Acupuncture effect on digestion in critically ill postoperative oral and hypopharyngeal cancer patients

A protocol for double-blind randomized control trial

Eyal Ben-Arie, MSa, Pei-Yu Kao, MDb,c, Wen-Chao Ho, PhDd,g, Yu Chen Lee, PhDa,e,f,*

Abstract

Introduction: Head and neck cancer patients are at a high risk to suffer from malnourishment, a risk that increases in postoperative condition and with the use of enteral nutrition (EN). Until now patients who are suffering from indigestion in the intensive care unit (ICU) received treatment in the form of prokinetic drugs, drugs that can lead to serious side effects and only can partially improve digestion functions. Acupuncture was used successfully in several clinical trials to improve postoperative indigestion in cancer patients without any reported adverse events. The study aims to investigate acupuncture effect in combination with prokinetic drugs in the treatment of indigestion in postoperative oral and hypopharyngeal cancer patients in the ICU.

Methods: Single-center, double-blind randomized control trial will compare between 2 equal groups. A total of 28 patients that will meet the inclusion criteria: age 30 to 80, postplastic surgery for oral cancer or hypopharyngeal cancer, developed feeding intolerance 2 times in the first postoperative day, Apache score <20, and needed EN. Patients will be randomly divided (1:1) into treatment group or control group for 3 treatments in 3 days along with routine ICU treatment. The main outcome measurement will be the number of days a patient needs to reach his total energy expenditure.

Expected outcome: The results will shed light on the effectiveness and safety of acupuncture in a double-blind design treating postoperative ICU cancer patients. In addition, the study presents a revolutionary double-blind design that if, will prove as successful might influence the way double-blind acupuncture studies are performed today.

Other information: The study will be conducted in the surgical ICU department, of China medical university hospital, Taichung 404, Taiwan. The study is conducted on stable ICU patients and is anticipated to have minimum risk for adverse events. Patients enrollment and data collection will start from May 15, 2019. The study expected completion time: June 2021.

Abbreviations: ACU = treatment group, CON = control group, EN = enteral nutrition, GI = gastrointestinal, ICU = intensive care unit, NG = nasogastric, TEE = total energy expenditure.

Keywords: acupuncture, critically ill, digestion, hypopharyngeal cancer, intensive care, intensive care unit, oral cancer

1. Introduction

Up to 80% of head and neck cancer patients will suffer malnourishment during the course of the disease, malnutrition can increase the risk of postoperative complications as well as the rate of mortality.[1] Postoperative oral and hypopharyngeal cancer patients will usually lose the ability of oral feeding as a result of the surgery, a fact that when combined with chemotherapy and radiotherapy will only increase malnutrition...
risk. Postoperative intensive care unit (ICU) patient often required parenteral nutrition or enteral nutrition (EN) to prevent malnourishment. EN is considered as the superior nutrition choice that assists the maintenance of gut mucosal integrity, improved utilization of nutrients, reduced respiratory infections, and hospital total stay. Unfortunately EN carry a number of side effects such as delayed gastric emptying, diarrhea, constipation, reflux, nausea, vomiting, gastrointestinal (GI) bleeding, contamination, and EN feeding tube clogging. To prevent the side effect of EN, prokinetic drugs are often used. A recent systemic review and meta-analysis found that although prokinetic drugs can reduce high gastric residual volume, prokinetic drugs failed to decrease vomiting, diarrhea, mortality risk, and length of stay in the ICU. Metoclopramide, a popular and commonly used prokinetic drug, can lead to serious neurological and cardiac adverse reactions.

