Comparative Study on the Effect of Intraperitoneal Hyperthermia Chemotherapy on Cancerous Ascites of Different Temperatures

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Abstract:

Objective: The difference of curative effects of intraperitoneal hyperthermia chemotherapy in the treatment of cancerous ascites with different action temperatures was studied.

Methods: 200 cases of patients with malignant ascites from our hospital that treated with the intraperitoneal hyperthermia chemotherapy during 2004 to 2020 were selected, among which 100 cases in observation group had hyperthermia temperature of 43℃ and 100 cases in control group had hyperthermia temperature of 42℃. The short/long-term curative effects, half-year and one-year survival period, and post-treatment complications of the two groups of patients were compared and analyzed.

Results: The total efficacy of 43℃ intraperitoneal hyperthermia chemotherapy group of patients was 91%, and the total efficacy of control group 42℃ was 62%. The half-year survival of 43℃ observation group was 96%, and one-year survival was 87%; while the half-year survival of control group was 66%, and one-year survival was 51%.

Conclusion: the clinical treatment efficacy of patients treated with 43℃ intraperitoneal hyperthermia chemotherapy was notably better than the patients treated with 42℃ intraperitoneal hyperthermia chemotherapy. There was statistical difference in the adverse reactions between the two groups of patients after treatment.

Key words: Intraperitoneal hyperthermia chemotherapy, cancerous ascites, hyperthermia temperature

Malignant ascites is the abnormal accumulated liquid that caused by intraperitoneal malignant cells, occupying about 10% of all ascites causes. Gastrointestinal tumors are common in the cause of malignant ascites, among which gastric cancer, pancreatic

cancer, and liver cancer are the most common. In female patients, ovarian cancer is the most common, which accounting for 30% to 54 %. The treatment of malignant ascites is a major challenge in clinical treatment [1]. Since 2004, our hospital had used 42 ℃ intraperitoneal hyperthermia chemotherapy to treat cancerous ascites and had achieved satisfactory results. A comparative study had conducted on the efficacy of patients with different hyperthermia temperature.

1. Materials and methods

a) General information

Hospitalized cancerous ascites patient cases with all kinds of malignant tumor caused cancerous ascites in our hospital from 2004 to 2020 were reviewed. 200 cases of a complete course of treatment records and over one year follow-up records had screened out, which included 100 cases in control group treated with 42℃ intraperitoneal hyperthermia chemotherapy and 100 cases in observation group treated with 43℃ intraperitoneal hyperthermia chemotherapy. The basic conditions of the two groups of patients are shown in Table 1 and Table 2. There was no statistical difference after statistical processing.

Hyperthermia temperature	Number of cases (male/female)	Average age (oldest/youngest)	Hypoproteinemia	kps score
42 ℃	100 (57/43)	50 (79/21)	66	≥60
43 ℃	100 (52/48)	49.5 (80/19)	69	≥60

Table 1. Comparison of allocation of patients in 2 groups, P > 0.05 (no statistical difference).

Hyperthermia temperature	**Total number of cases**	**Liver cancer**	**Gastric cancer**	**Pancreatic cancer**	**Ovary cancer**	**Metastatic cancer**

42 ℃	100	14	29	17	26	14
43 ℃	100	13	31	16	25	15

Table 2. Comparison of the distribution of the disease types of the two groups of patients, $P > 0.05$ (no statistical difference).

b) Treatment methods and temperature measurement

i.

Both groups of patients were given DDP 20 mg + 5-Fu250 mg intraperitoneal injection before treatment. After the injection, the patient was instructed to turn over several times to achieve uniform distribution of the drug in the abdominal cavity. Then Jiangsu Nuowan J-9000 microwave hyperthermia machine was applied for heating abdominal treatment. The temperature of intraperitoneal hyperthermia chemotherapy observation group was 43℃ and of control group was 42℃, which both have 60 minutes hyperthermia action time.

