Journal of Interventional Medicine 4 (2021) 203–207

Contents lists available at ScienceDirect

Journal of Interventional Medicine

journal homepage: www.keaipublishing.com/cn/journals/journal-of-interventional-medicine/

Safety study of Folfox-HAIC in relieving bed restriction

Xiaoyun Zhao, Xingwei Sun, Jian Jing, Huimin Zhou, Yong Jin *

The Second Affiliated Hospital of Soochow University, 215000, Suzhou, China

ARTICLE INFO

Keywords:
Bed rest lifting
Malignant liver tumor
Hepatic arterial infusion chemotherapy

ABSTRACT

Objective: To investigate the safety of relieving bed restriction in hepatic arterial infusion chemotherapy (HAIC) and its effects on patient comfort.

Methods: A prospective study was conducted. Patients with malignant liver tumors, who met the enrollment criteria, were randomly divided into experimental and control groups. During HAIC treatment, the patients in the experimental group, who were not confined to bed and could get out of bed, used electronic injection pumps to infuse chemotherapy drugs. The patients in the control group, who were strictly confined to bed and prohibited from getting out of bed, used infusion pumps to infuse chemotherapy drugs. The complications of the two groups were observed. The Christenson standard improved method was used to evaluate the bleeding and hematoma of limbs on the operation side. The Kolcaba General Comfort Questionnaire (GCQ) and Barthel Index (BI) were used to evaluate the two groups.

Results: Ninety patients with malignant liver tumors were enrolled, including 53 with primary liver cancer and 37 with colorectal liver metastasis. There were 70 males and 20 females, aged 41–81 years old, with an average age of 61.6 ± 9.248 years old. There were 60 patients in the experimental group and 30 patients in the control group. All patients underwent HAIC. The study showed that, during the treatment period, there were 3 cases of postoperative puncture point hematoma formation in the two groups, including 2 cases in the experimental group (2/60, 3.3%) and 1 case in the control group (1/30, 3.3%). The difference was not statistically significant ($p > 0.05$). There were 5 cases of postoperative puncture point bleeding, including 4 cases in the experimental group (4/60, 6.7%) and 1 case in the control group (1/30, 3.3%), and the difference was not statistically significant ($p > 0.05$). A total of 23 cases, with 6 cases in the experimental group (6/60, 10%) and 17 cases in the control group (17/30, 56.7%), complained of back pain after the operation, and the difference was statistically significant ($p < 0.05$). Twenty-one cases complained of poor defecation after the operation, including 10 cases in the experimental group (10/60, 16.7%) and 11 cases in the control group (11/30, 36.7%). The difference was statistically significant ($p < 0.05$). During the period of infusion chemotherapy, the two groups of patients had there was a significant difference between the two groups in terms of comfort status (GCQ) (88.78 ± 6.705, 78.47 ± 9.519, $p < 0.001$) and self-care ability (BI) (74.25 ± 9.152, 66.83 ± 6.628, $p < 0.001$).

Conclusion: During HAIC treatment, getting out of bed is safe and reliable and can increase the patients' comfort and self-care ability. Hence, it merits clinical application.

Malignant liver tumors mainly include primary liver cancer, intrahepatic cholangiocarcinoma and liver metastatic cancer. Primary liver cancer is a malignant tumor that originates from hepatocytes. Once diagnosed, most patients are at an advanced stage and have lost the opportunity for radical treatment. The liver is also one of the most common sites for malignant tumor metastasis. Liver metastasis often indicates a poor prognosis.[1-4] Hepatic arterial infusion chemotherapy (HAIC) has been applied to patients with advanced malignant liver tumors and has been suggested to have a good response rate and survival rate.[5] The guidelines for the diagnosis and treatment of primary liver cancer (2019 edition)[3] also noted that, for some patients with malignant liver tumors, if the effect of transarterial chemoembolization is not good, the HAIC treatment method can be used as appropriate. Because of its reproducibility, accuracy, safety, and few complications, it is recommended by the Japanese liver cancer guidelines as the standard treatment for liver cancer accompanied by portal vein tumor thrombus.[6] HAIC

Abbreviations: HAIC, Hepatic Arterial Infusion Chemotherapy.