Acupuncture is an ancient treatment that was used for thousands of years and is considered to be a safe treatment when applied by a certified acupuncturist. A review investigating acupuncture for postoperative delayed gastric emptying patients including abdominal surgery, esophageal cancer, and laparotomy found promising effectiveness of acupuncture when comparing to prokinetic drugs. Two additional studies suggest that electrical acupoint stimulation might be superior to prokinetic drug usage in the treatment of delayed gastric emptying in EN patients in the ICU resultant from stroke or traumatic brain injury. Another study proves that electrical acupoint stimulation might be superior to prokinetic drugs when applied by a certified acupuncturist. A review investigating acupuncture, along with Chinese herbal medicine, can decrease acute GI injury incidence in elderly patients with severe sepsis.

As a control treatment, we will use nonspecific acupuncture, which uses “real” acupuncture but the points selected have no relation to improving digestion function. We believe that the use of nonspecific acupuncture might enable proper blinding to the acupuncturist. As far as we know, there is no double-blind randomized controlled study that investigates the effect of acupuncture on total energy expenditure (TEE) days and other accompanying digestive signs present in postoperative oral and hypopharyngeal cancer patients receiving EN. The goal of our study is to conduct a double-blind randomized controlled trial to investigate the effect of acupuncture on treating indigestion of postoperative oral and hypopharyngeal cancer patients receiving EN in the surgical ICU; furthermore, we hypothesize that specific acupuncture (treatment group) will have a greater beneficial effect on digestion indicators when compared with the control.

2. Methods
2.1. Design and setting
Our study is a single-center, parallel arm, double-blind randomized control trial that will take place from May 2019 until June 2021. Our study will be performed in the surgical intensive care department of China Medical University Hospital in Taichung city, Taiwan. Our trial was approved by the Ethics Committee of China Medical University Hospital (CMUH108-REC2-037) and registered study protocol on www.clinicaltrial.gov (NCT03934294). The goal of our study is to assess the efficacy of acupuncture in treating indigestion and accompanying indigestion symptoms of surgical ICU patients. This will be achieved through analysis of 2 parallel groups; treatment group (ACU): specific acupuncture treatment alongside routine ICU treatment; control group (CON): nonspecific acupuncture treatment with routine ICU treatment (Fig. 1).

An informed consent form will be filed and signed by the legal representative of the patient before the initiation of our study. Patients will be randomly divided into 2 equal groups to ACU, and CON. Two qualified acupuncture doctors with at least 2 years of experience, from the acupuncture department of China medical university hospital, will perform the ACU and the CON treatments, ICU routine treatment will be carried out by ICU staff in all groups (ACU, CON). Prokinetic drug treatment will be prescribed by an ICU medical doctor if needed in all study groups. Researchers, statisticians, doctors, acupuncturists, and patients along with nurses (with the exception of study nurse) will be blinded to the patient allocation. Patients’ assessment will be done on a daily basis by ICU medical doctors and ICU nurses who will be blind to the patients’ allocation.

2.2. Participants
A total of 28 patients that required EN and admitted to the surgical intensive care department in china medical hospital for estimated ICU duration stay of at least 3 days will be enrolled in this study if the patient met the study inclusion criteria and after patient’s legal representative will sign an informed consent form.

2.3. Inclusion criteria

- Age 30–80
- Apache score <20
- Patients needed EN
- Patients who developed feeding intolerance 2 times in the first postoperative day.
- Postplastic surgery, including oral cancer or hypopharyngeal cancer

2.4. Exclusion criteria

- Coagulopathy
- Prolong prothrombin time activated partial thromboplastin time >4 times
- Thrombocytopenia—low platelet count
- Clinically unstable: receiving 2 inotropic agents or Fraction of Inspired Oxygen >70%
- Estimated ICU stay <3 days

2.5. Recruitment strategies
Patients recruiting will be done from May 2019 to July of 2021 or until a total of 28 patients will be recruited. A study personal (KP-Y) that is responsible for communicating with patient’s families and legal guardians will inform the patients family of the study along with its potential pros and cons and will ask the patients legal guardian to fill an informed consent form in case of willingness to join the study.
2.6. Informed consent

