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Efficacy and safety of HIFU in combination with TACE in unresectable pediatric HB

A randomized, controlled, single-center clinical trial

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Abstract

Background: Hepatoblastoma (HB) is the most common liver tumor in children, and the main treatment for HB is currently surgery. Studies have shown that transcatheter arterial chemoembolization (TACE) combined with high intensity focused ultrasound (HIFU) has significant efficacy, but there are relatively few studies on TACE combined with HIFU in China.

Objective: To investigate the effect of using HIFU combined with TACE on patients' liver function impairment and immune function in pediatric HB patients and to analyze the effectiveness and safety.

Materials and methods: The clinical data of 110 unresectable pediatric HB patients treated in our hospital from December 2019 to December 2021 were selected as the subjects and divided into 2 groups. The comparison group was treated with TACE, and the combination group was treated with HIFU on the basis of the comparison group. The differences in immune function, survival, treatment side effects and clinical efficacy between the 2 groups were observed.

Results: In the combined group, the 1-year survival rate was 100%, the 3-year survival rate was 84.0%, the 5-year survival rate was 16.0%; while in comparison group, it was 82%, 16%, 0%, respectively. The ratio of $CD4^+/CD8^+$ in the combined group were significantly higher than in the comparison group after treatment ($P < .05$). Granulocytopenia, mucositis, thrombocytopenia, and cardiac and renal toxicity were significantly lower in the combined group than in the comparison group, and the effective rate of the combined group was 98.00% which was significantly higher than that of the control group (76.00%) ($P < .05$).

Conclusion: Comparative study of HB in children treated with HIFU combined with TACE is more effective, effectively improving the immune level of patients, significantly increasing the remission rate, which can improve the tumor necrosis and improve the survival quality of patients, and is a better choice for HB in children.

Abbreviations: AFP = alpha-fetoprotein, CR = complete remission, HB = hepatoblastoma, HIFU = high intensity focused ultrasound, PD = disease progression, PR = partial remission, SD = disease stabilization, TACE = transcatheter arterial chemoembolization.

Keywords: HB in children, HIFU, immune function, survival analysis, TACE

1. Introduction

Hepatoblastoma (HB) is an embryonic solid malignancy and is the most common primary tumor of the liver in children, especially in infants and young children.[1] Surgery is the most definitive treatment for HB, but a significant proportion of children presenting to the clinic are lost to stage I surgical resection.[2] In recent years, studies have pointed out that neoadjuvant chemotherapy for HB can reduce tumor size and improve surgical resection rate, especially transcatheter arterial chemoembolization (TACE) as selective local tissue chemotherapy is a practical and effective treatment modality.[3] However, after embolization, the adhesion between the tumor and the surrounding area will be aggravated, which will increase the difficulty of surgical separation.[4,5] Besides, TACE is only local treatment and has little effect on portal vein tumor thrombus and extrahepatic metastasis. Based on these shortcomings of TACE, researchers at home and abroad began to explore the effect of TACE combined with other treatment methods for HB.

High intensity focused ultrasound (HIFU) is an external low-intensity ultrasound focused on the lesion area in vivo, using the mechanical, thermal and cavitation effects of ultrasound to cause instantaneous coagulative necrosis of tissue.[6] In a variety of tumor treatments, HIFU can greatly improve the surgical resection rate, reduce the side effects of chemotherapy,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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and combine with other means, such as surgery, to achieve improved treatment outcomes.[7] There have been reports of TACE combined with HIFU in the treatment of other hepatocellular carcinoma, but there were few reports on the efficacy and safety for HB, especially in children with HB. Therefore, the purpose of this study was to explore the effects of HIFU combined with TACE on liver function damage and immune function in children with Hb, and to analyze its effectiveness and safety.