* Corresponding author.
E-mail address: jinyong@suda.edu.cn (Y. Jin).

https://doi.org/10.1016/j.jimed.2021.10.003
Received 13 July 2021; Received in revised form 8 October 2021; Accepted 9 October 2021

Table 1
Comparison of general information between the two groups.

Item	Traditional infusion pump group (n = 30)	Electronic injection pump group (n = 60)	Statistical value	P value
Gender [case, percentage (%)]			0.129[a]	0.720
Male	24 (80)	46 (77)		
Female	6 (20)	14 (23)		
Age (years, $\overline{X} \pm S$)	59.40 ± 9.818	62.72 ± 8.826	1.618[b]	0.109
BMI (kg/m^2, $\overline{X} \pm S$)	23.39 ± 3.356	22.75 ± 2.784	-0.964[b]	0.338
Child-pugh classification [case, percentage (%)]			1.023[a]	0.312
A	24 (80)	42 (70)		
B	6 (20)	18 (30)		
Cancer type classification [case, percentage (%)]			0.367[a]	0.545
primary liver cancer	19 (63)	34 (57)		
colorectal liver metastasis	11 (37)	26 (43)		

[a] is the χ^2 value.
[b] is the t value.

refers to percutaneous catheterization of the femoral artery (or other arteries, such as the radial artery and subclavian artery) and catheterization and arteriography of the celiac trunk and superior mesenteric artery, respectively. According to the condition of the tumor's supplying arteries, the catheter is superselectively inserted into the tumor's main supplying arteries and infused with chemotherapy drugs. Patients stay in bed during the drug infusion period and are restricted from getting out of bed, so they are prone to many discomforts, such as back pain, poor bowel movements, and loss of appetite. In the twentieth century, the concept of comfort medicine was proposed, that is, relieving discomfort and reducing the occurrence of complications by implementing relevant measures to meet the needs of patients for physical and psychological comfort during treatment.[7] Based on the concept of humanistic care, our center optimized and improved the treatment plan for malignant liver tumor patients treated with HAIC from November 2020 to May 2021 and achieved satisfactory results. The summary report is as follows.

1. Materials and methods

1.1. General information

A total of 90 patients with malignant liver tumors who underwent HAIC from November 2020 to May 2021 and met the enrollment criteria were selected: 60 in the experimental group and 30 in the control group. Among them, there were 53 cases of primary liver cancer and 37 cases of colorectal liver metastases; there were 70 males and 20 females, aged 41–81 years old, with an average age of 61.61 ± 9.248 years old. All patients successfully completed HAIC. There was no statistically significant difference between the two groups in terms of age, sex, body mass index (BMI), liver function status (using the Child–Pugh modified grading method), etc. ($p > 0.05$). See Table 1.

The study was approved by the ethics committee of The Second Affiliated Hospital of Soochow University. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient before the study was conducted. Written informed consent was obtained from patients for publication of these case reports and any accompanying images. The enrollment criteria were as follows: (1) patients with liver cancer and liver metastases who cannot undergo surgical resection or are unwilling to undergo surgery; (2) massive liver cancer, with the tumor accounting for less than 70% of the liver; (3) multiple nodular liver cancer, with the number of lesions >3 and the largest tumor >3 cm; (4) patients defined as stages IIb, IIIa and IIIb by the guidelines for diagnosis and treatment of primary liver cancer in China (2019 Edition),[3] with liver function classification Child–Pugh A or B, and an Eastern Cooperative Oncology Group (ECOG) score of 0–2 points; and (5) the main portal vein is not completely blocked, or although the main portal vein is completely blocked, many compensatory collateral vessels have formed in the hepatic portal. The exclusion criteria were as follows: (1) Child–Pugh C liver function; (2) severe reduction in coagulation function that could not be corrected; (3) extensive metastasis of the tumor and patient survival of fewer than 3 months; and (4) cachexia and failure of multiple organs.

1.2. Method

1.2.1. Medication program

Both groups used the FOLFOX-HAIC scheme (oxaliplatin + calcium folinate + 5-fluorouracil), and the total dosage was calculated according

Table 2
Comparison of puncture point bleeding and other symptoms between the two groups.

