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Original Article

The influence of hypertonic sodium chloride hydroxyethyl starch 40 on patient recovery after gastrointestinal carcinoma radical resection

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Abstract: Objective: This randomized controlled trial aim to evaluate the impact of hypertonic sodium chloride hydroxyethyl starch 40 (HSH 40) on postoperative recovery time after undergoing the gastrointestinal carcinoma radical resection procedure. Methods: A total of 60 patients with gastrointestinal carcinoma in our hospital from January 2017 to January 2018 were divided randomly into two groups, each containing 30 cases. The control group was treated with conventional treatment, and the observation group was treated with HSH 40. The length of hospital stay and the time of gastrointestinal motility recovery was observed. The volumes of abdominal drainage and urine output in two groups were analyzed at 24, 48, and 72 hours after operation. The levels of plasma inflammatory cytokines (complement C3a, IL-6 and IL-8) were compared between two groups at 24, 48, and 72 hours after radical surgery. Results: HSH 40 significantly shortened the length of hospital stay and the time of gastrointestinal motility ($P<0.05$). The plasma levels of complement C3a, IL-6 and IL-8 were reduced significantly by HSH 40 injection at 24 and 48 hours after operation ($P<0.05$). Higher volumes of abdominal drainage and urine in the observation group were recorded at postoperative time of 24 and 48 hours ($P<0.05$), while it had no significant difference 72 hours ($P>0.05$) beyond postoperative. The postoperative urine volume peak was earlier in the observation group than the control group ($P<0.05$). Conclusions: HSH 40 injection was able to shorten the length of hospital stay and improved gastrointestinal motility. It is plausible that HSH 40 injections enhance recovery after the gastrointestinal carcinoma radical resection through the lowering of plasma inflammatory cytokines and improving the third-space sequestration process.

Keywords: HSH 40, gastrointestinal carcinoma radical resection, recovery

Introduction

Gastrointestinal carcinoma radical resection is an important way of clinical treatment of gastrointestinal cancer, and this surgical approach in patients produces disorders in immune and hemodynamic responses, which can delay postoperative recovery [1, 2]. Hypertonic sodium chloride hydroxyethyl starch 40 (HSH 40) is increasingly recognized as an important liquid in clinical practices recently, because it can suppress plasma inflammatory cytokines release, maintaining effective circulating blood volume, and reduce the third-space sequestration [3]. However, it is unclear whether HSH 40 can improve the recovery process after surgery. Thus, the purpose of this randomized controlled trial was to identify the effect of HSH 40 injection on surgical recovery when patients were undergoing gastrointestinal carcinoma radical resection, and hopefully to elucidate the underlying mechanisms.

Patients and methods

Subjects

A total of 60 patients admitted with gastrointestinal carcinoma from January 2017 to January 2018 in our hospital for radical resection were divided into two groups. The observation group of patients was selected according to the random number table method, and there were 30 patients in each group. This study was conducted in accordance with the Declaration of Helsinki and with the approval from the Ethics

Committee of the People's Hospital of Guangxi Zhuang Autonomous Region. All participants gave their informed consent to participate in this biomedical research activity. Inclusion criteria: (a) American society of anesthesiologists (ASA) physical status of the patients was I to III; (b) Ages were between 16 and 80 years old; (c) Patients were undergoing treatment for gastric cancer, colon cancer or rectum cancer; (d) TNM stage was I to III. Exclusion criteria: (a) concomitant medical disease; (b) reject an operation; (c) accept the preoperative neoadjuvant therapy; (d) a need to perform diverting stoma; (e) emergency patients; (f) surgery-related complications

Treatment methods

The patients in two groups accepted the surgical radical resection procedures, general anesthesia and received one drainage tube. Patients with rectum cancer were given low anterior resection; patients with gastric cancer were given D2 radical gastrectomy with billroth II gastrojejunostomy; patients with colon cancer were given D3 radical colonic cancer surgery. The two groups were given similar conventional treatment, such as antibiotics, nutritional support and any other suitable treatment after the operation. The observation group was given the HSH 40 by using intravenous medication and infusion in addition to the basic treatment; the whole process was completed within 15 minutes; the applied dosage was 2.0 mL/kg/day of drugs at 24, 48, and 72 hours after surgery. The control group received an equal volume of saline solution at the same time.

Outcome measures

The primary outcome measure was length of hospital stay and the time of gastrointestinal motility recovery which was assessed by the time of first bowel sounds, first flatus, and tolerating solid food. Secondary outcome measure was volume of abdominal drainage and urine output at 24, 48, and 72 hours after the operation. Third outcome measures was levels of plasma inflammatory cytokines (C3a, IL-6 and IL-8) at 24, 48, and 72 hours after the operation. General assessments involved demographic characteristics (age, BMI, gender, ASA, nicotine abuse, type of cancer, TNM stage and type of operation) and intraoperative data (duration of surgery, blood loss, fluid resuscitation, and intraoperative urine output).