ii. Treatment plan design

Applied weekly hyperthermia twice: the first one was hyperthermia combined with chemotherapy infusion and the second one was simple hyperthermia, which both have 60 minutes hyperthermia action time and 72 hours interval between each hyperthermia. 4 weeks were a course of treatment with 4 to 8 weeks of interval between each course of treatment. There were 71 patients applied with over 2 courses of treatment in the patient group that treated with 43℃ intraperitoneal hyperthermia chemotherapy, which account for 71%. And 69 patients applied with over 2 courses of treatment in the patient group of which treated with 42℃ intraperitoneal hyperthermia chemotherapy, and account for 69%.

iii. Temperature measurement method during treatment

The J-9000 type microwave hyperthermia machine was equipped with a temperature measuring line and the heat-sensing tip was inserted into the abdominal

cavity through a puncture needle to measure the temperature.

iv. Efficacy evaluation standards and statistical processing methods

The evaluation criteria of efficacy were in accordance with tumor hyperthermia Chinese Experts consensus that established by 2020 Chinese Society of Clinical Oncology Hyperthermia Special Committee (CSCO-HSC) [2].

A: CR ascites disappeared completely, and maintained >4 weeks

B : PR ascites disappeared ≥50% and <100% , and maintained for >4 weeks.

C : SD ascites disappeared <50% or increased ≤ 25% , and maintained for >4 weeks

D: PD ascites increased >25%.

The statistical method processed with SPSS17.0 statistical software for statistical processing.

2. Results

a) Contrastive analysis of curative effects

Patients' B-Scan reports, medical records, and the one-year follow-up records after 6 weeks and 16 weeks treatment of 32 CR patients, 30 PR patients, 18 SD patients, and 20 PD patients with 42℃ of hyperthermia were statistically analyzed and had a total effective rate of 62%. While the effective rate of 43℃ of hyperthermia group was 91% with 60 CR patients, 31 PR patients, 4 SD patients, 5 PD patients. There were significant differences in treatment, see Table 3:

Hyperthermia temperature	Total number of cases	CR (%)	PR (%)	SD (%)	PD (%)	Total effect rate (%)
42℃	100	32	30	18	18	20
43℃	100	60	31	4	5	91

Table 3. Comparison of curative effects, $P < 0.05$ (with significant statistical difference)

2.2 Comparative analysis of survival

After statistical analysis of group that treated with 42℃ intraperitoneal hyperthermia chemotherapy, 66 patients were found to reach a half-year survival and 51 patients were found to reach one-year survival; while with 43℃ intraperitoneal hyperthermia chemotherapy, 96 patients were found to reach half-year survival and 87 patients were found to reach one-year survival. Which had significant differences, as shown in Table 4.

Hyperthermia temperature	Total number of cases	Half-year survival cases (%)	One-year survival cases (%)
42℃	100	66	51
43℃	100	96	87

Table 4. Comparison of patients' survival rate, $P < 0.05$ (with significant statistical difference)

2.3 Comparative analysis of complications

The complications occurred in the two groups of patients in the course of treatment were classified and statistically processed, and there was no statistical significance, as shown in Table 5.

Hyperthermia temperature	Total number of cases	Skin burn	Induration of subcutaneous fat	Perineum edema	Collapse	Total (%)
42℃	100	7	11	6	0	24
43℃	100	10	13	4	0	27

Table 5. Complications ratio of two groups, $P > 0.05$ (no statistical difference)

3. Conclusion

Through comparative analysis of the short/long-term treatment efficacy, half-year and one- year survival period, and post-treatment complications of the two groups of patients. In the treatment of malignant ascites, group that treated with 43℃ intraperitoneal hyperthermia chemotherapy has the efficacy and survival time better than the patient group that treated with 42℃ intraperitoneal hyperthermia chemotherapy, but there was no significant difference in complications after treatment.