Item	Traditional infusion pump group (n = 30)	Electronic injection pump group (n = 60)	Statistical value (χ^2 value)	P value
Puncture point hematoma [case, percentage (%)]			<0.001	1.000
No	29 (97)	58 (97)		
Yes	1 (3)	2 (3)		
Bleeding from puncture point [case, percentage (%)]			0.424	0.515
No	29 (97)	56 (93)		
Yes	1 (3)	4 (7)		
Back pain [case, percentage (%)]			22.894	<0.001
No	13 (43)	54 (90)		
Yes	17 (57)	6 (10)		
Poor defecation [case, percentage (%)]			4.472	0.034
No	19 (63)	50 (83)		
Yes	11 (37)	10 (17)		
Difficulty urinating [case, percentage (%)]			2.022	0.155
No	29 (97)	60 (difference 100)		
Yes	1 (3)	0 (0)		
Loss of appetite [case, percentage (%)]			6.923	0.009
No	16 (53)	48 (80)		
Yes	14 (47)	12 (20)		

Table 3
Comparison of comfort and self-care ability between the two groups.

Item	Traditional infusion pump group (n = 30)	Electronic injection pump group (n = 60)	Statistical value (t value)	P value
GCQ (score, $\overline{X} \pm S$)	78.47 ± 9.519	88.78 ± 6.705	5.957	<0.001
BI (score, $\overline{X} \pm S$)	66.83 ± 6.628	74.25 ± 9.152	3.947	<0.001

Table 4
Comparison of the four dimensions of comfort between the two groups.

Four dimensions of GCQ	Traditional infusion pump group (n = 30)	Electronic injection pump group (n = 60)	Statistical value (Z value)	P value
Physiological dimension [Score, M(P_{25},P_{75})]	12.00 (10.00, 13.00)	16.00 (15.00, 17.00)	-4.638	<0.001
Mental dimension [Score, M(P_{25},P_{75})]	27.50 (25.75, 31.00)	33.00 (31.00, 34.00)	-4.863	<0.001
Social dimension [Score, M(P_{25},P_{75})]	16.00 (14.75, 18.00)	17.00 (14.00, 22.00)	-1.288	0.198
Environmental dimension [Score, M(P_{25},P_{75})]	22.00 (20.75, 24.00)	24.00 (20.00, 26.00)	-1.866	0.062

to patient body surface area. Oxaliplatin (85 mg/m^2) was pumped through the arterial duct for 2 h, calcium folinate (400 mg/m^2) was pumped intravenously for 2 h, 5-fluorouracil (2400 mg/m^2) was pumped through the arterial duct for 46 h, and the chemotherapeutic drug was continuously infused into the artery for approximately 48 h.[1,8]

1.2.2. Patients in the experimental group could get out of bed during HAIC treatment

The specific requirements were as follows: return to the room and stay in bed without moving for 4 h, activities in bed after 4 h, and out-of-bed activities after 6 h.[9,10] A portable drug infusion pump was used to connect the femoral artery catheter, and chemotherapy drugs were infused through the duct. Combined with the femoral artery pressure and operating conditions, the alarm value of the output pressure of the infusion pump was set to medium, and the threshold range was 50 ± 20 kPa. For the rest of the care, refer to the HAIC nursing routine.

1.2.3. Patients in the control group stayed in bed and were confined to bed during HAIC treatment

A traditional suspension infusion pump was used to connect the femoral artery catheter, and HAIC was performed through the duct. Combined with the femoral artery pressure and operating conditions, the alarm value of the output pressure of the infusion pump was set to medium, and the threshold range was 50 ± 20 kPa. For the rest of the care, refer to the HAIC nursing routine.

1.2.4. HAIC nursing routine

Vital signs were monitored until the end of the drug delivery. The puncture point was observed for bleeding and hematoma. Venous foot pump treatment was given on both lower limbs to prevent thrombosis. Postoperative urine output was recorded to avoid nephrotoxicity caused by contrast agent. The femoral artery catheter was properly fixed to avoid distortions. Accurate delivery of chemotherapy drugs was ensured, and attention was given to the complications, toxicity side effects of chemotherapy drugs.

