Study Title: Oral Supplementation of Glutamine on Gastric Cancer Patients After Gastrectomy

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Specific aims

Glutamine has the potentials of immunomodulation and adjustment of protein metabolism. The primary objective of this study is to evaluate the efficacy of glutamine on sarcopenia in gastric adenocarcinoma patients undergoing gastrectomy. The secondary endpoints, including the physical activity, weight loss, and nutritional profiles, will be evaluated among these patients.

Background and significance

Gastric adenocarcinoma (GA) is one of the most common foregut cancers worldwide and is often diagnosed at advanced stages unless routine endoscopy is done.[1] Dysphagia and loss of body weight are often encountered in GA patients with advanced stages of cancer. Radical gastrectomy plus lymphadenectomy is considered as the only potentially curative treatment. However, it is accompanied by a high rate of morbidity and mortality, especially in the GA patients with major comorbidities, poor physical activity, or malnutrition.[2-4] Notably, in the postoperative period, GA patients suffer from the deterioration of strength in skeletal muscles and poor quality of life due to the complex reconstruction of the gastrointestinal tract and gastrointestinal tract sequelae.[5] Since physical activity is associated with outcomes in GA cases, its improvement is crucial.

Sarcopenia, previously known as muscle weakness [6] or cancer-related cachexia [7], is measured as the skeletal muscle index (SMI), ≤55 cm^2/m^2 for men and ≤39 cm^2/m^2 for women.[8] SMI is strongly correlated with the cross-sectional area of psoas major muscle (PMMA) at the third lumbar vertebra (L3), which provides an easier method to assess the severity of sarcopenia among GA patients.[9] This parameter is often measured using abdominal computed tomography (CT). Recently, there are increasing studies investigating the association between sarcopenia and outcomes, and this correlation is highlighted in surgical patients for foregut cancer.[6,10]

Moreover, physical activity (PA) is a well-known parameter to both assess the general condition and monitor the recovery of patients.[11,12] Among the patients undergoing major surgery, the physical activity also deteriorated because of the surgical stress and insults, which caused afterward decreased quality of life and poor outcomes.[13,14] Although the double-labeled water method is recognized as the gold standard for assessing total energy expenditure, it is rarely implemented in clinical practive due to expensive costs and complicated process. [15,16] As a result, other modalities, such as self-report questionnaires, self-report activity diaries, direct observation, and smart watch, have been developed to replace the DLW method. [16]

Glutamine is the most abundant non-essential amino acid in humans; it is depleted under hypermetabolic and hyper catabolic conditions, such as severe illness or major surgery.[17,18] Since glutamine is involved in diverse processes, including protein metabolism[19] and immune system modulation[20], its insufficiency results in negative nitrogen balance causing significant dysfunction of the gut barrier and wound healing.[21] Several studies support that glutamine supplementation is beneficial for the recovery of patients from critical illness as well as chemotherapy-related side effects.[22-24] However, the impact of glutamine supplementation on sarcopenia was inconclusive.[25]

Therefore, this study was conducted to evaluate whether postoperative oral use of glutamine aids in improving sarcopenia and physical activity in GA patients undergoing gastrectomy. We hypothesized that glutamine might play a role in improving sarcopenia and physical activity. As CT is routinely performed in surgical GA patients to check for cancer recurrence, we used

PMMA to assess the severity of sarcopenia. The primary endpoint was the perioperative change in PMMA. Further, the physical activity is defined as the daily walking steps recorded by one smart watch. The secondary end-points are the change of walking steps between the data from the preoperative period and three months post gastrectomy, weight loss, and nutritional profiles. A linear regression model was used to predict this association.

Experimental design and methods

Protocol Synopsis

Test immunomodulating formula:

1. Name: Glutamine

2. Dosage Form: Dry powder

3. Dose(s): 10 g glutamine + 5 g Maltodextrin /pack

4. Dosing Schedule:

(1) Control Group:

15 g Maltodextrin for 28 days after surgery with tolerable oral intake or enteral feeding

(2) Treatment Group:

10 g glutamine +5 g Maltodextrin for 28 days after surgery with tolerable oral intake or enteral feeding

Study Design:

1. ☑Control: ☑placebo
☐active (please specify name and dosage)_____
☐other
☐Uncontrolled

2. Blinding: ☐open-label ☐evaluator blind ☐single blind ☑double blind
☐double dummy ☐other _____

3. Randomized: ☑yes ☐no

4. ☑Parallel ☐Cross-over ☐Other _____

5. Duration of treatment: 28 days ____ weeks____ months ____ years

6. Titration: ☐forced ☐optional ☑none

7. ☐Multi-national ☐Multi-center (in Taiwan) ☑Single center

Endpoints

1. Primary Endpoint:

Change of area of psoas muscle

2. Secondary Endpoint:

(1) Walking steps

(2) Weight loss

(3) Change of serum albumin value, pre-albumin value, white blood counts, and lymphocyte counts

