Nutrition protocol implemented in ERAS of hypopharyngeal cancer: a single center nutrition protocol in China

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ABSTRACT

The objective was to investigate the safety and efficacy of the nutrition protocol in enhanced recovery after surgery (ERAS) of hypopharyngeal cancer. Protocol focus was patient consumption of nutritional supplements perioperatively. In this retrospective study, a total of 78 patients with hypopharyngeal cancer were divided into the ERAS group (n = 39) and the control group (n = 39). The data were collected from two groups of three time points: 1 day before surgery, 1 day after surgery, and 7 days after surgery. The difference between two groups of the nutritional and immune status, postoperative exhaust time, hospitalization expense and hospitalization time were compared. The nutritional and immune status in the ERAS group were better than that in the control group at 7 days after surgery (P < .05); The hospitalization expense and hospitalization time in the ERAS group were lower comparing with the control group (P < .05). Our nutrition protocol is effective and safe in ERAS of patients with hypopharyngeal cancer. It’s significant to implement ERAS of hypopharyngeal cancer patients with nutritional protocol during peroperative period, which will improve immune system, maintain health metabolic functions, and reduce the hospitalization time as well as the hospitalization expense.

Introduction

Hypopharyngeal cancer is one of the most common malignant tumors in head and neck. Patients with hypopharyngeal cancer are difficult to treat because they typically present with advanced disease, poor general health status and severe nutritional problems. With these reasons, we have been looking for various ways to promote early recovery. One strategy is the enhanced recovery after surgery (ERAS) protocol, which aims to accelerate recovery. The ERAS protocol was first implemented in colorectal surgery to standardize perioperative care and was shown to improve patients’ postoperative function, decrease postoperative complications, and reduce hospital length of stay. Recently, ERAS is used as a new model in clinical surgical treatments, a series of evidence-based peroperative measures are taken to change traditional surgical therapy at some degrees.

The incidence of malnutrition is high in patients with hypopharyngeal cancer because of insufficient food intake due to esophageal obstruction and tumor consumption. One element of the ERAS protocol focuses on perioperative nutritional protocol. The nutritional support plays a very important...
role in ERAS, but the specific nutritional support scheme (how much energy is the most appropriate) is still inconclusive. However, to date, there is nor a unified standard for nutritional support perioperation in patients with hypopharyngeal cancer. In our study, we applied ERAS to nutritional support procedures among hypopharyngeal cancer patients during perioperative periods, and explored its effect on postoperative recovery. Good results have been achieved. Now our experiences are introduced as follows.

Methods
Seventy-eight hypopharyngeal cancer patients were selected from April 2020 to October 2020, among them 53 were men and 25 were women. All of the subjects were divided into the ERAS group (Eg, n = 39) and the control group (Cg, n = 39). The ERAS group was applied to ERAS of hypopharyngeal cancer patients with nutritional support during perioperative periods, while the control group fasted before operation according to the traditional way, and ate after anal exhaust. For comparison purposes, 39 patients were case matched regarding tumor site, tumor stage, demographics, and procedure performed were used. The Ethics Committee of the Yuhuangding Hospital approved the present study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Type of surgery
All patients underwent open operation and the endoscopic technique played an auxiliary role in the operation. Because of its minimal invasiveness and safety, combined with the progress in endoscopic technology over recent years, this surgical treatment is being clinically applied more widely. Enteral nutrition (EN) (i.e. feeding access) was achieved via a nasogastric tube placed intraoperatively.