The study characteristics, objectives, risks, and benefits along with details on patient’s rights according to the declaration of Helsinki will be explained to the patient’s legal guardian by a study personal (KP-Y). In the event of willingness to enroll in the study, an informed consent form will be signed by the patient’s legal guardian that can decide on withdrawal from the study at any moment. In case of withdrawal from the study, the patient’s available data will be reserved for the final analyses (for the full informed consent form see Supplementary Information).
2.7. Randomization and allocation concealment

Patients will be randomized to 1 of 2 groups by study nurse (EB-A): ACU/CON using a computer-based simple random sampling with 1:1 ratio without stratification using the IBM SPSS statistics version 22 software (SPSS Inc, Chicago, IL). A number (1–28) will be affiliated to each patient at the time of ICU admission and after achieving informed consent. The number and patient name will be written down on a nontransparent envelope by the study nurse. The study nurse will provide an envelope containing a sheet depicting the acupoint name, location, and picture (ACU/CON) to acupuncture doctor 1. Acupuncture doctor 1 (blind) will mark the acupoints on the patients’ skin with a green sticker and leave the room. Acupuncture doctor 2 will enter the room and perform acupuncture on the marked points with “DE Qi” manipulation. After 30 minutes’ acupuncture doctor 2 will withdraw the needles.

Figure 2. Blinding flow chart. Patients and acupuncturist blinding process: after random allocation study nurse will provide 14 nontransparent sealed envelopes containing acupoint name and picture for both treatment and control groups for a total of 28 envelopes. Acupuncture doctor 1 will receive the envelope, will mark the acupoints on the patient skin with a green sticker and will leave the room. Acupuncture doctor 2 will enter the room and needle the marked acupoints with “DE Qi” manipulation. After 30 minutes’ acupuncture doctor 2 will withdraw the needles.

2.8. Interventions

Patients of the surgical intensive care department in China medical university hospital Taiwan, which have met the inclusion criteria, will be randomized and divided into 2 groups and receive specific acupuncture treatment with routine ICU treatment (ACU); nonspecific acupuncture with routine ICU treatment (CON). The patients will receive everyday treatment for 3 days for a total of 3 treatments. The treatment will start after 2 failed tube feeding sessions in both groups.

2.9. Treatment group (ACU)

In addition to routine ICU treatments, patients in the specific acupuncture group (ACU) will also receive daily bilateral traditional Chinese medicine style acupuncture on the following acupuncture points: ST36 (Zusanli), ST37 (Shangjuxu), ST39 (Xiajuxu), PC6 (Neiguan), and LI4 (Hegu). The acupoints indications in this group are specific to treat indigestion related conditions. ST36 (Zusanli), ST37 (Shangjuxu), ST39 (Xiajuxu), PC6 (Neiguan), and LI4 (Hegu). The patients or themselves about the study goals or patients’ allocation (Fig. 2).

Figure 2. Blinding flow chart. Patients and acupuncturist blinding process: after random allocation study nurse will provide 14 nontransparent sealed envelopes containing acupoint name and picture for both treatment and control groups for a total of 28 envelopes. Acupuncture doctor 1 will receive the envelope, will mark the acupoints on the patient skin with a green sticker and will leave the room. Acupuncture doctor 2 will enter the room and needle the marked acupoints with “DE Qi” manipulation. After 30 minutes’ acupuncture doctor 2 will withdraw the needles.

Figure 3. Acupoints for indigestion as selected in the Treatment group (ACU). The following acupoints will be applied for the treatment group (ACU). The acupoints indications in this group are specific to treat indigestion related conditions. ST36 (Zusanli), ST37 (Shangjuxu), ST39 (Xiajuxu), PC6 (Neiguan), and LI4 (Hegu).
who will not be allowed to communicate with the patients. At the end of the treatment, acupuncture doctors 1 and 2 will be asked to guess if they treated the specific or nonspecific acupuncture group to assess and maintain the integrity of the blindness in the study.