1.2.5. Observation indicators

1.2.5.1. The Christenson standard improved method was used to evaluate the bleeding of the limbs on the operation side[11]. ① No bleeding: no bloody exudate was seen on the dressing; ② No obvious bleeding: no palpable hematoma or hematoma diameter was less than 2 cm, i.e., the diameter of bloodstains on gauze was less than 2 cm; ③ Obvious bleeding: the blood volume on the dressing was great, with a diameter of more than 2 cm, the diameter of the hematoma was more than 2 cm, or hemostasis by compression needed to be done again to stop the bleeding.

1.2.5.2. The Kolcaba General Comfort Questionnaire (GCQ) was used to evaluate the postoperative comfort of patients. The GCQ was developed by Kolcaba, an American comfort care expert, as a measurement tool to assess the comfort needs of patients,[12] and Zhu Lixia[13] translated it and tested its reliability and validity. It is suitable for comfort measurement of various groups of people and has reliability and applicability. The GCQ includes four dimensions: physiology, psychology, social culture, and environment. The higher the score is, the higher the comfort.

1.2.5.3. The Barthel Index (BI) was used to assess the self-care ability of patients. The higher the score is, the stronger the self-care ability; the lower the score is, the worse the self-care ability and the heavier the need to be taken care of. BI scores below 40 mean that patients are severely dependent on others, 40–60 points mean moderately dependent, and 60 points or more mean mildly dependent.

1.2.6. Statistical method. SPSS 20.0 software was used for statistical analysis of data. Measurements conforming to a normal distribution are represented by $\overline{X} \pm S$, and measurements conforming to a nonnormal distribution are represented by M (P_{25}, P_{75}). The two independent samples *t*-test was used if the intergroup comparison values conformed to the normal distribution, and the Mann–Whitney U nonparametric test was used if the values did not conform to the normal distribution. The count data were described by the number of cases and percentages. The chi-square test was used for intergroup comparisons and $p < 0.05$ was considered statistically significant.

2. Results

2.1. The occurrence of bleeding and other complications at the femoral artery puncture point for the two groups (see Table 2)

There was no statistically significant difference between the experimental group and the control group in terms of bleeding and hematoma ($p > 0.05$). There were statistically significant differences in postoperative back pain and poor bowel movements ($p < 0.05$).

2.2. The comfort and self-care ability of the two groups during the infusion of chemotherapy drugs (see Table 3 and Table 4)

This study showed that there was a statistically significant difference between the two groups in terms of comfort and self-care ability during the drug delivery period ($p < 0.001$). In the evaluation of the four dimensions of comfort, the difference between the experimental group and

the control group in physical and psychological aspects was statistically significant ($p < 0.05$), and the difference in social and environmental aspects was not statistically significant ($p > 0.05$).

3. Discussion

HAIC can directly deliver chemotherapy drugs to tumors that supply the hepatic artery, maintain a higher exposure of chemotherapy drugs to malignant cells through the first pass effect in the liver, and reduce the risk of systemic adverse events.[14,15] The FOLFOX-HAIC scheme (oxaliplatin + calcium folinate + 5-fluorouracil) is currently the main clinical treatment method. 5-Fluorouracil is mainly metabolized in the liver. Because of its short half-life, high one-time uptake rate (95%), 400-fold increase in tumor exposure and low incidence of systemic toxicity, Oxaliplatin is widely used in HAIC treatment and has shown good results. In clinical trials, patients have obtained a high effective rate.[16]