4. Discussion

a)

Malignant ascites is a common complication of abdominal and pelvic malignant tumor, which is caused by cancer cell planting and invasion and involving peritoneum, or caused by the blocked portal venous return system by tumor compression. Refractory malignant ascites is difficult to cure in general, and common survival is about 3 to 6 months. Nearly 70% of patients died within six months [3]. A large amount of ascites will affect the respiratory function, digestive function, and the further multi-organ metastasis of the tumor. Although repeated aspiration of ascites can relieve the patient's symptoms in a short time, the loss of a large amount of protein and microelements may accelerate the death of the patient. Intraperitoneal hyperthermia chemotherapy is an effective treatment method for malignant ascites, with small side effects, and has been widely used in clinical practice. Therefore, by seizing the temperature and time of action to maximizing the efficacy and controlling the patient's tolerance time reasonably is the problem we should pay attention to.

b) The mechanism and principle of intraperitoneal hyperthermia chemotherapy

Intraperitoneal hyperthermia chemotherapy can be effective in treating malignant ascites, which mechanism is as follows: (1) the intraperitoneal filled with perfusate that containing a chemotherapeutic agent increased the probability of contact of medicine and cancer cells in abdomen, particularly the cancer cells that infiltrated in ascites. While a decrease in the drug clearance rate lead by the barrier function of peritoneum, the drug intraperitoneally residence time increased, which significantly

enhanced the action concentration and action time of intraperitoneal chemotherapy. (2) Due to the clearance of the peritoneal barrier, the concentration of chemotherapy drugs in the bloodstream significantly reduced and the patient's tolerance to the side effects of chemotherapy drugs increased, which improved the safety of treatment. (3) 41℃ to 43℃ hyperthermia can inhibit DNA replication, transcription, and repair, thereby directly killing cancer cells [4]. (4) after a certain time of hyperthermia, the temperature of the tumor will be 3 to 7 ℃ higher than surrounding normal tissues in order to cause apoptosis of cancer cells and not to damage the normal tissues [5]. At the same time, the cell membrane permeability and blood flow rate increased, so that chemotherapeutic drugs can quickly enter tumor cells in large quantities, which effectively enhanced the concentration of chemotherapeutic drugs, thereby improving the efficacy of chemotherapeutic drugs [6]. The increase in the temperature of hyperthermia further effectively increased the energy accumulation in the tumor per unit time, and rapidly increased the temperature in the tumor and the temperature in the abdominal cavity, which was beneficial to the overall tumor cell inactivation in the abdominal cavity.

c)

(1) Approved by the relevant experimental studies, 42℃ hyperthermia with 60 minutes reaction time has the cell survival rate $10^{-0.8}$, and 43℃ hyperthermia with 60 minutes reaction time has the cell survival rate of $10^{-1.8}$; the effect of identical hyperthermia action time was proportional to the temperature [5]. (2) Studies have shown that high temperature can promote the combination of alkylating agents and platinum drugs with the DNA of cancer cells, and ultimately lead to the death of cancer cells [7]. The prolonged effective temperature action time objectively extends the effective action time of the drug and cancer cells, and then achieves the purpose of further improving the curative effect. (3) Hyperthermia can also effectively inhibit the expression of drug-resistant genes and enhance the sensitivity of chemotherapy drugs [8]. So, when hyperthermia stops inhibiting, the drug resistance gene expression may terminate. The longer the duration of hyperthermia action, the longer the chemotherapy drugs can effectively affect the duration of

action [9]. (4) Hyperthermia has immune system suppression like reinforcing autoimmunity effect, destroying or deblocking tumor cells secreted blocking factors, and phagocytic cells migration inhibitory factors, etc., so that the body could restore tumor immune response and stimulate immunity enhancement [10]. (5) Studies have shown that hyperthermia can enhance the sensitivity of tumor cells to NK cells and increase the anti-tumor activity of parenchymal cells that stimulate T lymphocytes. Meanwhile hyperthermia produces a large amount of heat shock protein (HSP), and forms compound with a variety of tumor complex antigens that enhance the overall B proliferative activity of cells, which induce an immunogenic effect [11].

In summary, the temperature of intraperitoneal hyperthermia chemotherapy is directly related to curative effect through the research and discussion of short/long-term clinical curative effect, survival time comparison, and related theoretical experimental research. The 43℃ intraperitoneal hyperthermia chemotherapy has a better curative effect than 42℃ intraperitoneal hyperthermia chemotherapy with the same action time. So, 43℃ intraperitoneal hyperthermia chemotherapy with 60 minutes action time for treatment of malignant ascites has certain clinical promotion value and further in-depth research value.

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