2.10. Control group

Patients’ in the nonspecific acupuncture group (CON) will receive routine ICU treatment and a total of 3 daily indigestion-related traditional Chinese medicine style acupuncture treatments at the following acupoints: LI 15 (Jianyu), SJ 14 (JianLiao), LU3 (Tianfu), GB35 (Yangjiao), BL 59 (Fuyang). The selected control points are not indicated for the treatment of digestion-related pathologies and are not reported to improve digestive function (Fig. 4).

The blind acupuncture procedure will be the same as in the specific acupuncture group, whereby acupuncture doctor 1 (blind) will mark the points in green marker, and acupuncture doctor 2 (blind) will disinfect the acupoint with a 70% alcohol pad and insert the needles into the marked points. A total of 10 bilateral sterile “Yu Kuang” acupuncture needles 40 mm with 30 G will be inserted perpendicularly into the depth of the muscle level with up and down stimulation and 180° rotation of the needles to both directions to generate a “De Qi” sensation. The needles will be retained for 30 minutes until removal by acupuncture doctor 2 who will not be allowed to communicate with the patients. During the session the patients will stay in a supine position. At the end of the treatment acupuncture doctors, 1 and 2 will be asked to speculate if they treat the specific or nonspecific acupuncture group to assess and maintain the integrity of the blindness in the study.

2.11. Drug treatment

Patients in all groups will receive metoclopramide 10 mg/8 hours in the case of poor digestion, alongside the individualized drug treatment prescribed by the ICU medical doctor as per individual patient needs.

2.12. Enteral feeding protocol

Nasogastric (NG) tubes will be inserted for the patients during surgery for the duration of surgery and postoperative time to service the nutritional need as per the patient prognosis/requirement. NG tubing depth and function will be fixed and checked every 24 hours and will be retained as long as the patient needs it. TEE will be calculated by the weight, height, and physical factors of the patient as assessed by the nutritionist in ICU to calculate daily nutritional needs. In postoperation day 1 ICU staff will start with a feeding amount of 30% of the TEE and gradually increase to 100% by day 4. Every 3 days the nutritionist will reassess the patient’s condition (and percentage of nutrition intake).

2.13. Outcome measures

The main outcome measurements will be the number of days of intakes for each patient to achieve the TEE.

Secondary outcomes measures are the amount of prokinetic drugs prescribed by the ICU doctor in total dosage, the need of nasojejunal tube (5 consistent days of indigestion with conservative therapy), the need of parental nutrition (patients who cannot digest with daily NG tube drainage of >500 mL/day or severe diarrhea of >1000 mL/day), incidents of vomit or diarrhea (total number of times and volume in microliters), incidents of constipation (no stool passage in 3 days will be considered as constipation), reflux, nausea (number of times, measured by patient complains), GI bleeding (positive occult blood test of the NG tube drainage and in the stool), and incidents of fever episodes (body temperature >38°C) will also be recorded when they occur, albumin blood levels, total ICU stay, total hospital stay, total mechanical ventilation in days (a day of mechanical ventilation is at least 6 hours of mechanical ventilation in 1 day), and total mortality will also be measured as a secondary outcome.

In order to compare the effect of the control treatment, heart rate and blood pressure will be measured 1 hour before and after the acupuncture in both groups.

Acupuncturists will be asked to speculate if they treated the specific or nonspecific acupuncture group to assess and maintain the integrity of the blindness in the study (acupuncturists speculation questioner, see Supplementary Information).

2.14. Follow-up

Daily follow up on TEE, NG tube depth, parenteral/enteral feeding, and prokinetic drug amounts will be collected by ICU staff along with incidents of vomiting, diarrhea, constipation,
reflux, nausea, and GI bleeding. After 3 days, the data collected will be used for calculating study results. Mechanical ventilation days needed and total ICU stay along with total hospital inpatient duration and mortality will be collected by the time of hospital discharge or until June 2021 (Fig. 5).