Selection Criteria:

1. Inclusion Criteria:

1. gastric cancer patients undergoing gastric surgery

2. age ≧20 years old

2. Exclusion Criteria:

- Hepatic insufficiency
- Renal insufficiency
- can not tolerate oral or enteral feeding 7 days after gastrectomy
- can not receive computed tomograph
- can not waer the wearable devices

Study Procedures:

This will be a double-blind, randomized, and placebo-controlled study. At least 80 evaluable patients who are scheduled for gastrectomy for gastric adenocarcinoma cancer will be randomly assigned to the control or treatment group. Each group will have at least 40 patients. The CT scan will be evaluated before surgery and on POD 90. Moreover, the patient will wear the smart watch to record daily walking steps. Laboratory data will be check before gastrectomy and on POD 90.

The detailed clinical schedule is as shown in Appendix I.

Statistics:

1. Primary hypothesis: ☑superiority ☐non-inferiority
☐equivalence ☐other_____

2. Sample size: Enrolled 100 (estimated)
Evaluable at least 80

- Given a one-sided α level of 2·5 percent and assuming a treatment response rate of 92 percent for glutamine and to have 80 per cent power to test this RCT. The final planned sample size was 100 patients.
- After enrolment, patients were randomized in a 1 : 1 ratio, using opaque, sealed, sequentially numbered envelopes containing computer-generated allocation numbers.

3. Efficacy population: ☑ITT ☑PP ☐other_____

4. Statistical method(s) for efficacy/safety evaluations:

To compare differences in terms of the efficacy parameters, between the study groups, parametric or non-parametric approaches will be applied as appropriate, mainly, paired t-test, two-sample t test, Wilcoxon two-sample test, or chi-square test (or the Fisher's exact test). Linear regression models will be developed to validate the association between outcomes and intervention.

5. Planned interim analysis: ☐yes ☑no

Appendix I: Clinical Schedule

Period		Screening Period	Gastrectomy	Study Drug Treatment Period		Follow-up Period		
Postoperative Day (POD)		-1	0	3~7	31~35	28	56	84
Informed Consent		V						
Inclusion/Exclusion Criteria		V						
Randomization			V					
Medical History		V						
Gastrectomy			V					
Blood laboratory Test	AST	V						V
	ALT	V						V
	BUN	V						V
	Creatinine	V						V
	CBC, D/C	V						V
	Prealbumin	V						V
	Serum albumin	V						V
CT scan		V						V
Smart watch				V	V	V	V	V
Study formula Administration				V	V			
Weight Measurement		V		V				V
Adverse Events		V		V	V	V	V	V

References

1. WHO. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Accessed June 21, 2017. http://globocan.iarc.fr/Default.aspx
2. Watanabe M, Miyata H, Gotoh M, et al. Total gastrectomy risk model: data from 20,011 Japanese patients in a nationwide internet-based database. *Annals of surgery*. Dec 2014;260(6):1034-9. doi:10.1097/SLA.0000000000000781
3. Viste A. Predicted morbidity and mortality in major gastroenterological surgery. *Gastric Cancer*. Jan 2012;15(1):1-2. doi:10.1007/s10120-011-0108-3
4. Wu JM, Ho TW, Chang YT, et al. Wearable-Based Mobile Health App in Gastric Cancer Patients for Postoperative Physical Activity Monitoring: Focus Group Study. *JMIR Mhealth Uhealth*. Apr 23 2019;7(4):e11989. doi:10.2196/11989
5. Hu Y, Vos EL, Baser RE, et al. Longitudinal Analysis of Quality-of-Life Recovery After Gastrectomy for Cancer. *Ann Surg Oncol*. Jan 2021;28(1):48-56. doi:10.1245/s10434-020-09274-z
6. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in

