A preoperative whey protein and glucose drink before hip fracture surgery in the aged improves symptomatic and metabolic recovery

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Running title: ERAS in hip fracture surgery in the aged

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ABSTRACT

Background and Objectives: We investigated the effects of a carbohydrate-whey protein solution on aged patients undergoing hip fracture surgery. **Methods and Study Design:** Forty patients were randomly assigned to the carbohydrate-whey protein (CHP) group or the control group (CTL). In the CHP group, a mixed solution of CHP was orally administered to patients before surgery: 400 mL was administered on the day before surgery, and 200 mL was administered 3 h before surgery. The size of the liquid dark area in the gastric antrum was measured by ultrasound, and the bleeding volume during surgery was assayed. The incidence of nausea, vomiting, thirst, hunger, and days of hospitalization and the levels of blood glucose, C-reactive protein (CRP) and serum albumin were assessed. **Results:** There was no obvious liquid dark space in the gastric antrum. CHP administration improved postoperative thirst and hunger and resulted in increased albumin levels and decreased CRP concentrations and blood glucose fluctuations. **Conclusions:** Oral CHP before hip fracture surgery reduces the incidence of postoperative thirst and hunger and improves recovery in the aged.

Key Words: elderly, nutrition, whey protein, perioperative period, hip fracture

INTRODUCTION

Hip fracture is one of the most common traumatic diseases in aged patients, and 98% of aged patients with hip fracture require surgery.[1,2] Moreover, most aged patients tend to have a variety of concurrent systemic diseases with high morbidity and mortality.[3,4] Therefore, reducing the incidence of perioperative complications in aged patients with hip fracture is a serious challenge in the clinical practice.

The traditional standard fasting method, which entails fasting solid food for 6-8 h and clear liquid for 2 h before surgery, reduces the risk of perioperative aspiration. However, a previous study showed that most patients fasted from solid food for more than 12 h.[5] Adversely, long fasting times may result in many detrimental reactions, such as thirst, hunger, dehydration, low blood glucose levels, increased postoperative stress and insulin resistance, and an unbalanced body environment.[6] The oral administration of a carbohydrate solution 2~3 h before an operation could effectively reduce postoperative insulin resistance and blood glucose fluctuations and improve thirst, hunger, and anxiety; however, it has little effect on postoperative recovery and length of hospital stay.[7] Researchers have constantly explored new solutions, including carbohydrate solutions with added amino acids or peptides.[8] As the patient's protein catabolism increases, which is coupled with a loss of appetite and decreased

digestion and absorption, it is easy for the patient to reach a negative balance of protein metabolism after surgical trauma; therefore, preoperative and postoperative supplementation with high-quality protein helps prevent postoperative complications. Perrone et al reported that preoperative feeding with a whey protein plus carbohydrate drink reduced the inflammatory response and diminished insulin resistance.[9] However, its effect on aged patients is unknown.

The whey protein used in this study can be easily digested and absorbed, and it contains eight essential amino acids for rapid protein synthesis in the body; moreover, the ratios of amino acids in the whey protein are similar to those that the body requires. In the current study, we explored whether whey protein plus carbohydrate administration decreased the incidence of choking, reduced the incidence of postoperative thirst and hunger, improved the recovery of patients after surgery.

MATERIALS AND METHODS

This was a randomized, double-blind, clinical study carried out at the Suzhou Science and Technology Town Hospital. Forty patients (16 males and 24 females) undergoing elective hip fracture surgery were selected for this study. They were randomized into two groups: the carbohydrate-protein (CHP) group and the control (CTL) group. The criteria for eligibility included the following: age over 65 years; body mass index (BMI) less than 35 kg/m^2; not taking medication that could affect intermediary metabolism or gastric emptying; no symptoms or signs of metabolic, hepatic, renal, or gastric disease; preoperative serum albumin >30 g/L or hemoglobin >90 g/L; not combined with other fractures or systemic organ damage; and normal ranges of fasting circulating glucose concentrations, C-reactive protein (CRP), liver function tests, and creatinine (Table 1). Informed consent was obtained from each subject. The protocol was approved by the Institutional Ethics Committee at the Suzhou Science and Technology Town Hospital and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Five patients were excluded from the study. Two of these patients had low preoperative hemoglobin (<90 g/L). Two other patients in the CHP group and one patient in the CTL group experienced excessive bleeding during surgery.