The nutritional protocol focused on the consumption of perioperative nutritional supplements. Nutrition protocol before surgery: (i) 8 hours before anesthesia: 800 ml carbohydrate beverage (12.5% glucose, OutFAST); (ii) 2 hours before surgery: 200 ml carbohydrate beverage (12.5% glucose, OutFAST). Nutrition protocol after surgery: (i) 6 hours after surgery: glucose in normal saline or warm water by nasogastric feeding tube at 30 ml/h (pump), the target volume was 500 ml; (ii) 1 day after surgery: EN 100 ml*5, Q4 h; (iii) 2 days after surgery: EN 150 ml*5, Q4 h; (iv) 3 days after surgery: EN 200 ml*5, Q4 h; (v) 4–6 days after surgery: EN 250 ml*5, Q4 h; (vi) 7–8 days after surgery: The nasogastric tube could be removed after eating through the mouth without choking and coughing. The diet started with the liquid diet, then changed to semi-liquid food and returned to general diet finally. The oral nutrition supplements (ONS) should be applied as well, which target total energy was 1500 kcal (25 kcal/kg). EN with “Nutren Optimum” (Nestlè Health Science) started at 6 AM on the first postoperative day, which energy density was 1 kcal/ml; 4.07 g protein, 3.85 g fat and 11.704 g carbohydrate/100 ml. All patients complied with postoperative nutrition recommendations.

The preoperative preparation, operative techniques and the total energy of nutritional support of the control group were same as for the ERAS group. The patients in the control group were treated with the conventional postoperative parenteral nutrition (PN) intervention, and then EN after anal exhaust. PN was reduced and EN was increased gradually according to the gastrointestinal tolerance, and the total energy was the same as that in ERAS group.

Data collection
Body mass index (BMI) was calculated and used in the analysis. The blood samples were collected from patients at different time points, including 1 day before surgery, 1 day and 7 days after surgery. With these samples, laboratory data were surveilled to reflect nutritional and immunological state of
patients. These lab data included total protein (TP), albumin (ALB), prealbumin (PA), transferrin (TF), IgG, IgA, IgM, total lymphocyte count (TLC). Besides that, the postoperative exhaust time, the hospitalization expense and the hospitalization time were also needed to be collected to reflect the effectiveness of ERAS and nutrition protocol.

**Statistical analyses**

We performed all statistical analyses using SPSS 22.0. The two-tailed paired t-test was used for comparing the difference in the tested parameters between the two groups of the baseline. The values were reported as mean ± SD in all the tables. Time since baseline randomization was included in the model as a categorical variable, and the group × time interaction was treated as the fixed effect in the model and was the primary effect of interest. Other potential confounders included in the model as fixed effects were age and sex. \( P < .05 \) was considered to be significant.

**Results**

**Baseline information**

The baseline information of all enrolled patients is presented in Table 1. There were no significant differences in the baseline characteristics of the two groups \( (P > .05) \).

**Comparison of nutritional status**

Nutritional laboratory values (TP, ALB, PA and TF) were reassessed on the 1st day before surgery, 1st day after surgery and 7th day after surgery to monitor nutrition stability. As shown in Table 2, compared with the control group, there was no significant difference between these indicators at 1st day before surgery and 1st day after surgery \( (P > .05) \). But at 7th day after surgery, the levels of TP, ALB, PA and TF in the ERAS group were higher than that in the control group \( (P < .05) \).

**Comparison of immune function**

The IgG, IgA, IgM and TLC were assessed on the 1st day before surgery, 1st day after surgery and 7th day after surgery to monitor immune function changes. As shown in Table 3, there was no difference between the two groups at 1st day before surgery and 1st day after surgery \( (P > .05) \). However, compared with the control group, the humoral immune function was significantly increased in the ERAS group at 7th day after surgery \( (P < .05) \).

| Table 1. Baseline data of patients with hypopharyngeal cancer. |
|---------------------------------------------------------------|
| **Eg**(n = 39) | **Cg**(n = 39) | \( P \) |
| Age(year) | 61.3 ± 11.2 | 62.7 ± 12.6 | 0.291 |
| Height(cm) | 167.4 ± 6.4 | 165.5 ± 6.1 | 0.377 |
| Weight(Kg) | 67.3 ± 13.2 | 66.5 ± 12.6 | 0.894 |
| BMI(Kg/cm²) | 23.1 ± 3.2 | 23.0 ± 4.0 | 0.918 |
| TP(mg/L) | 67.2 ± 3.2 | 66.3 ± 3.4 | 0.582 |
| ALB(g/L) | 44.7 ± 3.1 | 42.6 ± 3.4 | 0.437 |
| PA(mg/L) | 280.2 ± 20.4 | 278.3 ± 18.2 | 0.676 |
| TF(mg/L) | 2756 ± 167 | 2712 ± 186 | 0.563 |
| IgA (g/L) | 3.3 ± 0.4 | 3.0 ± 0.2 | 0.443 |
| IgG (g/L) | 9.6 ± 0.5 | 9.3 ± 0.6 | 0.334 |
| IgM (g/L) | 1.8 ± 0.3 | 1.5 ± 0.4 | 0.185 |
| TLC (×10³/L) | 1.23 ± 0.29 | 1.19 ± 0.31 | 0.263 |

