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Randomised Controlled Trial
Reconstructive Surgery

Preoperative oral carbohydrates in elderly patients undergoing free flap surgery for oral cancer: randomized controlled trial

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Abstract. The aim of this study was to evaluate the safety of carbohydrate intake 2 hours before surgery in elderly patients undergoing free flap surgery for oral cancer. Elderly patients undergoing free flap surgery between September 2019 and January 2021 were randomly divided into control ($n = 43$) and intervention ($n = 43$) groups. Control group patients fasted for 6 hours and were forbidden from drinking water for 4 hours before surgery. Intervention group patients fasted for 6 hours and were forbidden from drinking after the oral administration of 5 ml/kg carbohydrate ($\leq$400 ml) 2 hours before surgery. The main outcome measures were aspiration, fasting blood glucose level, insulin concentration, insulin resistance index (fasting at admission, prior to anaesthesia induction, immediately after surgery, and at 6 a.m. on postoperative days 1 and 2), and comfort before and after surgery. No aspiration occurred in any of the patients during anaesthesia. There were significant differences in fasting blood glucose, insulin concentration, and insulin resistance index between the control and intervention groups prior to anaesthesia induction, immediately after surgery, and on day 1 after surgery ($P < 0.01$). Thirst ($P = 0.001$) and hunger ($P = 0.003$) differed significantly between the two groups prior to anaesthesia induction. The intake of oral carbohydrate 2 hours before surgery was both safe and effective for elderly patients with oral cancer undergoing free flap surgery and could relieve the physiological stress response.

Key words: insulin resistance; carbohydrates; oral cancer; free tissue flaps; elderly; randomized controlled trial.

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Patients are routinely fasted for 6 hours before surgery and water is forbidden for 4 hours before surgery to prevent severe intraoperative complications such as asphyxia and aspiration pneumonia caused by gastroesophageal reflux[1]. However, long-term fasting before surgery can lead to insulin resistance (IR), which reduces the sensitivity and responsiveness of peripheral tissues such as muscle and fat to insulin, reduces glucose uptake by muscle and adipose tissue, and weakens the effect

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of insulin on inhibiting liver glucose output. This is manifested as hyperglycaemia and hyperinsulinemia and increases the mortality risk of surgical patients and the incidence of complications of postoperative wound infection[2,3]. IR is an independent predictor of length of hospital stay[4]. In addition, the prolonged restriction of water intake before surgery can also cause adverse reactions such as thirst and hunger in patients[5].

In recent years, increasing attention has been focused on the administration of oral liquid carbohydrates 2 hours before surgery. A large number of studies have confirmed that this method can improve postoperative insulin resistance, promote postoperative patient rehabilitation, and shorten the length of hospital stay. In 2016, the American Society for Enhanced Recovery (ASER) and the European Society of Parenteral and Enteral Nutrition (ESPEN) successively included the consumption of carbohydrates 2 hours before surgery in an expert consensus statement and guidelines[6,7]. This practice has been promoted in the fields of general surgery, gynaecology, and orthopaedics.

Most head and neck squamous cell carcinomas (HNSCCs) arise between the fifth and seventh decades of life; 25% of HNSCCs are diagnosed in older patients[8,9], and most HNSCC patients have comorbidities[10,11]. Free flap surgery is widely used in reconstruction and the repair of tissue defects to improve patient quality of life. This type of surgery is complicated and risky, with an average surgery time of 3.8–7.1 hours[12,13], and patients are prone to IR after surgery. In older patients, as the cells, organs, physiological structure and function, and enzyme and hormonal activity are all degenerative, pancreatic islet function declines and the body's ability to metabolize sugar and fat decreases. The resulting postoperative IR and insulin secretion defects are therefore more serious in these elderly patients[14]. In addition, the guidelines do not recommend the administration of oral carbohydrates 2 hours preoperatively in elderly patients with reduced gastrointestinal function and a prolonged gastric emptying time[15]. Furthermore, there is a lack of reports on pre-surgical oral carbohydrate administration in patients undergoing free flap repair for oral cancer. Therefore, a prospective randomized controlled trial was performed with the aim of exploring the effects of oral carbohydrate intake 2 hours before surgery on postoperative insulin resistance, postoperative complications, and comfort before and after surgery in elderly patients undergoing reconstructive surgery.