Anesthesia and surgery

In the CHP group, 400 mL of an oral whey protein and carbohydrate solution (containing 14% whey protein hydrolysates with 10% glucose solution as the solvent) was given 24 h

before surgery, and 200 mL was given 3 h before surgery (this volume was consumed within 10 min). In the CTL group, patients were given distilled water at equal volumes to the solutions given to CHP patients at the same time points.

Each patient received 0.05 mg/kg intramuscular midazolam 30 min before entering the operating room.

The gastric antrum was assayed by ultrasound; the gastric residual margin was observed as an assessment of gastric emptying function. The patient position was Fowler's position with the head of the patient's bed is raised 45 degrees above the level. The probe was placed under the xiphoid process perpendicular to the abdomen. The left lobe of the liver and abdominal aorta were used as markers to obtain images of the gastric antrum. Probes were slightly rotated to obtain clear images. The gastric antrum along with the body's craniocaudal direction and the maximum diameter directions (D1 and D2) were measured on ultrasound. The area of the gastric antrum (antral cross-sectional area, CSA) was calculated. The formula used was as follows:

$CSA = \pi \times D2 \times D1 / 4$; CSA = 230 + 4.6 × gastric residual volume.

Similar to Bouvet's study,[10] this study used 0.4 mL/kg or less of gastric residual volume as the fasting state standard. Therefore, once the gastric residual volume reached more than 0.4 mL/kg, surgery was postponed.

A subarachnoid block with 1.8~2.4 mL of 0.5% ropivacaine hydrochloride in the L2-3 or L3-4 segment after opening the portal vein was applied. Ringer's solution plus hydroxyethyl starch 130/0.4 and sodium chloride was infused during surgery. The intravenous injection of 50 mg of flurbiprofen axetil 30 min before surgery was completed, and 1~2 μg/kg sufentanil, 50 mg of flurbiprofen axetil and 6 mg of tropisetron in 100 mL of saline was given for postoperative analgesia by an analgesia pump. The epidural catheter was removed, and the patients were sent back to the ward. The bleeding volume and whole surgery time were recorded.

After the operation, patients were encouraged to resume drinking, eating or supplementary nutrient solution as soon as possible. Patients were also encouraged to urinate; urination times and urine volume were recorded for 24 h. Postoperative nausea, vomiting, thirst, hunger, postoperative complications and length of stay in the hospital were also recorded. Fasting blood glucose, albumin and CRP levels were measured on the day before surgery and 24 h after surgery.

Statistical analysis

All values are shown as the mean±SD. Two-way ANOVA for repeated measures was used when appropriate (SPSS 18.0 for Windows, SPSS, Inc.). Post hoc analysis and other comparisons were performed using Student's t-test for paired and unpaired data. Statistical significance was accepted at $p<0.05$.

RESULTS

There were no differences in patient conditions between the two groups before surgery (Table 1). All patients in the fasting state were examined by ultrasonography 30 min before anesthesia. In this study, no obvious liquid dark space was seen in any patient. The gastric residual volume was 0.4 mL/kg or less. Operation times, intraoperative blood loss and infusion liquid volumes were not different between the two groups (Table 2).

The incidence of postoperative nausea and vomiting in both the CHP and CTL groups was similar, and the incidence of thirst and hunger after surgery was lower in the CHP group than in the CTL group (thirst 2 vs 10 patients, and hunger 2 vs 11 patients, $p<0.05$). Postoperative pulmonary ultrasonography showed that the CHP group did not have postoperative pleural effusion, whereas 4 patients in the CTL group showed pleural effusion, but there was no significant difference between the two groups ($p>0.05$).