Values are presented as mean ± SD. TP: total protein, ALB: albumin, PA: prealbumin, TF: transferrin, TLC: total lymphocyte count; Eg: the ERAS group; Cg: the control group;
Table 2. Comparison of nutritional status between two groups.

|                | Eg(n = 39) | Cg(n = 39) | P-time | P-group | P-time×group interaction |
|----------------|------------|------------|--------|---------|--------------------------|
| TP (g/L)       | 1 day before surgery | 67.2 ± 3.2 | 66.3 ± 3.4 | 0.381 | 0.031 | 0.357 |
|                | 1 day after surgery  | 51.5 ± 4.1 | 50.1 ± 3.8 |        |        |        |
|                | 7 day after surgery  | 66.8 ± 3.6 | 62.3 ± 4.2 |        |        |        |
| ALB (g/L)      | 1 day before surgery | 44.7 ± 3.1 | 42.6 ± 3.4 | 0.198 | 0.026 | 0.286 |
|                | 1 day after surgery  | 33.8 ± 3.3 | 29.7 ± 3.5 |        |        |        |
|                | 7 day after surgery  | 35.6 ± 3.2 | 31.8 ± 4.1 |        |        |        |
| PA (mg/L)      | 1 day before surgery | 280.2 ± 20.4 | 278.3 ± 18.2 | 0.317 | 0.038 | 0.283 |
|                | 1 day after surgery  | 198.3 ± 19.8 | 178.5 ± 20.6 |        |        |        |
|                | 7 day after surgery  | 253.4 ± 24.5 | 208.7 ± 21.1 |        |        |        |
| TF (mg/L)      | 1 day before surgery | 2756 ± 167 | 2712 ± 186 | 0.305 | 0.042 | 0.337 |
|                | 1 day after surgery  | 2151 ± 109 | 1899 ± 124 |        |        |        |
|                | 7 day after surgery  | 2358 ± 186 | 2104 ± 132 |        |        |        |

Values are presented as mean ± SD. TP: total protein, ALB: albumin, PA: prealbumin, TF: transferrin.
Eg: the ERAS group; Cg: the control group; Groups sharing the same superscript (a or b) have no significant difference from each other in the post hoc analysis (p ≥ 0.05)

Table 3. Comparisons of immunological indicators between two groups.

|                | Eg(n = 39) | Cg(n = 39) | P-time | P-group | P-time×group interaction |
|----------------|------------|------------|--------|---------|--------------------------|
| IgA (g/L)      | 1d before surgery | 3.3 ± 0.4 | 3.0 ± 0.2 | 0.421 | 0.045 | 0.338 |
|                | 1d after surgery  | 2.3 ± 0.2 | 2.2 ± 0.3 |        |        |        |
|                | 7d after surgery  | 3.2 ± 0.7 | 2.8 ± 0.4 |        |        |        |
| IgG (g/L)      | 1d before surgery | 9.6 ± 0.5 | 9.3 ± 0.6 | 0.326 | 0.036 | 0.335 |
|                | 1d after surgery  | 7.4 ± 0.9 | 7.2 ± 1.0 |        |        |        |
|                | 7d after surgery  | 9.1 ± 1.2 | 8.1 ± 1.3 |        |        |        |
| IgM (g/L)      | 1d before surgery | 1.8 ± 0.3 | 1.5 ± 0.4 | 0.232 | 0.043 | 0.485 |
|                | 1d after surgery  | 1.1 ± 0.2 | 0.9 ± 0.3 |        |        |        |
|                | 7d after surgery  | 1.6 ± 0.2 | 1.5 ± 0.2 |        |        |        |
| TLC (×10^9/L)  | 1d before surgery | 1.23 ± 0.29 | 1.19 ± 0.31 | 0.246 | 0.039 | 0.239 |
|                | 1d after surgery  | 0.84 ± 0.15 | 0.83 ± 0.22 |        |        |        |
|                | 7d after surgery  | 1.29 ± 0.23 | 1.17 ± 0.13 |        |        |        |