2.15. Adverse events

Before patients’ enrollment, the patient’s legal guardian will be informed on possible acupuncture adverse events including minor bleeding, hematoma, infections, alcohol allergy, etc. Any case of acupuncture-related severe adverse events taking place, the event will be reported immediately to primary investigator and to the ethics committee, adverse events details such as treatment site, acupoint selected, patient recovery outcome, and the number of events on 1 patient will be recorded. Acupuncture will be stopped and treatment groups will be unblind. The patient will be provided with suitable ICU treatment. China medical hospital ethics committee will be in charge of deciding whether the study can continue, should be altered, or shut down.

2.16. Sample size calculation

The sample size was calculated using G*power version 3.1.9.2 software, the sample size was based on data of 51 patients that visit the ICU department 9 months before the experiment and are similar to the study target population. A 95% power was calculated with an effect size of 1.68 and a calculation of 20% patient dropout rate required 14 patients in each group for a total of 28 patients.

2.17. Data management

In order to maintain the integrity of measured data and providing proper data reporting, patients’ data will be recorded manually as a case report form and uploaded to the hospital electronic database by ICU staff, the manual case reports will be stored in a secure location in the ICU and will be destroyed after trial completion. Regular meeting and presentations will ensure that the entire study staff is aware of the study protocol and follow it. At the beginning of the study, the principal investigator will make sure that patients enrolled are meeting inclusion criteria, the informed consent form is properly signed and all study

| Time point: | Enrolment | Intervention | Close-out |
|------------|-----------|-------------|-----------|
|            | ICU submission | t*1-3 | t* 2-4 | t* 3-5 | ICU discharge | Hospital discharge | 30, June 2021 |
| Enrolment: | | | | | | | |
| Eligibility screen | x | | | | | | |
| Informed consent | x | | | | | | |
| Allocation | x | | | | | | |
| Interventions: | | | | | | | |
| ACU | x | x | x | | | | |
| CON | x | x | x | | | | |
| Data collection: | | | | | | | |
| *Total Energy Expenditure | x | x | x | x | | | |
| - Amount of prokinetic drug | | | | | | | |
| - The need of naso-jejunal tube | | | | | | | |
| - Parental nutrition used | | | | | | | |
| - Incidents: vomitus, diarrhea, constipation, reflux, nausea and GI bleeding | | | | | | | |
| - Albumin blood levels | | | | | | | |
| - Acupuncture doctor treatment speculation | | | | | | | |
| - Total ICU stay in days | x | x | x | x | | | |
| - Total hospital stay in days | | | | | | | |
| - Total mechanical ventilation in days | | | | | | | |
| - Total mortality | | | | | | | |

(*) main outcome measurement.

(t*) time point

Figure 5. Trial schedule. Schedule of enrolment, eligibility screen, informed consent, allocation, interventions, and data collection following the SPIRIT 2013 statement[22]. (*) Main outcome measurement, (t) time point.
procedures are following the study protocol. Any modification in
the study protocol will be done upon agreement with China
Medical University Hospital Ethics Committee and with www.
clinicaltrial.gov.

2.18. Statistical analysis
A researcher who is blind to patient allocation will conduct the
statistical analysis. Statistical data will be described as a
percentage (n %) for categorical data and as mean ± standard
deviations for continuous data. Continuous variables will be
analyzed using the t test or the Mann-Whitney U test
and categorical variables using the Chi-square (χ²) test or the
Fishere test with a best applicable basis. Repeated
measurements will use the generalized linear model generalized
estimating equation to conduct the analysis. The analysis will
be performed using the IBM SPSS Statistics version 22.0 (SPSS
Inc, Chicago, IL), the results will be marked as significant at
P value <.05.