There was no apparent difference in the preoperative blood glucose concentrations between the two groups ($p>0.05$). However, the postoperative blood glucose level in the CHP group was lower than that in the CTL group ($p<0.05$), and the changes in blood glucose after surgery were lower in the CHP group than in the CTL group (0.65±0.56 vs 2.19±1.04 mmol/L, $p<0.05$, Figure 1).

There were no significant differences in serum albumin levels or CRP values between the two groups before surgery ($p>0.05$). After surgery, the serum concentration of albumin was higher and the CRP value was lower in the CHP group than in the CTL group (albumin 32.45±2.17 vs 29.94±1.89 mmol/L; CRP 30.15±8.16 vs 43.45±12.82 mmol/L, $p<0.05$, Figure 2).

DISCUSSION

Shortening the preoperative fasting time is an important part of enhanced recovery after surgery (ERAS),[11] and this study observed the effects of a carbohydrate-whey protein solution on aged patients undergoing hip fracture surgery. Ultrasound confirmed a lack of liquid dark space and a gastric residual volume of less than 0.4 mL/kg 30 min before anesthesia in all

patients. The results showed that the oral carbohydrate solution did not increase the gastric residual volume or the risk of aspiration.

Surgical trauma, blood loss and infection are all factors that can cause severe stress reactions, increasing the release of adrenaline, glucagon and other hormones. Stress also induces insulin resistance, which reduces the sensitivity of tissues to insulin, resulting in hyperglycemia due to lower glucose metabolism and higher gluconeogenesis and hepatic glucose output, which is associated with fat and protein metabolism disorders. Therefore, aged patients with hip fracture surgery are prone to insulin resistance and hyperglycemia. Finney et al reported that stress-induced hyperglycemia was directly associated with a poor prognosis in critical patients.[12] Nygren found that the oral administration of 800 mL of carbohydrate solution the night before surgery and 400 mL at 2~3 h before anesthesia increased preoperative blood glucose and plasma insulin levels.[13] The state of low plasma insulin levels and reduced glycogen reserves changed into a state of increased insulin release and glycogen synthesis after treatment, that is, the hunger state changed into an energy storage state. This change is beneficial, as it increases the surgical tolerance of patients while simultaneously increasing their preoperative blood glucose and insulin levels. The solution reduced the incidence of insulin resistance after surgery and decreased postoperative hyperglycemia and blood glucose fluctuations.

Henriksen and Perrone demonstrated that a preoperative oral carbohydrate solution containing amino acids or whey protein reduced postoperative insulin resistance in patients undergoing abdominal surgery.[9,14] Our study also found that an oral solution containing whey protein and carbohydrate decreased postoperative blood glucose fluctuations in elderly patients with hip fracture before and after surgery. This finding suggests that the application of a new rapid solution may reduce insulin resistance and blood glucose elevation in elderly patients with hip fracture before and after surgery.

The serum albumin concentration in the CHP group increased 24 h after surgery. Plasma osmotic pressure and serum albumin are important for maintaining physiological functions, and they are key indexes for the evaluation of patient nutritional status and prognosis. A low serum albumin concentration reduces plasma colloid osmotic pressure and increases the incidence of pleural effusion. Many factors may cause a low serum albumin level, such as blood loss, an infusion of high-volume crystal solution, a decrease in liver protein synthesis, an increase in catabolism and severe trauma. Postoperative serum albumin concentrations were higher in the CHP group than in the CTL group, which may be related to the oral solution containing 14% whey protein.