2. Material and methods

2.1. Research object

In this study, the clinical data of 110 unresectable children with HB who were treated in our hospital from December 2019 to December 2021 were selected as the research objects. The grouping method was divided into a comparison group and a combined group, and each group dropped out 5 cases due to hospital transfer, COVID-19, loss to follow-up, etc., and finally each group remained 50 cases. The diagnosis was confirmed by imaging methods including clinical manifestations, B-mode ultrasound, CT scan, alpha-fetoprotein (AFP) determination and digital subtraction angiography. Based on the ultrasound and pathological findings, the PRETEXT staging system and the international consensus criteria for classification of pediatric liver tumors were recorded. The parents chose the treatment plan voluntarily and signed the consent form for the treatment. The present study was approved by the Ethical Committee of Xiantao First People's Hospital.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria: Patients with HB on puncture biopsy or postoperative pathology and unable to undergo surgical resection, patients who were diagnosed for the first time and had not received treatment; tumors located in the top of the liver diaphragm and could not be completely exposed under ultrasound; and patients selected were treated with HIFU for the first time.

Exclusion criteria: Patients whose pathology was not clearly diagnosed as HB or with a revised diagnosis of other tumors; patients who had received surgery or chemotherapy before admission; patients who abandoned treatment after diagnosis, patients with incomplete pathological findings and clinical data; patients with severe heart disease, renal disease and respiratory disease, taking B-blockers and opioids before surgery; and Child-Pugh grade C or above, ASA grade V, sufficient amount of pleural effusion (compressed lung tissue does not exceed 1/3) were injected, the lesion was still not fully exposed, and pleural effusion could not be tolerated (SpO_2 continues to be lower than 94% after adjusting respiratory parameters), and those who have pleural effusion extracted or those with incomplete clinical data.

2.3. TACE treatment

After general anesthesia using the Seldinger technique, patients undergoing TACE underwent percutaneous puncture of the femoral artery with the application of a pediatric puncture needle, and after successful placement of a 4F pediatric vascular sheath and injection of heparin, the tumor-donating artery was also clarified. The 2.7F microcatheter was then super-selectively cannulated to the optimal level of the tumor-donating artery, injected with chemotherapeutic drug emulsion, and injected with chemotherapeutic drug emulsion. After the injection was completed, the microcatheter was flushed with 9 g/L saline, and then 300 to 500 μm polyvinyl alcohol particles were injected to embolize the tumor blood supply artery. The chemotherapeutic drug dose was calculated according to the body surface area, using 60 mg/m^2 cisplatin and 30 mg/m^2 pyrazine.

2.4. HIFU treatment

The JC-type focused ultrasound tumor treatment system (JC200D, Haifu Knife, Chongqing), which includes 2 major parts: ultrasound real-time positioning and monitoring equipment and HIFU stereo combination scanning treatment equipment. Under computer control, it can automatically locate the predetermined target area of the tumor, determine the treatment range and 3-dimensional conformal scanning treatment, monitor and analyze the treatment effect in real time, as well as control the treatment dose with feedback. Main treatment parameters: treatment frequency: 0.8 MHz; average diameter of focal field: 1.1 mm; focal field length: 9.8 mm; focal distance: 135 mm; treatment power: 160 to 240 W. Two courses of systemic chemotherapy were performed before HIFU treatment, followed by 3 weeks after TACE, before HIFU ablation. Under intravenous compound anesthesia, the diagnostic ultrasound probe of the JC-type focused ultrasound tumor treatment system was used to display the tumor location on the ultrasound imaging device and adjust the treatment parameters according to the depth and extent of the ablated tumor. The transducer was moved on the degassed water bag, which emits a treatment frequency of 0.8 MHz. The ablation started at 1cm from the periphery of the liver tumor tissue and was repeated in some deeper central areas of the tumor, and the grayscale changes in the ablation area were observed intraoperatively.