Data collection

The length of hospital stay was decided by the time when patients returning to a painless status with oral analgesics, absence of increased infectious parameters, wound healing disturbances, light diet without nausea and vomiting, self-care ability, and bowel movements. To determine the exact time towards gastrointestinal motility recovery, bowel sounds were auscultated and the patients were asked (twice a day) about their first flatus and whether defecation had occurred.

Blood samples for measuring plasma cytokine were taken 2 hours after receiving an injection of HSH 40 postoperatively at 24, 48, and 72 hours. Quantitative measurements of plasma cytokine levels were made using commercial enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. C3a (Quidel, USA). IL-6, IL-8 (Shibayagi, Gunma, Japan), Sensitivities of the assays used were 0.7, 4.4, 3.9, 0.5, 0.3, 4.0 pg/ml and 1.0 ng/ml, respectively. Intra-assay and inter-assay coefficients of variation were all less than 10% in each measurement. Cross reactivity with other factors was negligible. All samples and standards were run in duplicate.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, United States). Measurement data are expressed as mean ± Sd. Baseline values were compared using Student t test, Wilcoxon test, and Fisher exact test. The effect of treatment on gastrointestinal motility, piritramide consumption, and length of hospital stay was analyzed by Student t test or Mann-Whitney U test, depending on distributional properties. Differences in cytokine plasma levels were assessed using repeated-measures analysis of variance and corrected with a post hoc Bonferroni test. A value of $P<0.05$ was considered as statistically significant difference.

Results

Demographic characteristics and intraoperative data

A total of 71 patients undergoing gastrointestinal carcinoma met our research criteria. Of those, 9 patients refused to operation. Thus,

Table 1. Demographic data

	Observation group (n=30)	Control group (n=30)	*P* value
Age (yr)	60.95±10.95	60.64±13.28	0.725
BMI	27.13±3.21	26.73±7.33	0.821
Gender (M/F) (n)	14/16	17/19	0.547
ASA score (I/II/III) (n)	3/20/7	5/17/8	0.353
Nicotine abuse (Y/N) (n)	7/23	6/24	0.571
Gastric cancer/Colon cancer/Rectum cancer (n)	9/11/10	7/12/11	0.734
TNM stage (I/II/III) (n)	6/10/14	5/10/15	0.684
Operation method (L/O) (n)	14/16	16/14	0.587

Data are mean ± SD, BMI: Body Mass Index, Y/N, yes or no, TNM: Tumor, Node, Metastasis, L/O: Laparoscopic/Open.

Table 2. Intraoperative data

	Observation group	Control group	*P* value
Duration of surgery (min)	136.14±40.98	122.05±20.81	0.055
Blood loss (ml)	169.09±96.11	177.05±95.90	0.599
Fluid resuscitation (ml)	3113±107.14	2917±176.18	0.374
Intraoperative urine output (ml)	883.77±640.34	725.01±326.64	0.306

Data are mean ± SD.

Table 3. Data of length of hospital stay and gastrointestinal motility

	Observation group	Control group	*P* value
Length of hospital stay (d)	6.13±1.33	8.81±1.55	0.032
Return of gastrointestinal motility (h)	49.16±8.33	69.35±10.18	0.029

Data are mean ± SD, d: day, h: hour after operation.

62 patients were randomized and assigned equally to both groups. Because 2 patients dropped out because of preoperative unrecognized chronic drug abuse (analgesics). Altogether, 60 patients (30 in the observation group and 30 in the control group) completed the study and were analyzed. Among the 60 subjects, there were 29 females and 31 males aged 50-71 years. All the relevant demographic and intraoperative data, such as age, BMI, etc., showed no significant differences between the two groups (P>0.05) (see **Tables 1** and **2**). Therefore, the two groups were able to compare directly.

HSH 40 could shorten length of hospital stay and accelerat gastrointestinal motility

Analysis of the primary endpoint showed a significant difference (P<0.05) in length of hospital stay. Patients treated with HSH 40 were discharged home about 2 days earlier than their control counterparts (see **Table 3**). Additionally, return of bowel function was significantly accelerated in patients receiving HSH 40 injection. Bowel sounds and first flatus occurred approximately 20 hours earlier compared with control and time until first defecation was significantly decreased in patients after injection of HSH 40. The time until to tolerating solid food was also earlier in observation group than the control group (see **Table 3**).

HSH 40 could decrease the volume of abdominal drainage and increase urine output after operation

The total volume of abdominal drainage and urine output is shown in **Table 4**. Observation group showed a significant decrease in the abdominal drainage especially at 24 and 48 hours after operation (P<0.05), whereas there was not significant difference at 72 hours (P>0.05). Meanwhile, the urine output was significantly increase in observation group at 24 and 48 hours after the operation (P<0.05), whereas there was no significant difference at 72 hours (P>0.05). The time of postoperative

Table 4. Volume of abdominal drainage and urine at different times after surgery

	Time	Observation group	Control group	*P* value
Volume of abdominal drainage (ml)	24 h	38.63±10.27	53.24±11.25	0.014
	48 h	20.04±6.25	35.47±7.19	0.033
	72 h	15.51±5.08	23.51±8.94.	0.759
Volume of urine (ml)	24 h	2319.09±446.93	1836.36±663.76	0.007
	48 h	2961.36±732.59	2064.77±669.8	0.003
	72 h	2772.18±589.59	2795.45±627.76	0.218

Data are mean ± SD, h: hour after operation.