Whey protein contains β-lactoglobulin, α-whey protein, protease, serum albumin and immunoglobulin, which are the main elements of proteins in human milk. Whey protein is rich in essential amino acids, especially branched chain amino acids. It promotes the release of insulin and growth hormone and accelerates protein synthesis. Whey protein has a high absorption rate in the intestine. Studies have found that postoperative whey protein promoted extension strength rehabilitation and prevented posttransplant bacteremia and posttransplant hyperglycemia.[15,16] In addition, preoperative whey protein intake increased protein synthesis and nutrition reserves while increasing the release of insulin and decreasing the reaction of blood glucose levels to stress. Fasting is considered a stress in aged patients with hip fracture, and it intensifies postoperative metabolism. Protein catabolism is greater than protein anabolism, which reduces postoperative serum albumin concentrations. In this study, preoperative whey protein intake in aged patients with hip fracture increased nutritional support and maintained postoperative serum albumin concentrations.

CRP is a common inflammation index, and increases in its plasma concentration levels correspond to an increased intensity of inflammation.[17] It may predict the occurrence of postoperative complications, as Kim et al. revealed that CRP was an independent risk factor for 1-year mortality after hip fracture surgery in the elderly.[18] Increased levels of inflammatory cytokines after surgery or trauma inhibit the synthesis of serum albumin and decrease the concentration of serum albumin.[19] Therefore, an elevation of plasma CRP and serum albumin concentrations indicates acute inflammation. In this study, the postoperative CRP concentration was lower and the serum albumin concentration was higher in the CHP group than in the CTL group one day after surgery, illustrating that acute inflammation was lower in the CHP group. Therefore, the oral administration of a carbohydrate solution containing whey protein is beneficial for reducing the acute inflammatory reaction in aged patients with hip fracture.

In conclusion, a preoperative oral whey protein carbohydrate solution in aged patients with hip fracture did not increase gastric contents. It reduced postoperative thirst and hunger and postoperative blood glucose fluctuations and serum albumin concentrations. It also improved postoperative nutrition and reduced postoperative inflammatory reactions. All of these actions improved patient recovery after surgery.

AUTHOR DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int. 2004;15:897-902.
2. Craig J, Murray A, Mitchell S, Clark S, Saunders L, Burleigh L. The high cost to health and social care of managing falls in older adults living in the community in Scotland. Scott Med J. 2013;58:198-203.
3. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int. 2009;20:1633-50.
4. Tsuboi M, Hasegawa Y, Suzuki S, Wingstrand H, Thorngren KG. Mortality and mobility after hip fracture in Japan: a ten-year follow-up. J Bone Joint Surg Br. 2007;89:461-6.
5. Lamacraft G, Labuschagne C, Pretorius S, Prinsloo MC, Smit MD, Steyn JR. Preoperative fasting times: Prescribed and actual fasting times at Universitas Hospital Annex, Bloemfontein, South Africa. S Afr Med J. 2017;107:910-4.
6. De Jonghe B, Fajardy A, Mérian-Brosse L, Fauconnier A, Chouillard E, Debit N, Solus H, Tabary N, Seguier JC, Melchior JC. Reducing pre-operative fasting while preserving operating room scheduling flexibility: feasibility and impact on patient discomfort. Acta Anaesthesiol Scand. 2016;60:1222-9.
7. Kehlet H. Enhanced Recovery After Surgery (ERAS): good for now, but what about the future? Can J Anaesth. 2015;62:99-104.
8. Lobo DN, Hendry PO, Rodrigues G, Marciani L, Totman JJ, Wright JW, Preston T, Gowland P, Spiller RC, Fearon KC. Gastric emptying of three liquid oral preoperative metabolic preconditioning regimens measured by magnetic resonance imaging in healthy adult volunteers: a randomised double-blind, crossover study. Clin Nutr. 2009;28:636-41.
9. Perrone F, da-Silva-Filho AC, Adôrno IF, Anabuki NT, Leal FS, Colombo T, da Silva BD, Dock-Nascimento DB, Damiao A, da Aguilar-Nascimento JE. Effects of preoperative feeding with a whey protein plus carbohydrate drink on the acute phase response and insulin resistance. A randomized trial. Nutr J. 2011;10:66.
10. Bouvet L, Mazoit JX, Chassard D, Allaouchiche B, Boselli E, Benhamou D. Clinical assessment of the ultrasonographic measurement of antral area for estimating preoperative gastric content and volume. Anesthesiology. 2011;114:1086-92.
11. Xia Z, Qiao K, Wang H, Ning X, He J. Outcomes after implementing the enhanced recovery after surgery protocol for patients undergoing tuberculous empyema operations. J Thorac Dis. 2017;9:2048-53.
12. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003;290:2041-7.
13. Nygren J, Soop M, Thorell A, Sree Nair K, Ljungqvist O. Preoperative oral carbohydrates and postoperative insulin resistance. Clin Nutr. 1999;18:117-20.
14. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA. Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. Acta Anaesthesiol Scand. 2003;47:191-9.

