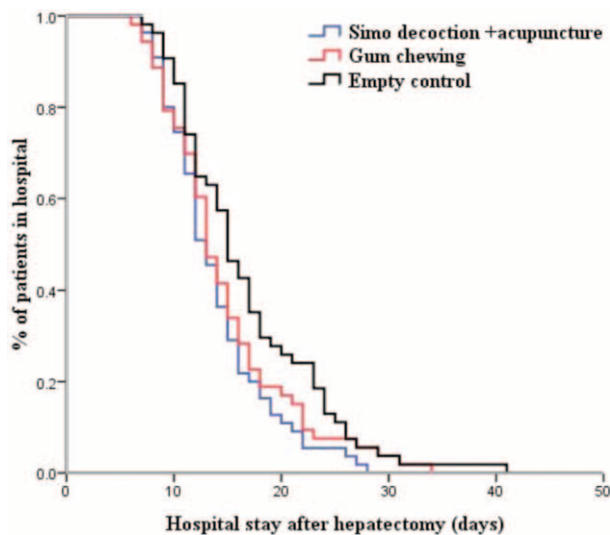


FIGURE 2. Kaplan–Meier curves showing length of hospital stay in the three groups. Significant differences were observed between the group receiving SMD with acupuncture and the control group receiving no intervention ($P=0.014$), but not between the group receiving SMD with acupuncture and the group who chewed gum ($P=0.295$), or between the group who chewed gum and the control group ($P=0.147$).

Our findings in this randomized controlled trial are consistent with our previous small retrospective study, in which SMD with acupuncture reduced incidence of postoperative ileus in HCC patients after hepatectomy.¹⁷ Our observation that chewing gum reduced the incidence of postoperative ileus is supported by findings in other randomized trials^{11–13} and meta-analyses,^{4,21} as well as a small prospective case–control study from South Korea in which HCC patients who chewed gum after hepatectomy recovered bowel function faster than those who did not.²² Thus the available evidence suggests that SMD combined with acupuncture may be the most promising strategy for reducing the incidence of postoperative ileus and shortening the length of hospital stay for HCC patients after hepatectomy. Incidence of grade I and II postoperative complications was significantly lower in the group receiving SMD with acupuncture than in the no-intervention group. We did not observe any adverse events related to SMD, acupuncture, or chewing gum in the present study, similar to the lack of adverse events in previous trials.^{10,17,21,23}

Postoperative ileus may have multiple causes, though surgically induced intestinal inflammation appears to be the most frequent one.^{24,25} Inflammatory infiltration into the intestinal muscularis can lead to hypomotility along the entire gastrointestinal tract.²⁶ Consistent with this, early inhibition of inflammation reduces the incidence of postoperative ileus,^{27,28} usually by vagus nerve-mediated activation of the autonomic nervous system.^{29,30} This may help explain

TABLE 3. Clavien–Dindo Classification of Postresection Complications in Patients With Hepatocellular Carcinoma Treated With Simo Decoction + Acupuncture, Chewing Gum, or No Intervention

Variable	Simo Decoction + Acupuncture (n = 55)	Chewing Gum (n = 53)	No Intervention (n = 54)	P
No complications	21 (38)	18 (34)	2 (4)	<0.001*
I: deviation from normal postoperative course	19 (35)	23 (43)	31 (57)	0.055*
II: complications requiring pharmacological treatment	6 (11)	7 (13)	13 (24)	0.146*
IIIa: intervention not under general anesthesia	5 (9)	2 (4)	3 (6)	0.608†
IIIb: intervention under general anesthesia	0 (0)	1 (2)	0 (0)	0.663†
IV: life-threatening complications	3 (5)	2 (4)	4 (7)	0.841†
V: death	1 (2)	0 (0)	1 (2)	1.000†

Values shown are n (%).

* χ^2 test.

† Fisher exact test.

why we observed that gum chewing promoted recovery of gastrointestinal function: chewing gum not only activates the cephalic-vagal reflex as a form of sham feeding,³¹ but it also reduces systemic inflammation.¹¹

Whether SMD, long used in traditional Chinese medicine to boost gastrointestinal hypomotility, works by a similar mechanism is unclear. Evidence from animal models suggests that SMD can reduce serum levels of proinflammatory cytokines and white blood cells.^{32,33} That it may also directly promote gastrointestinal motility is suggested by the observation that it promotes contraction of antral circular strips by activating muscarinic M3 receptors.³⁴ Acupuncture may help regulate the gastrointestinal tract via the autonomic nervous system,^{35,36} and acupuncture at the tsusanli acupoint, located on the stomach meridian, is thought to regulate the intestines. Administering vitamin B1 at acupoints is thought to intensify and prolong acupoint stimulation synergistically. This may help explain why we found that SMD with tsusanli acupoint injection with vitamin B1 promoted gastrointestinal hypomotility to a greater extent than chewing gum. The ability of tsusanli acupoint injection to reduce incidence of postoperative ileus has been demonstrated in numerous studies.^{10,23,36} We extend these findings to the combination of SMD with tsusanli acupoint injection.

In our population, SMD with acupuncture reduced hospital stay duration by 2.5 d, which was significant, while chewing gum reduced it by 1.8 d, which was not significant. It is possible that the effects of chewing gum would become significant with a larger sample. These results have several possible explanations. One is that either chewing gum or the combination of SMD with acupuncture stimulates gastrointestinal motility, leading to shorter time to first peristalsis, flatus, and defecation. Such patients will more quickly achieve euphagia without vomiting and start to ambulate. Another possible explanation is that the lower incidence of grade I and II postoperative complications in the 2 intervention groups translated to shorter hospital stay.

The results of the present study should be interpreted with caution given several limitations. One is that length of stay within each group was calculated over patients undergoing minor and major hepatectomies, which may have confounded the analysis. Nevertheless the frequencies of hepatectomy type were similar among the groups. A second limitation is lack of blinding, which was not feasible because of the nature of the interventions. A third limitation is that patients within each

group differed in whether they received opioid analgesia, which may have confounded our analysis. Nevertheless, the frequencies of these treatments were similar among the groups.

In conclusion, the present study suggests that acupuncture, SMD, and chewing gum can be safely administered in a postoperative setting to HCC patients after hepatectomy. This is consistent with previous studies.^{10,17,21,23,36} Our data also suggest that gum chewing or the combination of SMD with acupuncture can prevent postoperative ileus in these patients, and that at least SMD with acupuncture significantly shortens hospital stay. Future studies should examine whether chewing gum or SMD with acupuncture can treat postoperative ileus after it has already developed.

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