older patients. *J Am Coll Surg*. Jun 2010;210(6):901-8. doi:10.1016/j.jamcollsurg.2010.01.028
7. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. Jul 2008;9(7):629-35. doi:10.1016/S1470-2045(08)70153-0
8. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. May 2011;12(5):489-95. doi:10.1016/S1470-2045(10)70218-7
9. Lu J, Zheng ZF, Li P, et al. A Novel Preoperative Skeletal Muscle Measure as a Predictor of Postoperative Complications, Long-Term Survival and Tumor Recurrence for Patients with Gastric Cancer After Radical Gastrectomy. *Ann Surg Oncol*. Feb 2018;25(2):439-448. doi:10.1245/s10434-017-6269-5
10. Chang GJ, Skibber JM, Feig BW, Rodriguez-Bigas M. Are we undertreating rectal cancer in the elderly? An epidemiologic study. *Annals of surgery*. Aug 2007;246(2):215-21. doi:10.1097/SLA.0b013e318070838f
11. Macfarlane DJ, Lee CC, Ho EY, Chan KL, Chan D. Convergent validity of six methods to assess physical activity in daily life. *J Appl Physiol (1985)*. Nov 2006;101(5):1328-34. doi:10.1152/japplphysiol.00336.2006
12. Lee IM, Hsieh CC, Paffenbarger RS, Jr. Exercise intensity and longevity in men. The Harvard Alumni Health Study. *JAMA*. Apr 19 1995;273(15):1179-84. doi:DOI 10.1001/jama.273.15.1179
13. Takiguchi S, Fujiwara Y, Yamasaki M, et al. Laparoscopy-assisted distal gastrectomy versus open distal gastrectomy. A prospective randomized single-blind study. *World journal of surgery*. Oct 2013;37(10):2379-86. doi:10.1007/s00268-013-2121-7
14. Yu W, Park KB, Chung HY, Kwon OK, Lee SS. Chronological Changes of Quality of Life in Long-Term Survivors after Gastrectomy for Gastric Cancer. *Cancer Res Treat*. Jul 2016;48(3):1030-6. doi:10.4143/crt.2015.398
15. Westerterp KR. Assessment of physical activity: a critical appraisal. *Eur J Appl Physiol*. Apr 2009;105(6):823-8. doi:10.1007/s00421-009-1000-2
16. Sylvia LG, Bernstein EE, Hubbard JL, Keating L, Anderson EJ. Practical guide to measuring physical activity. *J Acad Nutr Diet*. Feb 2014;114(2):199-208. doi:10.1016/j.jand.2013.09.018
17. Hammarqvist F, Wernerman J, von der Decken A, Vinnars E. Alanyl-glutamine counteracts the depletion of free glutamine and the postoperative decline in protein synthesis in skeletal muscle. *Ann Surg*. Nov 1990;212(5):637-44. doi:10.1097/00000658-199011000-00012
18. Windle EM. Glutamine supplementation in critical illness: evidence, recommendations, and implications for clinical practice in burn care. *Journal of burn care & research : official publication of the American Burn Association*. Nov-Dec 2006;27(6):764-72. doi:10.1097/01.BCR.0000245417.47510.9C
19. Munene G, Francis W, Garland SN, Pelletier G, Mack LA, Bathe OF. The quality of life trajectory of resected gastric cancer. *J Surg Oncol*. Mar 15 2012;105(4):337-41. doi:10.1002/jso.22139

20. Braga M, Wischmeyer PE, Drover J, Heyland DK. Clinical evidence for pharmaconutrition in major elective surgery. *JPEN J Parenter Enteral Nutr*. Sep 2013;37(5 Suppl):66S-72S. doi:10.1177/0148607113494406
21. Sandini M, Nespoli L, Oldani M, Bernasconi DP, Gianotti L. Effect of glutamine dipeptide supplementation on primary outcomes for elective major surgery: systematic review and meta-analysis. *Nutrients*. Jan 9 2015;7(1):481-99. doi:10.3390/nu7010481
22. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks M. A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. *Clin Nutr*. Apr 2013;32(2):213-23. doi:10.1016/j.clnu.2012.11.003
23. Wischmeyer PE, Dhaliwal R, McCall M, Ziegler TR, Heyland DK. Parenteral glutamine supplementation in critical illness: a systematic review. *Crit Care*. Apr 18 2014;18(2):R76. doi:10.1186/cc13836
24. Noe JE. L-glutamine use in the treatment and prevention of mucositis and cachexia: a naturopathic perspective. *Integr Cancer Ther*. Dec 2009;8(4):409-15. doi:10.1177/1534735409348865
25. Mochamat, Cuhls H, Marinova M, et al. A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project. *Journal of cachexia, sarcopenia and muscle*. Feb 2017;8(1):25-39. doi:10.1002/jcsm.12127
26. Stehle P, Ellger B, Kojic D, et al. Glutamine dipeptide-supplemented parenteral nutrition improves the clinical outcomes of critically ill patients: A systematic evaluation of randomised controlled trials. *Clin Nutr ESPEN*. Feb 2017;17:75-85. doi:10.1016/j.clnesp.2016.09.007
27. Wu JM, Lin MT. Effects of specific nutrients on immune modulation in patients with gastrectomy. *Ann Gastroent Surg*. Jan 2020;4(1):14-20. doi:10.1002/ags3.12299
28. Mates JM, Segura JA, Campos-Sandoval JA, et al. Glutamine homeostasis and mitochondrial dynamics. *Int J Biochem Cell Biol*. Oct 2009;41(10):2051-61. doi:10.1016/j.biocel.2009.03.003