15. Niitsu M, Ichinose D, Hirooka T, Mitsutomi K, Morimoto Y, Sarukawa J, Nishikino S, Yamauchi K, Yamazaki K. Effects of combination of whey protein intake and rehabilitation on muscle strength and daily movements in patients with hip fracture in the early postoperative period. Clin Nutr. 2016; 35:943-9.
16. Kaido T, Ogura Y, Ogawa K, Hata K, Yoshizawa A, Yagi S, Uemoto S. Effects of post-transplant enteral nutrition with an immunomodulating diet containing hydrolyzed whey peptide after liver transplantation. World J Surg. 2012;36:1666-71.
17. Neumaier M, Braun KF, Sandmann G, Siebenlist S. C-Reactive Protein in Orthopaedic Surgery. Acta Chir Orthop Traumatol Cech. 2015;82:327-31.
18. Kim BG, Lee YK, Park HP, Sohn HM, Oh AY, Jeon YT, Koo KH. C-reactive protein is an independent predictor for 1-year mortality in elderly patients undergoing hip fracture surgery: A retrospective analysis. Medicine. 2016;95:e5152.
19. Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. Int J Gen Med. 2016;9:229-55.

Table 1. General patient descriptors

Generally	CHP group	CTL Group	*p*-value
Age (years old)	82.5±4.1	81.4±5.2	0.443
Gender (male / female)	6/14	6/14	1.000
ASA classification (II / III)	8/12	10/10	0.751
Body mass index (kg / m^2)	20.10±1.71	19.85±2.06	0.679
Type			
Femoral neck fracture (number)	10	9	0.752
Intertrochanteric fracture (number)	10	11	
Days before surgery (days)	4.3±1.1	4.2±1.1	0.765

Table 2. Comparison of two groups of patients during operation

	Blood loss (mL)	The operative time (h)	24h input (mL)	24h output (mL)
CHP group	219.0±149.1	1.33±0.32	2770.8±230.8	1817.8±698.2
CTL group	226.5±160.2	1.28±0.30	2695.0±396.7	1710.8±555.2
p-value	0.879	0.622	0.188	0.595