2.5. Observation indicators

Tumor responses were classified into 4 categories using the following criteria: complete remission (CR), complete disappearance of all tumors and normal levels of AFP for more than 4 weeks; partial remission (PR), decline of ≥50%, significant reduction in tumor volume and AFP levels, no evidence of new lesions or progression of any lesions; disease stabilization (SD), decline of <50%, tumor volume, no evidence of new lesions; disease progression (PD), >25% increase in tumor size or the appearance of new lesions. Efficacy = CR + PR/CR + PR + SD + PD × 100%. Assessment of treatment side effects: all patients were monitored weekly for blood counts and liver and kidney function, and evaluated by physical examination, blood chemistry analysis (Sysmex XN-9000 automatic blood analyzer) and CT about 1 month after HIFU. Patients after HIFU were followed up by telephone every month, and acute toxic reactions associated with combination therapy were graded using the National Cancer Institute Common Toxicity Criteria Version 3.0 (NCI-CTCAE V3.0) grading. The 2 groups of patients were examined by flow cytometry (CytoFLEX; Beckman Coulter) before and after treatment for peripheral blood T lymphocyte subsets ($CD4^+$, $CD3^+/CD8^+$), the ratio of $CD4^+/CD8^+$ was calculated. $CD4^+$, $CD8^+$, and $CD3^+$ detection kits were purchased from BD company in the United States.

2.6. Statistical analysis

All statistical data in this study were entered into excel software by the first author and the corresponding author respectively, and the statistical processing software was SPSS25.0 for calculation. Shapiro–Wilk test was used to test the normality of the data. When $P > .05$, the data was normal distribution. Repeated measures analysis of variance between groups was used to measure the measurement expressed as mean ± standard deviation (mean ± SD). Count data expressed as a percentage (%) were tested by χ^2. Differences between 2 groups and among multiple groups were analyzed by Student's t test. The statistical significance was $P < .05$.

3. Results

3.1. General data comparison

There was no statistically significant difference between the comparison group and the combined group in terms of general data such as mean age, tumor diameter, methemoglobin, and tumor stage by *t* test and chi-square test ($P > .05$). The data are shown in Table 1.

3.2. Survival comparison

The median survival time in the combined group was 48.5 months, with a 1-year survival rate of 100%, a 3-year survival rate of 84.0%, a 5-year survival rate of 16.0. After treatment in the comparison group, 6 of the patients with follow-up surgery survived, with a median survival time of 21.5 months. Two of the patients who underwent chemotherapy only survived, with a median survival time of 16 months. The comparison group had a median survival time of 18 months, a 1-year survival rate of 82.0%, a 3-year survival rate of 6.0% ($P < .0001$). The results are shown in Figure 1.

3.3. Comparison of immune levels

There was no significant difference in the immune level comparison between the 2 groups before treatment, and the comparison of $CD4^+$, $CD3^+$, and $CD4^+/CD8^+$ after 1 week of treatment was significantly different and higher in the combined group than in the comparison group, with statistical significance ($P < .05$). The results are shown in Figure 2.

3.4. Comparison of clinical efficacy

The effective rate of the combined group was 98.00%, which was significantly higher than that of the control group, 76.00%, and the difference was statistically significant ($P < .05$). The results are shown in Figure 3.

3.5. Comparison of treatment side effects

The clinical efficacy of the 2 groups showed that granulocytopenia, mucositis, thrombocytopenia, and cardiac and renal toxicity were significantly lower in the combined group than in the comparison group, and the difference was statistically significant by test ($P < .05$). The results are shown in Figure 4. Our research shows that the average chemotherapy cycle of children receiving HIFU treatment is reduced. Although the toxicity and side effects are not statistically significant, the patient's acceptance and compliance have significant advantages due to the reduction of children's hospitalization time and times. Two patients were followed up for 1 month and found that chest X-ray examination after ablation showed mild rib deformity, which did not affect thoracic morphology or respiratory muscle movement. Most patients had transient impairment of liver function and fever within 1 or 2 weeks after surgery, and no other serious complications were found. It can be seen that the complication rate of HIFU treatment is low and safe and feasible.

Table 1

Comparison of general information between the 2 groups (n, mean ± SD).

	Comparison group (n = 50)	Combined group (n = 50)	χ^2/t	*P*
Gender (male/female)	27/23	29/21	0.162	.687
Average age (mo)	13.9 ± 2.3	14.1 ± 1.6	0.505	.615
Tumor diameter (mm)	10.14 ± 1.25	9.81 ± 0.64	1.662	.100
AFP (μg/L)	3600.34 ± 110.25	3592.31 ± 150.64	0.316	.753
PRETEXT stage				
II	36	35	0.327	.849
III	8	10		
III	6	5		

AFP = alpha-fetoprotein.