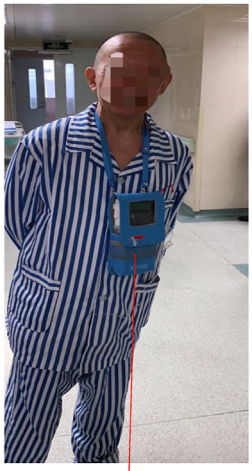
At present, FOLFOX mostly uses the femoral artery approach in clinical practice, and there is currently no uniform requirement for postoperative bedtime. Some scholars have performed research on the effect of bed rest time on vascular complications. Studies have confirmed that getting out of bed early does not increase bleeding, hematoma, pseudoaneurysm, arteriovenous fistula or other vascular complications compared with getting out of bed late. However, the incidence of back pain decreases significantly, and there is no clear conclusion on the optimal bed rest time.[9,10,17,18] Our center optimized the postoperative bedtime of the FOLFOX-HAIC scheme. First, the patients were confined to bed within 48 h after drug delivery, and then the patients could get out of bed during treatment. The specific plan was as follows: after returning to the room, the patients stayed in bed, with limbs on the puncture side immobilized for 4 h; they could turn over after 4 h and get out of bed after 6 h. The study showed that there were 4 cases of postoperative bleeding at the puncture site in patients with this program, and the diameter of the bloodstains on gauze was less than 2 cm; all patients had insignificant bleeding. After dressing change, no secondary bleeding occurred. Compared with the control group, there was no significant difference. Of the 4 patients with local bleeding at the puncture point, 3 were related to repeated punctures during the operation, and 1 was related to excessive activity. There were 2 cases of postoperative hematoma at the puncture point, and the incidence was 3.3% (2/60), consistent with the report by Wu Heping.[19] For two cases of hematoma at the femoral artery puncture point, after hemostasis by compression, the area of the hematoma did not expand and subsided after 48 h. This study suggests that for patients who got out of bed with a tube during the drug infusion, the occurrence of vascular complications such as hemorrhage and hematoma at the femoral artery puncture point did not increase.

At present, HAIC mostly uses traditional infusion pumps to pump chemotherapy drugs at a constant speed. This method can meet the needs of patients for treatment. However, traditional infusion pumps are bulky and heavy and need to be suspended by infusion support to the patient's bedside; the infusion pump power storage time is short and can only realize 48-h continuous pumping by connecting to an external power source. The abovementioned problems limit patient off-bed activity and make patients reject the clinical need for HAIC treatment. To meet the needs of patients to get out of bed and to make patients feel comfortable,[20] our center applies portable electronic drug injection pumps in HAIC treatment. This study shows that the use of a portable drug injection pump ensures the same degree of mobility and freedom as before the operation. Patients are not confined to bed, so they feel comfortable and calm and have confidence in the treatment and their future life. In the GCQ assessment, the scores of the physiological and psychological dimensions of patients were significantly different from those of patients who used traditional infusion pumps. The portable drug injection pump is a medical device for the microinfusion of drugs. It is portable, has a comprehensive alarm function, and satisfies the dependence of tumor chemotherapy on the concentration and contact time of anticancer drugs.[21] This pump is small in size and easy to carry. Patients can take the pump to get out of bed and move freely. Combined with the optimization of postoperative bedtime, it can significantly reduce the patients' back pain, poor defecation, loss of appetite and other discomfort caused by bed rest and greatly improve the comfort of patients.

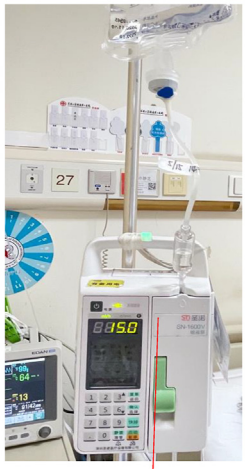
Although this study is a prospective controlled study, the number of samples included is limited. In future work, we will continue to collect relevant data to provide a basis for clinical work. In addition, the follow-up time of this study was relatively short, limited to the period of infusion chemotherapy. There is still a lack of long-term follow-up data to further clarify the safety of getting out of bed early.

4. Conclusion

The optimization of bed rest time after femoral arterial infusion chemotherapy and the application of portable drug injection pumps have lifted the limitation of bed rest for patients who used the FOLFOX-HAIC scheme (oxaliplatin + calcium folinate + 5-fluorouracil). For patients who got out of bed with a tube, the incidence of femoral artery puncture point bleeding, hematoma and tube broking did not increase, and the patients' comfort and acceptance of treatment were greatly improved. Thus, it merits clinical application.