Values are presented as mean ± SD. TLC: total lymphocyte count; Eg: the ERAS group; Cg: the control group; Groups sharing the same superscript (a or b) have no significant difference from each other in the post hoc analysis (p ≥ 0.05)

Table 4. Comparisons of prognosis between two groups.

|                  | Eg (n = 39) | Cg (n = 39) | P     |
|------------------|------------|------------|-------|
| Postoperative exhaustion (days) | 2.14 ± 0.89 | 3.82 ± 0.79 | 0.036 |
| Hospital stay (days) | 9.82 ± 0.79 | 13.41 ± 0.66 | 0.032 |
| Hospitalization expense (10^4 RMB) | 4.11 ± 1.13 | 4.75 ± 1.16 | 0.042 |

Values are presented as mean ± SD. Eg: the ERAS group; Cg: the control group

Comparison of prognosis

As shown in Table 4, compared with the control group, there was significant difference in the hospitalization expense in the ERAS group (P < .05). The postoperative exhaustion time and hospital stay in the ERAS group were all significantly shorter than in the control group (P < .05).

Discussion

The ERAS aims to reduce complications, reduce the stress from related operations, shorten length of stay, and improve patient recovery after surgery. Meanwhile, some issues like regulation of blood glucose, adding nutrients before surgery, regulation of catabolism during perioperative period, should also be considered as parts of ERAS. Nutritional support during perioperative periods should work together with ERAS. The ERAS protocol, which aims to accelerate recovery is showing promise for achieving better perioperative outcomes.
The patients with hypopharyngeal cancer were usually affected by dysphagia, tumor consumption and other factors, leading to them suffering from general malnutrition before treatment. The primary site of tumor involvement and tumor extent contributes to severity of dysphagia and resultant malnutrition. Nutritional deficiencies and significant weight loss predispose to an increased risk of complications and protracted admission. Furthermore, patients with hypopharyngeal cancer have medical morbidities associated with tobacco and alcohol abuse, which further increase the risk of postoperative complications and contribute to malnutrition. Malnutrition increases the rate of postoperative complications such as infection, delayed wound healing, and mortality. Reasonable nutritional support is very important for the recovery of patients with hypopharyngeal cancer. Nutritional supplementation is known to have a positive effect on perioperative outcomes. As the primary goal for this study was to determine feasibility of our protocol and if compliance with the perioperative nutritional protocol could improve patient outcomes.

In this study, all patients received adjuvant treatment with minimally invasive surgery. It is associated with less blood loss, shorter hospital stay, fewer pulmonary infections, better quality of life at 1 year, and equivalent oncological outcomes at 3 years. The minimally invasive approach to hypopharyngeal cancer is in keeping with the principles of ERAS. Many studies have confirmed that the nutritional status of patients with hypopharyngeal cancer is closely related to their prognosis, so it is very important to improve. Our study shows that the levels of TP, ALB, PA and TF in the ERAS group were higher than that in the control group at 7th day after surgery, which suggest that the recovery of nutritional state in the ERAS group was better. Combined with the surgical stress response, postoperative immune dysfunction is very likely, and the risk of postoperative complications is high. Compared with the control group, the humoral immune function of the ERAS group increased significantly at 7th day after surgery. In addition to malnutrition, sarcopenia and frailty from cancer also impact on patient outcomes and recovery. Previous studies have shown that ERAS has been shown to shorten the length of hospital stay, reduce surgical stress response, decrease morbidity, and expedite recovery. Our results show that compared with the control group, the hospitalization expense, the postoperative exhaust time and hospital stay decreased significantly in the ERAS group. The implementation of ERAS protocols has decreased the cost of overall treatment without compromising outcomes. A meta-analysis by Pisarska et al. revealed a significantly shorter hospital stay. Our results are consistent with the above results.