3. Discussion
In critically ill patients, the incidence of indigestion can be as high
as 46%; this may lead to malnutrition, increasing ICU stay, and
increased mortality. In order to treat indigestion prokinetic
drugs are commonly used, although prokinetic may carry some
adverse reactions. From data collected from our ICU
department before our study, oral and hypopharyngeal cancer
patients suffering from postoperative feeding intolerance will
reach their TEE after 9 days with the use of prokinetic drugs, on
the contrary, postoperative oral and hypopharyngeal cancer
patients that do not suffer from feeding intolerance will reach
their TEE in <3 days. This is a need to use a safe and effective
method to improve poor digestion in critically ill cancer patients.
Acupuncture has been reported to improve indigestion signs in
several studies.

For study design, we decided to conduct a double-blind design
to minimize the bias. A double-blind design is unusual in
acupuncture studies. Double-blind acupuncture studies are often
consisting of the usage of sham needles, which carry a number of
limitations; firstly, the needleling depth is limited 10 mm depth
which may not be ideal insertion depth in many acupuncture
drants. Secondly, sham needles do not allow a full up and
down manipulation which may be crucial in achieving “DE QI”
sensation (an important penman in successful acupuncture
treatment), and thirdly, in some cases, sham needles failed to
achieve a good level of acupuncturist blinding. Our study
design involves 2 groups; when both groups are using “real”
acupuncture needles at “real” acupuncture points. The differences
between acupuncture groups are the acupoint selected.
When in the treatment group (ACU) the selected acupoints are
specific for the treatment of indigestion, the CON is here to
present the placebo effect of acupuncture by needling acupoints
that do not have any indication to treat indigestion. In both
groups, the acupuncturist will perform needles stimulation that
will activate the “DE QI” sensation. The acupuncturists
performing the treatments will be blind to the study goal to
treat indigestion, a fact that we believe will make it difficult to
speculate which of the group is receiving the “real” treatment and
allow us to generate blinding of the acupuncturist and patients.
After a treatment session, we decided to ask the acupuncture
doctors to speculate which treatment was the “real” treatment to
calculate the level of doctor blindness. The patients will not be
asked to speculate on the treatment nature since both groups
will receive traditional medicine style acupuncture and due to
the nature of ICU patients that may not be in a fully conscious
state.
The acupoints selected in the treatment group (specific
acupuncture group) are; ST36 (Zusanli), ST37 (Shangjuxu),
ST39 (Xiajuxu), PC6 (Neiguan), and LI4 (Hegu). The acupoint,
PC6 (Neiguan) main characteristics are regulating the stomach,
relieve nausea and vomiting, and the point was used successfully
in reducing gastric emptying. The 3 acupoints, ST36 (Zusanli),
ST37 (Shangjuxu), and ST39 (Xiajuxu) are “He-Sea” points of stomach, large, and small intestines, respectively
and are used to benefit those organs, the points were also a part of
the acupoint combination used in a recent pilot study in
improving gastric emptying. The acupoint LI4 (Hegu) also showed to improve small intestines motility
in animal studies; additionally, ST36 (Zusanli) showed to
increased gastric motility through a vagal pathway. The acupoint LI4 (Hegu) a “Yuan-Source” point of the Large
Intestine channel is usually indicated for treating pain-related
conditions alongside with the ability to benefit the digestive
system, the points showed a beneficial effect on irritable bowel
syndrome and on rats with gastric carcinectomy.

The selected acupoint in the CON (nonspecific acupuncture
group) are LI 15 (Jianyu), SJ 14 (JianLiao) LU3 (Tianfu), GB35
(Yangjiao), and BL 59 (Fuyang). The acupoints LI 15 (Jianyu)
and SJ 14 (JianLiao) are located on the shoulder and used to treat
shoulder conditions. LU3 (Tianfu) is used mainly for mental
imbalance and for cough; GB35 (Yangjiao) is used for pain in the
knee and leg; and BL 59 (Fuyang) is used for low back and
thigh pain. None of the points in this group are used to benefit
the digestive system and we believe that the points can be suitable
to demonstrate the placebo effect of acupuncture treatment. An
acupuncturist might speculate that the patients receiving those
acupoints are suffering from shoulder pain.