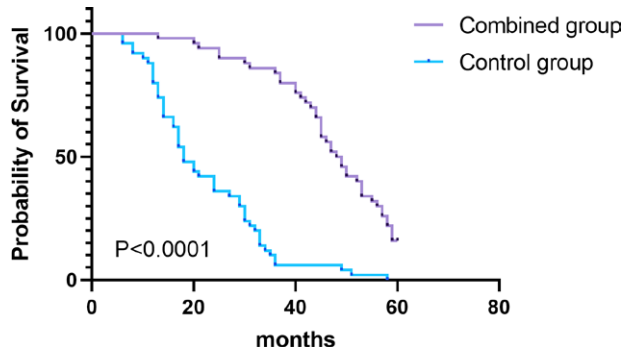

Figure 1. Comparison of survival conditions. The survival of the 2 groups was analyzed by Kaplan–Meier method, and the area under the curve of the combined group was significantly more than that of the control group ($P < .05$).

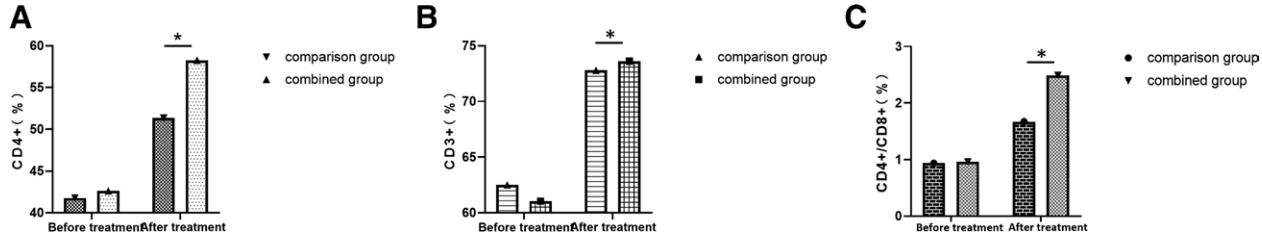

Figure 2. Comparison of immune levels. After the first author and the corresponding author entered the computer Excel system and proofread, the independent sample *t* test was carried out for SPSS25.0 using statistical software. The $CD4^+$ after 1 week of treatment (A), $CD3^+$ (B), and $CD4^+/CD8^+$ (C) were significantly different, and the combined group was higher than the control group, with statistical significance (*$P < .05$).

4. Discussion

HIFU treatment of HB in children utilizes the directionality, tissue penetration, and focus ability of ultrasound, and uses a special focusing device to focus ultrasound from outside the body to a selected treatment area within the body.[8] At its focal point, a high-energy density zone is formed, which instantly generates high temperature and causes irreversible coagulative necrosis, degeneration and apoptosis of the tissue in the treatment area.[9] Currently, it is believed to mainly consist of thermal, cavitation, acoustic-chemical and mechanical effects that destroy the membrane structure of tissue cells, leading to cell disintegration, lysis and necrosis, thus destroying the tissue.[10] Among them, thermal and cavitation effects are the main mechanisms of tissue damage by HIFU, while damage due to excessive cavitation effects is uncontrollable and unpredictable, and is prone to side effects such as bleeding and rupture.[11] HIFU has the following advantages in treatment: noninvasive, conformal treatment, which protects tissues outside the target area from damage.[12] The disposition of TACE combined with HFU in the treatment of HB in children is related to the efficacy, and if HIFU treatment is administered first, it may cause occlusion of the main nutrient vessels of the tumor, which will not facilitate the access of embolic agents and chemotherapeutic drugs to the tumor area through the tumor-bearing vessels and affect the effect of TACE treatment. Therefore, TACE is generally recommended before HIFU treatment.