Traditional surgery requires preoperative fasting. The American Society of Anesthesiologists practice guidelines for preoperative fasting recommend allowing clear fluids to patients undergoing elective surgery until 2 h prior to surgery. Preoperative carbohydrate loading is an integral part of the ERAS pathway and has been shown to positively influence several markers of perioperative outcomes. In this study, patients in the ERAS group were given carbohydrates before surgery. Oral glucose given before surgery can help patients deal with surgical trauma stress better, reduce loss of liquid and electrolytes, and prevent postoperative insulin resistance. It is also benefit for the recovery of postoperative gastrointestinal functions comparing with traditional preoperative routine bowel preparation, and shorten length of stay. This is consistent with our results. In our study, the control group focused on postoperative PN, EN gradually started after anal aerofluxus. The ERAS group was given warm glucose saline through feeding tube 6 hours after surgery, and then EN with slow infusion 24 hours after surgery. Some studies have confirmed that intestinal absorption and peristalsis can be restored 6 h after operation and suggested that EN should be actively carried out where the intestinal tract is functional and safe. The role of the food was not providing nutrients for body, but few nutrients could protect intestinal mucosa. Previous studies have shown that EN has significant advantages in reducing various complications of the cancer, because it effectively nourishes the intestinal mucosa, maintains the intestinal barrier, and is more conducive to postoperative recovery. One feature of intestinal mucosal enterocytes is that the nutrients requiring for cell growth, proliferation and repair come from intestinal mucosa-contacted chyme, which cannot be provided by PN. Meanwhile, the absorption of nutrients is mainly performed at small intestine.
Our results demonstrate that application of postoperative EN among hypopharyngeal cancer patients is safe, practicable and effective. It not only ameliorates the nutritional state, promotes the recovery of gastrointestinal functions, but also avoids the drawbacks of PN.

There are many types of nutritional support, of which EN is the first choice and active nutritional support can improve the therapeutic efficacy and reduce the incidence of complications. EN is an important part of ERAS, and influences the complete implementation of the ERAS process. However, to date, there is no uniform standard for the timing and mode of EN for patients with hypopharyngeal cancer. The purpose of this project was to design and implement the nutritional protocol of the ERAS to demonstrate the feasibility of our protocol. We demonstrate our process of perioperative nutrition management for our patients with hypopharyngeal cancer, as well as our standardized ERAS nutrition protocol. Our nutrition protocol is safety and efficacy in perioperative nutritional support for patients with hypopharyngeal cancer. With the help of ERAS, nutritional and immunological conditions of patients will be ameliorated effectively. Our ERAS nutrition protocol has evolved from our experiences. Nutritional support during perioperative periods is one of the most important measures in the ERAS program, along with the application of nutritional support among hypopharyngeal cancer patients during perioperative period, more and more patients will accept it and benefit from it, like changing survival quality of hypopharyngeal cancer patients, extending survival time, laying a good foundation for further comprehensive therapy.

The limitation of the present trial was that we did not make follow-up after discharge, such as the quality of life, 5-year survival rate and nutritional status. In addition, we did not pay attention to the postoperative weight changes of patients and did not compare the postoperative BMI. Third, the sample size has a limited statistic ability to detect significant difference in other indicators, thus large-scale studies are required to confirm our findings. Fourth, this study was a single-center study, and, therefore, may not be generalizable to the overall hypopharyngeal cancer patients.

**Conclusion**

The nutritional support plays a very important role in ERAS, which is significant for postoperative recovery. Our nutritional protocol is effective and safe in ERAS of patients with hypopharyngeal cancer.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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