Acknowledgments
The authors would like to thank the Chinese Medicine Research
Center, China Medical University for the support to our study.

The authors would like to show their gratitude to Wei Tsu-
Hsuan, MD and Chang Chiu-Ming, MD for performing
acupuncture.

Author contribution
Analysis and interpretation of the data: Ho Wen-Chao, Eyal Ben-
Arie, Kao Pei-Yu
Conceptualization: Eyal Ben-Arie, Kao Pei-Yu
Data curation: Eyal Ben-Arie, Kao Pei-Yu
Design: Eyal Ben-Arie, Kao Pei-Yu, Lee Yu Chen, Ho Wen-Chao
Formal analysis: Ho Wen-Chao
Funding acquisition: Lee Yu Chen.
Investigation: Eyal Ben-Arie, Kao Pei-Yu.
Methodology: Eyal Ben-Arie, Kao Pei-Yu, Ho Wen-Chao
Project administration: Eyal Ben-Arie, Kao Pei-Yu, Lee Yu Chen.
Resources: Lee Yu Chen
Software: Eyal Ben-Arie, Kao Pei-Yu, Ho Wen-Chao.
 Supervision: Lee Yu Chen.
Validation: Eyal Ben-Arie, Lee Yu Chen
References

[1] Muller-Richter U, Betz C, Hartmann S, et al. Nutrition management for head and neck cancer patients improves clinical outcome and survival. Nutr Res 2017;48:1–8.

[2] Nugent B, Lewis S, O’Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. Cochrane Database Syst Rev 2013;Cd007904.

[3] Shi J, Wei L, Huang R, et al. Effect of combined parenteral and enteral nutrition versus enteral nutrition alone for critically ill patients: a systematic review and meta-analysis. Medicine (Baltimore) 2018;97: e11874.

[4] Hartwell JL, Cotton A, Rozycki G. Optimizing nutrition for the surgical patient: an evidenced based update to dispel five common myths in surgical nutrition care. Am Surg 2018;84:831–5.

[5] Garrison CM. Enteral feeding tube clogging: what are the causes and what are the answers? a bench top analysis. Nutr Clin Pract 2018;33:147–50.

[6] Shimizu K, Kageyama M, Ogura H, et al. Effects of rhubarb on intestinal dysmotility in critically ill patients. Intern Med 2018;57:507–10.

[7] Plah F, Winhard M, Nowak-Machen M, et al. Acupuncture in critically ill patients improves delayed gastric emptying: a randomized controlled trial. Anesthesia and analgesia 2011;112:150–9.

[8] Nguyen DL. Guidance for supplemental enteral nutrition across patient populations. Am J Manag Care 2017;23(12 Suppl):S210–9.

[9] Reitam A, Parm P, Kitus R, et al. Gastrointestinal symptoms in intensive care patients. Acta Anaesthesiol Scand 2009;53:318–24.

[10] Lewis K, Alphatni Z, McIntyre I, et al. The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. Crit Care 2016;20:259.

[11] Van der Meer YG, Venhuizen WA, Heyland DK, et al. Should we stop prescribing metoclopramide as a prokinetic drug in critically ill patients? Crit Care 2014;18:502.

[12] MacPherson H, Thomas K, Walters S, et al. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. BMJ 2001;323:486–7.

[13] Zhang J, Shang H, Gao X, et al. Acupuncture-related adverse events: a systematic review of the Chinese literature. Bull World Health Organ 2010;88:915C–21C.

[14] Xu S, Wang L, Cooper E, et al. Adverse events of acupuncture: a systematic review of case reports. Evid Based Complement Alternat Med 2013;2013:581203.

[15] Lee H, Kim TH, Leem J. Acupuncture for heart failure: a systematic review of clinical studies. Int J Cardiol 2016;222:321–31.