Materials and methods

Patients

The 2010 CONSORT statement was applied in the reporting of this study (http://www.consort-statement.org/). This prospective randomized controlled trial was approved by the Ethics Committee of Peking University School of Stomatology (No. PKUSSIRB-201949145). Patients with oral cancer admitted to Peking University School of Stomatology between September 2019 and January 2021 were selected. The patients volunteered to participate in the study and provided signed informed consent.

The following inclusion criteria were applied: pathological diagnosis of oral cancer; surgery comprised an extended resection of oral and maxillofacial lesions + unilateral/bilateral neck lymph node dissection + free flap repair (forearm/fibula/iliac/anterolateral femur flap); the patient was $\geq$60 years of age and had a normal body mass index (BMI) ($18.5 \leq \text{BMI} \leq 23.9\ \text{kg/m}^2$); surgery was completed by the same group of surgeons; the patient had not participated in another clinical trial within 3 months; anaesthesia was induced at 8 a.m. for the first surgery.

Patients with the following conditions were excluded: diabetes and severe infection; a gastric emptying disorder (such as gastroesophageal reflux, chronic aspiration history, delayed gastric emptying); renal insufficiency (serum creatinine concentration >150 μmol/l) or liver disease; allergies or intolerance to maltodextrin or fructose.

Study design

After the surgery plan had been determined, patients who met the eligibility criteria were divided randomly into a control group ($n = 43$) and an intervention group ($n = 43$) using a random table. A nurse enrolled the participants and assigned them to the interventions; therefore, both the researchers and the patients were blinded to the trial grouping. The day before surgery, normal food was provided to the patients per the hospital's meals. An indwelling nasogastric tube was placed prior to anaesthesia induction.

The control group patients adopted the regular fasting and drinking regimen, wherein they fasted from 2 a.m. and were forbidden from drinking water from 4 a.m. onwards on the morning of the surgery.

The intervention group patients fasted from 2 a.m. and were given a 12% carbohydrate drink at 6 a.m. on the morning of the surgery. An oral dose of 5 ml/kg body weight was given, up to a maximum dose of 400 ml. The temperature of the liquid was approximately 37°C, and the patients drank it within 15 minutes.

Outcome measures

The intraoperative aspiration risk was evaluated. During the induction of anaesthesia and after sedation, the anaesthesiologist closely observed whether the patient experienced any gastric reflux into the oral cavity and monitored the changes in blood oxygen saturation during surgery. If aspiration was suspected, a chest computed tomography scan was performed for confirmation after surgery. Intraoperative aspiration was recorded as 'yes' or 'no'.

Serum glucose was assessed while the patient was fasting at admission (T1, basal value), prior to anaesthesia induction (T2), immediately after surgery (T3), at 6 a.m. on postoperative day 1 (T4), and at 6 a.m. on postoperative day 2 (T5). A 2.5-ml venous blood sample was drawn from the patient, and the glucose oxidase method was used to measure the blood glucose level.

Serum insulin was also measured at the five time points (T1–T5). This was measured using a chemiluminescent microparticle immunoassay with an insulin assay kit (Abbott Trading Shanghai Co., Ltd, Shanghai, China). Insulin resistance was calculated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), according to the following equation[16]: HOMA-IR = [fasting glucose (mmol/l) × fasting insulin (μU/ml)]/22.5.

Patient comfort scores were obtained for thirst and hunger at T2 and at 1 hour after the patient was awake. A visual analogue scale (VAS) was used to measure comfort, which was assessed and recorded by the ward nurse and the anaesthesia nurse. The VAS comprised a scale of 0–10, where 0 represents no discomfort and 10 represents the strongest discomfort. The patient's score was rated according to their subjective feelings.

Wound complications were also assessed, including the free flap outcome, wound infection, haematoma/haemorrhage, and fistula. These were evaluated and recorded by the physician. The evaluation index for the wound included three categories as follows[17]: grade A: complete healing of the incision, no redness or swelling, no infection; grade B: poor healing of the incision, slight redness or swelling, no infection; grade C: poor healing of

Table 1. Summary of patient characteristics.