In this study, HB in children was treated with simple TACE, with a low rate of complete tumor necrosis and unsatisfactory radical efficacy, generally requiring 2 to 6 treatments, and repeated TACE treatment often aggravates cirrhosis and causes complications such as liver failure or even death due to the toxic side effects of chemotherapy drugs.[13] HIFU is a new technique of local hyperthermia treatment of tumors, which is the focus of low-energy ultrasound outside the body on deep tumor lesions in the body, and through the instantaneous high temperature effect and cavitation effect generated by high-energy ultrasound in the focal area, the temperature of the treatment area rises abruptly to 65°C to 100°C, causing local tissue coagulation and necrosis.[14] Childhood HB has a dual blood supply of hepatic artery and portal vein, and HB tissues are predominantly supplied by the hepatic artery, but both have portal vein involved in blood supply.[15] If pediatric HB patients are treated with hepatic artery embolization alone, tumor portal vein blood supply may still lead to tumor residual and recurrence.[16] The iodine oil deposited in the tumor may dissociate with the blood flow of the dual blood supply to the liver and affect the efficacy.[17] The combination of HIFU and TACE not only facilitates ultrasound localization and conformal treatment of the tumor, but also can change the acoustic impedance difference and acoustic absorption coefficient in the tumor area during HIFU treatment. It facilitates the energy deposition at the focal domain and plays a synergistic warming effect to stimulate local high temperature to destroy the tumor target tissues and make the tumor tissues easy to undergo coagulative necrosis.[18] Meanwhile, TACE treatment can shrink the tumor and shorten the HIFU treatment time, which is more favorable for HIFU treatment.[19] Meanwhile, the present results suggest that combination therapy can reduce the number of TACE treatments, thus protecting patients' liver reserve function and effectively improving tumor treatment and prolonging patients' survival.

Except for liver transplantation, hepatectomy is generally considered as the best treatment for HB. However, local ablation is increasingly used to treat HB that cannot be operated for physical or social reasons. Many studies have confirmed that local ablation is the best treatment option. In addition, local ablation combined with TACE is superior to single treatment. In the follow-up of this study, it was also found that the survival rate of the combined group was higher than that of the control group, and there were fewer side effects and higher safety in the follow-up.

The toxic side effects that can occur during systemic chemotherapy with these TACE commonly used in this study are nausea, vomiting, electrolyte disturbances, liver and kidney function, hearing impairment, cardiotoxicity, bone marrow suppression, infection, alopecia, and skin pigmentation. In children with HB, the prognosis varies depending on the treatment modality, and the emergence of HIFU, which reduces the chemotherapy cycles and thus can reduce the toxic side effects associated with chemotherapy.[20] Our study showed a reduction in the mean chemotherapy cycle in children treated with HIFU, and although the toxic side effects were not statistically significant, there was a significant advantage in patient acceptance and compliance due to the reduced length and number of hospital stays in children. Possible complications after HIFU include skin burns and secondary infections, bleeding from ruptured liver tumors, the biliary tract injury, head of the pancreas, roof of the diaphragm, heart and lungs, intercostal nerves, ribs, and spinal cord. perforation of the gallbladder and gastrointestinal tract, etc.[21] Two patients in our study had lung tissue covering the subdiaphragmatic liver tumor, and in order to avoid lung injury, pleural cavity puncture was performed before ablation to create artificial pleural fluid, which did not cause lung injury. Two cases of post-ablation chest radiography suggested mild rib deformity, which did not affect thoracic morphology or respiratory muscle movement, and most patients had transient impairment of liver function and fever after surgery, and no other serious complications were found. It can be seen that the complication rate of HIFU treatment is low and safe and feasible.

The difference in $CD4^+$, $CD3^+$, $CD4^+/CD8^+$ after treatment in this study was significant and higher in the combined group than in the comparison group, indicating that HB in children is better treated with HIFU combined with TACE, which effectively improves the immune level of patients. T lymphocytes are divided into subpopulations according to their phenotype and

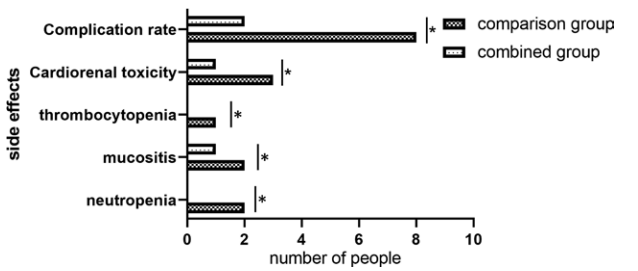

Figure 3. Clinical efficacy of 2 groups of patients. Clinical efficacy statistics are given as integers. After input into the computer Excel system for proofreading, independent sample *t* test was performed. The effective rate of the combined group, 98.00%, was significantly higher than that of the control group, 76.00% (*$P < .05$).