[16] Matsumoto-Miyazaki J, Ushikoshi H, Miyata S, et al. Acupuncture and traditional herbal medicine therapy prevent delirium in patients with cardiovascular disease in intensive care units. Am J Chin Med 2017;45:255–68.

[17] Feeney C, Bruns E, LeCompte G, et al. Acupuncture for pain and nausea in the intensive care unit: a feasibility study in a public safety net hospital. J Altern Complement Med 2017;23:996–1004.

[18] Matsumoto-Miyazaki J, Ushikoshi H, Suzuki K, et al. Efficacy of acupuncture treatment for improving the respiratory status in patients receiving prolonged mechanical ventilation in intensive care units: a retrospective observational study. J Altern Complement Med 2018;24:1076–84.

[19] Cheong KB, Zhang JP, Huang Y. The effectiveness of acupuncture in postoperative gastroparesis syndrome—a systematic review and meta-analysis. Complement Ther Med 2014;22:767–86.

[20] Kao ML, Chen YL, Lee SC, et al. Electroacupuncture improves gastric emptying in critically ill neurosurgical patients: a pilot study. Evid Based Complement Alternat Med 2017;2017:1892161.

[21] Wang Y, Zhang Y, Jiang R. Early traditional Chinese medicine bundle therapy for the prevention of sepsis acute gastrointestinal injury in elderly patients with severe sepsis. Sci Rep 2017;7:46015.

[22] Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Rev Panam Salud Publica 2015;38:506–14.

[23] Gupta E, Lee J.A. Diet and complementary medicine for chronic unexplained nausea and vomiting and gastroparesis. Curr Treat Options Gastroenterol 2016;14:401–9.

[24] Liu H, Yu B, Zhang M, et al. Treatment of diabetic gastroparesis by complementary and alternative medicines. Medicines (Basel) 2015;2:212–9.

[25] Zhu J, Guo Y, Liu S, et al. Acupuncture for the treatment of gastro-esophageal reflux disease: a systematic review and meta-analysis. Acupunct Med 2017;35:316–23.

[26] Chou PC, Huang YC, HsuCh CJ, et al. Retrospective study using MRI to measure depths of acupuncture points in neck and shoulder region. BMJ Open 2015;5:e007819.

[27] Zhang GS, Zhang CS, Tan HY, et al. Systematic review of acupuncture placebo devices with a focus on the credibility of binding of healthy participants and/or acupuncturists. Acupunct Med 2018;36:204–14.

[28] Jang JH, Lee DJ, Bae CH, et al. Changes in small intestinal motility and related hormones by acupuncture stimulation at Zusanli (ST 36) in mice. Chin J Integr Med 2017;23:215–20.

[29] Yuan M, Li Y, Wang Y, et al. Electroacupuncture at ST37 enhances jejunal motility via excitation of the parasympathetic system in rats and mice. Evid Based Complement Alternat Med 2016;2016:3840230.

[30] Fireman Z, Segal A, Kopelman Y, et al. Acupuncture treatment for irritable bowel syndrome. A double-blind controlled study. Digestion 2001;64:100–3.

[31] Lai M, Wang SM, Wang Y, et al. Effects of electroacupuncture of “Zusanli” (ST 36), “Hegu” (LI 4) and/or “Sanoyimiao” (SP 9) on immunofunction in gastric carcinomaey rats [in Chinese]. Zhen Ci Yan Jiu 2008;33:245–9.

[32] Koh PS, Seo BK, Cho NS, et al. Clinical effectiveness of bee venom acupuncture and phyotherapy in the treatment of adhesive capsulitis: a randomized controlled trial. J Shoulder Elbow Surg 2013;22:1053–62.

[33] Maciocia G, Ming SX. The Foundations of Chinese Medicine: A Comprehensive Text for Acupuncturists and Herbalists. 2nd edn.China: Health Sciences Division.; 2005. 1236 pages.