Table 5. Data of plasma inflammatory cytokines at different times after operation

	Time	Observation group	Control group	*P* value
C3a (pg/mL)	24 h	152±13	202±16	0.023
	48 h	146±24	297±18	0.014
	72 h	114±19	148±21	0.067
IL-6 (pg/mL)	24 h	63±12	88±11	0.043
	48 h	52±14	152±27	0.003
	72 h	44±17	62±13	0.082
IL-8 (pg/mL)	24 h	38±6	49±3	0.037
	48 h	27±8	55±4	0.002
	72 h	24±3	31±8	0.158

Data are mean ± SD, h: hour after operation.

urine volume peak in observation group also showed earlier than control group.

HSH 40 could decrease the production of plasma inflammatory cytokines at different times after operation

HSH 40 injection could significantly change the patient plasma complement C3a, IL-6, and IL-8 levels relative to those of the control group after gastrointestinal carcinoma radical resection. As shown in **Table 5**, the levels of plasma complement C3a, IL-6, and IL-8 in observation group was lower than control group ($P<0.05$). However, there was not significant difference between two groups at postoperative 72 hours ($P>0.05$).

Discussion

Although the risk of gastrointestinal carcinoma has declined for the past few years, it is still the most common malignant neoplasm around the world [4]. Radical resection is currently the primary therapeutic option [2]. Enhancing recovery after surgery is a primary consideration for the gastrointestinal surgeons, because it will significantly affect the prognosis of patients. The use of hypertonic sodium chloride hydroxyethyl starch 40 (HSH 40) injections has increased in recent years [5]. A large number of studies revealed that HSH 40 is a hypertonic colloidal volume expander that sustain effective blood circulation, reducing tissue edema and decreasing the release of inflammatory mediator [6-8]. Therefore, this randomized controlled trial was conducted to assess the influence of HSH 40 on patient recovery after undergoing a gastrointestinal carcinoma radical resection.

For the first time, HSH 40 injection was demonstrated to significantly shorten the length of hospital stay, and accelerate gastrointestinal motility. In addition, HSH 40 injection enhanced patient recovery after undergoing the gastrointestinal carcinoma radical resection, although the plausible mechanism remains elusive. Plasma inflammatory cytokines have important recovery roles after surgery and in this case complement C3a, IL-6, and IL-8 were the most important inflammatory cytokines for tissue repair [9]. Yu and his colleagues showed that after the injection of HSH 40, plasma anti-inflammatory mediator level was increased, and inflammatory mediator was reduced in patients with lung injuries [10]. Consistent with previous studies, this research also found that HSH 40 injection could decrease plasma complement C3a, IL-6, and IL-8 at 24 and 48 hours after the operation. This indicated that HSH 40 can suppress plasma inflammatory cytokines release in the early stage of post-operation, alleviating tissue injury, and promoting patient rehabilitation. Secondly, the concept of third-spacing was not new, typically implying that a space which has no effect or useful activity, exists in lung, peritoneum and the bowel wall [11, 12]. The third-space sequestration often

referred to burns, massive ascites, crush injury, and operational section [13]. Some medical colleagues revealed that the long operations and especially those involving extensive incision would cause intravascular fluid moving into the abdominal cavity or interstitial fluid of the peritoneum and the bowel wall, and subsequently causing third-space sequestration [13-15]. The common clinical features of third-space sequestration include lower urine output and increase in volume of abdominal drainage after surgery [16]. This pathology phenomenon will impede the recovery after surgery. Here, the volume of abdominal drainage was reduced, and urine output was increased when the patients were injected with HSH 40 at 24 and 48 hours after the operation. The time of postoperative urine volume peak was also earlier. The data further indicate that HSH 40 injection alleviated the problem of third-space sequestration, which led to enhanced recovery after surgery. The possibility of tissue swelling occurring exists and especially when the third-space is full of fluid, and this may be found in any of the dependent parts, such as lung or the intestinal wall [17, 18]. In practice, it is difficult to assess any patient's third-space accurately [19] and further research is needed.

In summary, for patients undergoing gastrointestinal carcinoma, injection of HSH 40 can enhance the recovery process after operation by suppressing the plasma inflammatory cytokines release and alleviating the third-space sequestration. The experiment may provide an inexpensive and convenient approach to enhance patient recovery after undergoing gastrointestinal carcinoma radical resection.

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Disclosure of conflict of interest

None.

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