Experimental group: portable electronic drug injection pump, **getting out of bed**



Control group: traditional suspension infusion pump, **confined to bed**

Declaration of competing interest

The authors declare that they have no conflicts of interests to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

References

1. Shi Ming, He Minke, Chen Minshan. Current status and prospects of hepatic artery infusion chemotherapy. *J Surg Concepts Pract.* 2020;25:10–14.
2. Chinese Anti-Cancer Association Interventional Oncology Committee. Chinese medical doctor association interventional physician branch, Chinese society of clinical Oncology (CSCO) radiological interventional therapy expert committee, etc. Expert consensus on clinical practice of multi-model ablation for treatment of liver malignant tumors. *Chin J Interventional Imaging Ther.* 2021;18:23–27.
3. Medical Administration and Hospital Administration of the National Health Commission of the People's Republic of China. Guidelines for diagnosis and treatment of primary liver cancer (2019 edition). *J Clin Hepatol.* 2020;36:277–292.
4. Chinese Medical Association Radiology Branch Intervention Cooperative Group. Expert consensus on the technical practice of transcatheter hepatic arterial

chemoembolization for primary hepatocellular carcinoma. *Chin J Radiol*. 2011;45:908–912.
5. Lee BH, Lee DS, Cho CW, et al. Role and limitation of neoadjuvant hepatic arterial infusion chemotherapy in advanced hepatocelluar carcinoma patients with Child-Pugh class A. *World J Surg Oncol*. 2019;17:143.
6. Kudo M, Matsui O, Izumi N, et al. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the liver cancer study group of Japan. *Liver Canc*. 2014;3:458–468.
7. Ma Yimin, Xiao Ling, Fu Rongchun, et al. Comfort- based nursing care for the management of incision exudate after percutaneous transhepatic biliary drainage: discussion on its clinical effect. *J Intervent Radiol*. 2017;27:691–694.
8. He M, Li Q, Zou R, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. *JAMA Oncol*. 2019;5:953–960.
9. Wei Mo, Xiang Hua, Yang Xiuchun, et al. Evidence - based study on optimal bed rest time after femoral artery puncture and interventional procedures. *J Intervent Radiol*. 2019;28:85–88.
10. Tang Ying, Yan Xueqin, Zhang Zhigang, et al. The time of getting out of bed after interventional therapy of hepatocellular carcinoma: meta analysis. *Chin J Pract Nurs*. 2017;33:791–796.
11. Yang Qing, Zhou Yujie, Nie Bin, et al. Effects of bandage compression and the specific radial hemostasis in patients undergoing transradial coronary intervention. *Chin J Cardiol*. 2010;38:720–723.
12. Kolcaba KY. Holistic comfort: operationalizing the construct as a nurse-sensitive outcome. *ANS Adv Nurs Sci*. 1992;15:1–10.
13. Zhu Lixia, Gao Fengli, Luo Honghui, et al. The study of testing the content validity and the internal consistency of general comfort questionnaire. *Chin J Pract Nurs*. 2006;22:57–59.
14. Ueshima K, Ogasawara S, Ikeda M, et al. Hepatic arterial infusion chemotherapy versus Sorafenib in patients with advanced hepatocellular carcinoma. *Liver Cancer*. 2020;9:583–595.
15. Long GB, Xiao CW, Zhao XY, et al. Effects of hepatic arterial infusion chemotherapy in the treatment of hepatocellular carcinoma: a meta-analysis. *Medicine (Baltim)*. 2020;99, e20745.
16. He Min-Ke, Le Yong, Li Qi-Jiong, et al. Intrahepatic arterial infusion chemotherapy with mFOLFOX versus hepatic arterial chemoembolization for unresectable large hepatocellular carcinoma: a prospective, nonrandomized study. *Cancer*. 2018;5:251–259.
17. Mohammady M, Atoof F, Sari AA, et al. Bed rest duration after sheath removal following percutaneous coronary interventions: a systematic review and meta-analysis. *J Clin Nurs*. 2014;23:1476–1485.
18. Tongsai S, Thamlikitkul V. The safety of early versus late ambulation in the management of patients after percutaneous coronary interventions: a meta-analysis. *Int J Nurs Stud*. 2012;49:1084–1090.
19. Wu Heping, Liu Yamin, Li Yaping, et al. Clinical Analysis of postoperative complications of liver cancer patients treated with interventional surgery. *Pract J Cancer*. 2015;30:1490–1492.
20. Kolcaba KY. A theory of holistic comfort for nursing. *J Adv Nurs*. 1994;19:1178–1184.
21. Chen Saihua. Problems in the use of automatic chemotherapy pumps and nursing countermeasures. *Healthmust-Readmagazine*. 2019;9:138.