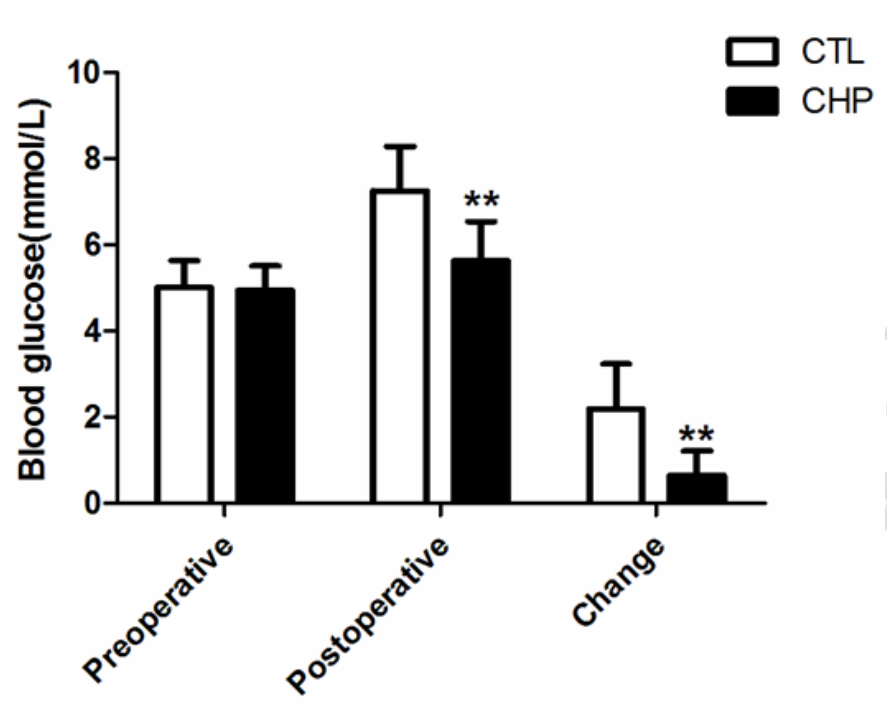

Figure 1. Differences in blood glucose levels between the CHP and CTL groups during the perioperative period (preoperative 4.95±0.55 vs 5.01±0.63 mmol/L, $p>0.05$, postoperative 5.63±0.91 vs 7.25±1.04 mmol/L, $p<0.001$). Changes in blood glucose were lower in the CHP group than in the CTL group after surgery (0.65±0.56 vs 2.19±1.04 mmol/L, $p<0.001$). $^{**}p<0.001$.

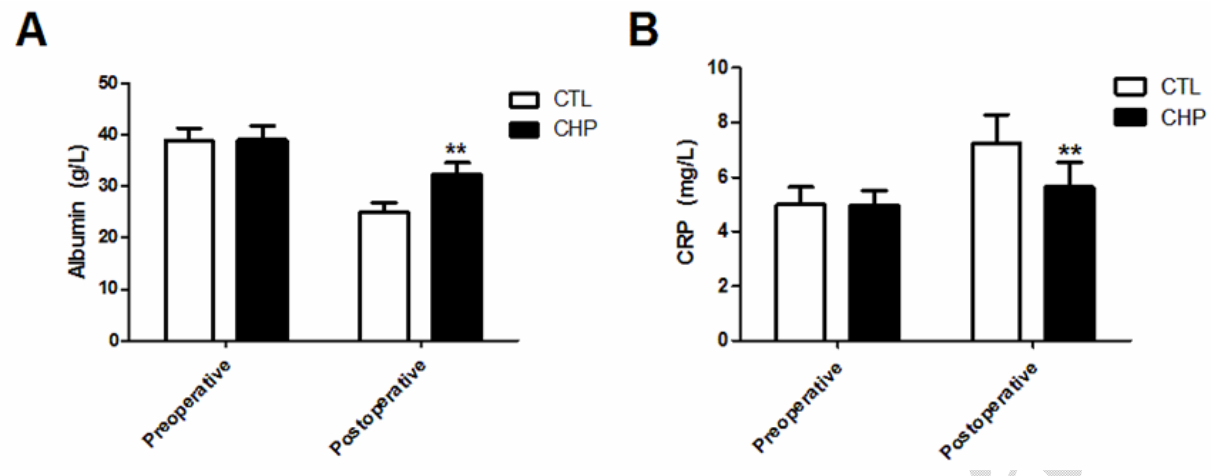

Figure 2. Differences in serum albumin between the CHP and CTL groups (preoperative 39.02±2.72 vs 38.90±2.35 g/L, $p>0.05$, postoperative 32.45±2.17 vs 29.94±1.89 g/L, $p<0.001$) (A) and differences in CRP between the CHP and CTL groups (preoperative 5.65±1.14 vs 5.70±1.56 mg/L, $p>0.05$, postoperative 30.15±8.16 vs 43.35±12.82 mg/L, $p<0.001$) (B). $^{**}p<0.001$.