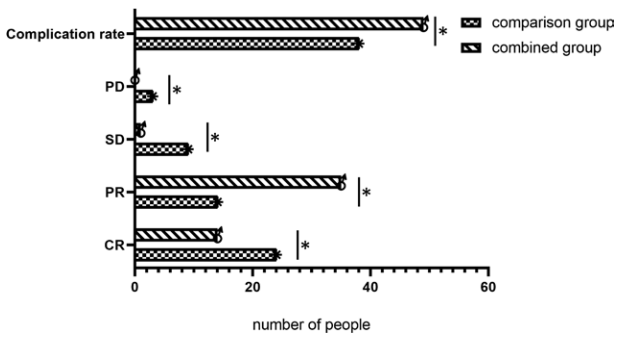

Figure 4. Comparison of side effects of treatment in 2 groups of patients. Treatment side effects statistics are given in whole numbers. After input into the computer Excel system for proofreading, an independent sample *t* test was performed. The neutropenia, mucositis, thrombocytopenia and cardio-renal toxicity of the combined group were significantly lower than those of the control group (*$P < .05$).

function, namely, killer T cells, suppressor T cells, delayed-onset metaplastic T cells, and inducible helper T cells.[22] The first 2 are $CD8^+$ subpopulations and the latter 2 are $CD4^+$ subpopulations, which induce and regulate each other, forming a T cell regulatory network that exerts its killing effect on target cells and its positive and negative feedback regulation of immune response processes, such as anti-infection and anti-tumor immunity.[23] HB in children leads to dysfunctional T-cell subsets in the body, a decrease in the $CD4^+/CD8^+$ cell ratio, and an imbalance in the immune regulatory network composed of various immune cells and cytokines, forming a pathological vicious circle that leads to the development and progression of liver disease.[24] It has been shown that HBV can invade the peripheral blood lymphocytes in patients and affect the normal functioning of cellular functions, and the lack of IL-2 in the body directly affects the normal functioning of killer T cells.[25] The low antiviral capacity of the body makes HBV infect the body for a long time, on the other hand, it aggravates the autoimmune response in the body and makes the disease worse.[26] In contrast, HIFU has the effect of regulating immunity and inhibiting viral replication, and has better efficacy in treating HB in children, and it is easy to take and has few adverse effects, which provides a new way and method for the treatment of chronic hepatitis.[27] Although this study is novel but also has shortcomings, HIFU has been widely recognized for the treatment of HB in children, but as an emerging treatment modality, there are still many basic theories, such as ultrasound dosimetry, thermal dosimetry, noninvasive temperature monitoring, and moderate modulation of cavitation effects, that need to be studied in depth. Meanwhile, the role and status of HIFU in the treatment of HB in children also needs to be confirmed by more data from large sample, multicenter prospective clinical randomized controlled studies. It is reasonable to believe that with the continuous improvement of HIFU research, the improvement of HIFU equipment and technology and the rapid progress of clinical studies, HIFU will definitely play a more important role in the treatment of HB in children.

5. Conclusion

In conclusion, the comparative study of HB in children treated with HIFU combined with TACE was more effective, but the presence of factors such as a small case base and poor patient compliance in this retrospective study requires further clinical prospective trials to confirm. This combined treatment modality showed a greatly increased chance of surgical resectability and significantly higher survival and remission rates; it is an effective, safe and feasible noninvasive treatment method and a better choice for unresectable patients.

Author contributions

Conceptualization: Han Jiang.
Data curation: Xiaobing He.
Writing – original draft: Xinliang Tang.
Writing – review & editing: Han Jiang.

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