	Control group ($n = 43$) Mean ± SD, or n (%)	Intervention group ($n = 43$) Mean ± SD, or n (%)	Z/χ^2	P-value
Age (years)	62.7 ± 6.3	64.1 ± 6.0	−1.055	0.295
Sex			0.454	0.500
Male	29 (67.4)	26 (60.5)		
Female	14 (32.6)	17 (39.5)		
BMI (kg/m^2)	23.07 ± 2.89	22.82 ± 2.87	0.406	0.686
Flap tissue			1.235	0.752
Fibula	12 (27.9)	9 (20.9)		
Anterolateral femur	20 (46.5)	24 (55.8)		
Forearm	2 (4.7)	1 (2.3)		
Ilium	9 (20.9)	9 (20.9)		
Anaesthesia score			1.452	0.560
0	6 (13.9)	3 (7.0)		
1	34 (79.1)	38 (88.4)		
2	3 (7.0)	2 (4.6)		
Duration of surgery (min)	333 ± 72	327 ± 77	0.400	0.690
Intraoperative bleeding volume (ml)	282 ± 104	280 ± 142	−0.888	0.375
Intraoperative urine volume (ml)	432 ± 348	407 ± 258	0.377	0.707

BMI, body mass index; SD, standard deviation.

Table 2. Blood glucose, insulin concentration, and HOMA-IR of the two groups of patients at different time points.

	Time	Control group ($n = 43$) Mean ± SD	Intervention group ($n = 43$) Mean ± SD	Z/t	P-value
Glucose (mmol/l)	Admission	5.2 ± 0.8	4.9 ± 0.5	−1.443	0.149
	Prior to anaesthesia induction	5.6 ± 0.9	7.6 ± 2.6	−4.227	0.001*
	Immediately after surgery	8.5 ± 2.0	7.3 ± 1.3	3.278	0.002*
	6 a.m. on pod 1	8.5 ± 2.1	7.3 ± 1.1	−2.696	0.007*
	6 a.m. on pod 2	6.7 ± 1.0	6.6 ± 1.1	0.704	0.484
Insulin (μU/ml)	Admission	6.90 ± 4.43	6.35 ± 3.05	−0.868	0.385
	Prior to anaesthesia induction	7.83 ± 3.38	12.67 ± 3.70	−6.327	0.001*
	Immediately after surgery	11.42 ± 4.78	7.00 ± 1.76	−5.169	0.001*
	6 a.m. on pod 1	17.04 ± 7.59	13.34 ± 3.17	−2.690	0.007*
	6 a.m. on pod 2	11.04 ± 5.10	11.56 ± 6.66	−0.194	0.846
HOMA-IR	Admission	1.63 ± 1.14	1.40 ± 0.71	−1.352	0.176
	Prior to anaesthesia induction	1.99 ± 1.03	4.38 ± 2.04	−5.757	0.001*
	Immediately after surgery	4.39 ± 2.54	2.25 ± 0.57	−5.739	0.001*
	6 a.m. on pod 1	6.65 ± 4.34	4.35 ± 1.36	−3.485	0.001*
	6 a.m. on pod 2	3.31 ± 1.66	3.38 ± 2.00	−0.220	0.826

HOMA-IR, homeostasis model assessment of insulin resistance; pod, postoperative day; SD, standard deviation. *$P < 0.05$.

the incision, severe redness or swelling, and fluid accumulation or skin necrosis, requiring incision and drainage.

Other objective information assessed included the length of stay and hospitalization costs.

Statistical analysis

A pilot study with immediate postoperative glucose as the outcome indicator was conducted on 17 patients. A sample size estimation was then performed using the two independent samples mean estimation formula, in which α was set at 0.05, β was set at 0.2, and a two-sided test was conducted; by lookup table, $t\alpha/2 = 1.96$ and $t\beta = 0.84$. According to the preliminary test, $\sigma = 3.56$ and $\delta = 2.26$, $N1 = N2 = 2 \times [(t\alpha/2 + t\beta)\sigma/\delta]^2 \approx 39$. Considering a dropout rate of 10%, no fewer than 43 patients per group were required.

The study data were entered into the trial database system twice by two independent researchers and the data in the database were compared twice and verified for accuracy. Two researchers performed the data analysis for the outcome measures using SPSS Statistics software version 17.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were described by number (percentage) or mean ± standard deviation. Count data were compared using the χ^2 test. Normally distributed measurement data were compared using the independent samples t-test, while non-normally distributed data were compared using the Wilcoxon rank sum test. $P < 0.05$ was considered to indicate statistical significance.

Results

Basic information on patients and surgery

A summary of the patient characteristics is given in Table 1. There was no statistically significant difference between the two groups in terms of sex, age, flap tissue, or surgery information.

Outcomes

No aspiration occurred during anaesthesia in any of the patients in either group.

Table 2 shows the results for blood glucose, insulin concentration, and HOMA-IR. Prior to anaesthesia induction, the glucose level, insulin concentration, and HOMA-IR in the intervention group were significantly higher than those in the

Table 3. Comfort scores of the two groups of patients.

		Control group ($n = 43$) Mean ± SD	Intervention group ($n = 43$) Mean ± SD	Z	P-value
Before induction of anaesthesia	Thirst	2.7 ± 2.1	1.3 ± 2.0	−3.524	0.001*
	Hunger	2.3 ± 2.0	1.2 ± 2.1	−3.018	0.003*
1 hour after awake postoperatively	Thirst	1.4 ± 2.5	1.7 ± 2.3	−1.082	0.279
	Hunger	0.7 ± 1.9	0.7 ± 1.7	−0.070	0.944

SD, standard deviation. *$P < 0.05$.

control group (all $P = 0.001$), while immediately after surgery and on the first postoperative day, the glucose level, insulin concentration, and HOMA-IR in the intervention group were significantly lower than those in the control group (immediately postoperative: $P = 0.002$, $P = 0.001$, and $P = 0.001$, respectively; day 1 postoperative: $P = 0.007$, $P = 0.007$, and $P = 0.001$, respectively).

Table 3 shows the comfort scores in the two groups. Prior to anaesthesia induction, the thirst and hunger scores of the intervention group patients were significantly lower than those of the control group patients, and the differences were statistically significant (thirst, $P = 0.001$; hunger $P = 0.003$).

Table 4 reports the results for wound complications and hospitalization factors. There was no statistically significant difference in postoperative wound infection, tissue flap outcome, length of stay, or hospitalization costs between the two groups.

Discussion

Oral cancer free flap surgery requires both head and neck surgery and donor area surgery, which is traumatic and time-consuming, and the intensity of the tissue trauma or injury during the surgery is proportional to the IR[18]. Therefore, such patients may develop severe IR after surgery. Glucose absorption slows with age. After the age of 30 years, the level of postprandial blood glucose can increase by 0.8 mmol/l for every additional decade of aging[19]. The decreased insulin sensitivity in elderly patients, combined with prolonged preoperative water fasting, further decreases the utilization of glucose by the body after being subjected to surgical trauma and increases the incidence of postoperative hyperglycaemia and hyperinsulinaemia[20]. Numerous studies have confirmed that the basic emptying of the patient's stomach within approximately 90 minutes after oral carbohydrate intake 2 hours before surgery does not increase the risk of intraoperative aspiration[21,22]. In addition, carbohydrate not only reduces postoperative IR[23], but also promotes gastrointestinal recovery. Moreover, it is conducive to early postoperative oral intake[5]. However, it appears that oral carbohydrate intake 2 hours before surgery in elderly patients undergoing free flap surgery for oral cancer has not yet been reported.

Aspiration is an important evaluation index of patient safety during anaesthesia, and the main patient factors affecting aspiration are a full stomach and delayed gastric emptying. Anaesthesia may be a contributing factor for reflux. Although elderly people have reduced gastrointestinal function and a prolonged gastric emptying time, no aspiration occurred in any of the patients in either group in this study. This shows that it was safe for elderly patients to drink carbohydrates 2 hours before surgery at the specific dose (5 ml/kg) calculated according to the patient's body weight, and with a maximum volume of 400 ml[24].

Under normal circumstances, the concentration of blood glucose under fasting status is 3.9–6.1 mmol/l, and insulin is the most important hormone in the body to promote metabolism, regulate blood glucose, and maintain blood glucose homeostasis. The fasting insulin concentration of most adults is in the range of 5–15 μU/ml, and the variation in the concentration is positively correlated with blood glucose. Elevated blood glucose and insulin concentrations are the common clinical manifestations of IR when the body is in the stress state, and the HOMA-IR can reflect the degree of IR in the patient. The greater the value, the more serious the IR, the greater the damage to the patient's body, and the more perturbed the metabolism of the internal body environment; this will eventually affect the postoperative patient's glucose metabolism and energy supply. In this study, the IR index prior to anaesthesia induction was higher in the intervention group patients who had consumed a carbohydrate drink than in the control group patients. This is likely because the main component of the carbohydrate drink is maltodextrin, which enters directly into the stomach without hydrolysis by salivary amylase; it is then rapidly broken down into smaller glucose molecules in the intestine, which will be absorbed immediately, leading to an increase in blood glucose, while stimulating the secretion of large amounts of insulin by pancreatic islet cells[12]. This increase in the IR index is a normal physiological response after feeding, to assist in the

Table 4. Wound complications, length of stay, and hospitalization costs in the two groups.

	Control group ($n = 43$) Mean ± SD, or n (%)	Intervention group ($n = 43$) Mean ± SD, or n (%)	$Z/t/\chi^2$	P-value
Wound infection			1.838	0.442
A	36 (83.7)	40 (93.0)		
B	5 (11.6)	2 (4.7)		
C	2 (4.7)	1 (2.3)		
Flap outcome			0.000	1.000
Normal	42 (97.7)	42 (97.7)		
Failed	1 (2.3)	1 (2.3)		
Length of stay	14.6 ± 3.7	14.4 ± 2.2	−0.279	0.781
Hospitalization costs (thousand dollars)[a]	12.1 ± 2.9	11.8 ± 3.5	−0.427	0.671

SD, standard deviation.

[a] Note: The exchange rate of RMB against USD is based on the average annual exchange rate in 2020 (6.90:1).

response to stress such as that caused by surgical trauma to the organism.

In the immediate postoperative period and on the first postoperative day after overnight fasting, the IR index of patients in the intervention group was lower than that of patients in the control group. This is because anaesthesia and surgical trauma can cause stress reactions in the body, and the body can maintain normal blood glucose and insulin concentrations through compensatory mechanisms in the early stage; in the later stage, after the body loses compensation, the metabolism of the pancreatic cells is disturbed, liver glycogen and muscle glycogen synthesis is impaired, and blood glucose and insulin concentrations increase. The HOMA-IR of patients in the control group at these two time points was significantly higher than normal values in the fasting state, indicating stress hyperglycaemia and IR after organism loss of compensation. The highest HOMA-IR on the first postoperative day indicates the most severe IR on the first postoperative day, which is consistent with the study by Rizvanović et al.[25]. In contrast, in patients in the intervention group who consumed carbohydrates 2 hours before surgery, this facilitated the postoperative anabolism of the body, increased the cellular uptake and utilization of glucose, and directly improved the postoperative hyperglycaemic and hyperinsulinaemic state[26], so that the HOMA-IR was lower than in the control group.

In terms of comfort, the preoperative thirst and hunger scores of patients in the intervention group were lower than those of the patients in the control group, indicating that oral carbohydrates can improve patient comfort levels. With prolonged preoperative water fasting, the body needs to break down glycogen and consume muscle to meet the metabolic demand, which can cause discomfort such as hunger, thirst, anxiety, and irritability, which in turn can lead to a state of preoperative tension in patients, aggravate the stress response of the body, and decrease the regulation and resistance of the body, all of which are not conducive to postoperative recovery[27].

It is reported in the literature that IR can induce stress hyperglycaemia and postoperative wound infection in the body, and hyperglycaemia can impair the self-repairing ability of the endothelium and affect the outcomes of free flap reconstruction[28,29]. Furthermore, preoperative oral carbohydrates can reduce the incidence of postoperative wound infection[3]. The lack of significance in postoperative wound complications may be related to the small sample size of this study.

The study period covered the hospitalization time. Out-of-hospital follow-up services were not provided for the patients as part of this study, therefore the long-term effect of preoperative oral carbohydrates on wounds in elderly patients is not clear. To explore the effect of this protocol on such patients, further studies with a larger sample size and longer follow-up period are recommended.

In conclusion, for elderly patients with oral cancer undergoing free flap surgery, it was found that oral carbohydrates given 2 hours before surgery was safe and could significantly relieve patient discomfort of preoperative hunger and thirst and reduce the degree of IR in the immediate postoperative period and on the first postoperative day.

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Competing interests

None.

Ethical approval

The study design, protocol, and informed consent were approved by the Biomedical Institutional Review Board of Peking University School and Hospital of Stomatology (No. PKUSSIRB-201949145).

Patient consent

Patient consent was obtained.

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