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Diagnosis and treatment of coagulopathy following percutaneous cryoablation of liver tumors: Experience in 372 patients ☆

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ABSTRACT

Coagulopathy after liver cryoablation was first reported many years ago; the cause is local platelet trapping and destruction within the margin of the cryolesion. However, the prognosis and therapeutic effects of coagulopathy remain unclear. This study retrospectively reviewed clinical data from 372 patients (525 sessions) who underwent liver cryoablation in our hospital during the past 4.5 years. Small tumors (major diameter < 6 cm) were treated with a single complete ablation; massive tumors (major diameter 6–10 cm or >10 cm) were divided into two or three parts that were dealt with in turn. Platelet counts decreased to an average of $(46.12 \pm 68.13) \times 10^9$/L after each session of cryoablation. The decline was most evident in patients with high pretreatment platelet counts, while those with low pretreatment counts had the highest risk of coagulopathy. Change in platelet count was not correlated with the diameter of the tumor. Slight coagulopathy (platelet count $(70–100) \times 10^9$/L) can resolve without treatment within 1 week and administration of recombinant human interleukin-11 can assist recovery from severe coagulopathy (platelet count $< 70 \times 10^9$/L).

Introduction

During the last decade, cryosurgery has become an interesting alternative in the treatment of nonresectable hepatic tumors, with promising results in terms of patient survival [21,23]. The incidence of complications and side effects of cryoablation may be as high as 40%, however, and they include fracture of the liver parenchyma, cryoshock, biliary fistula, hemorrhage, cold-induced lesions in nearby structures, thrombocytopenia and coagulopathy [19,24]. Theoretically, complications and side effects, with the exception of thrombocytopenia and coagulopathy, can be avoided or reduced by skilled operators and strict patient selection [5,9,22].

Systemic thrombocytopenia is generally defined as a platelet count $\leqslant 150 \times 10^9$/L or a greater than 30–50% decrease [1,26]. Multiple studies have shown that the development of thrombocytopenia is associated with increased length of hospital stay and mortality [11,16,17]. Thrombocytopenia is common in patients after chemotherapy or cryotherapy, which may cause bone marrow suppression [7] or local platelet trapping and destruction within the margin of the cryolesion [10,13,20]. In general, thrombocytopenia is considered to be related to the volume of tissue frozen [5,20], the number of freeze–thaw cycles and the number of cryoprobes used [22]. Systemic thrombocytopenia may be complicated by the development of coagulopathy (platelet count $\leqslant 100 \times 10^9$/L) [10].

In this retrospective study, 372 patients were observed for coagulopathy after cryoablation of liver tumor and the relationship between tumor diameter, ablation protocol, pretreatment platelet count and thrombocytopenia were analyzed. Therapeutic effects for slight and severe coagulopathy after cryosurgeries were analyzed afterwards.

Materials and methods

Ethics

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

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Patient selection

Between January, 2008 and July, 2012, 372 patients with liver tumor met our inclusion criteria and were enrolled in the study. All patients had a single tumor in the liver and were unwilling to undergo surgery, systemic chemotherapy or transcatheter arterial chemoembolization. Ideal patients for comprehensive cryoablation are those with: only one significant tumor in the liver; Karnofsky performance status score $\geqslant 70$; platelet count $\geqslant 100 \times 10^9$/L; white blood cell count $\geqslant 3 \times 10^9$/L; neutrophil count $\geqslant 2 \times 10^9$/L; hemoglobin $\geqslant 90$ g/L; prothrombin time international normalized ratio $\geqslant 1.5$; hepatic tumor not obviously invading the gallbladder, diaphragm or large vessels; absence of level 3 hypertension, severe coronary disease, myelosuppression, respiratory disease and acute or chronic infection; and adequate hepatic function (bilirubin <30 μM, aminotransferase <60 U/L and Child–Pugh score A or B) and renal function (serum creatinine <130 μM, serum urea <10 mM).

In all patients, the diagnosis of hepatocellular carcinoma (HCC, 241 lesions: 105 advanced and 136 metastatic) or liver metastasis (284 lesions: 64, 61, 87, 51 and 21 with breast, lung, colon, ovarian or pancreatic cancer, respectively) was confirmed by liver pathology; some cases were diagnosed by classical imaging techniques in advance, including computed tomography, magnetic resonance imaging and biochemical markers such as increased alpha-fetoprotein.

Cryoablation

Each procedure comprised two freeze–thaw cycles accomplished using an argon gas-based cryosurgical unit (Endocare, Irvine, CA, USA). Cryoprobes (3 or 5 mm in diameter) were inserted into the center of the tumor mass under ultrasonographic guidance, each reaching a temperature of −180 °C at the tip of the probe. The duration of freezing was dependent on the achievement of an ice ball that extended 1 cm beyond the boundary of the tumor and was visible as a hypoechoic region on ultrasonography. Generally, the maximal freezing time was 15 min, followed by thawing for 5 min; this cycle was then repeated. For masses smaller than 5 cm in long diameter, two or three cryoprobes were placed within the center of the tumor, to ensure freezing of the entire mass; for masses with a long diameter of 5–10 cm, the tumor was divided into two parts that were treated in turn, usually at an interval of 1 week; for masses with a long diameter of 10–18 cm, the tumor was divided into three parts treated at intervals of usually 1 week. The tracts formed were sealed with fibrin glue immediately after removal of the cryoprobes to ensure hemostasis.

Measurement of thrombocytopenia and treatment of coagulopathy

Blood platelet counts were measured daily for 1 week post-cryosurgery to detect the occurrence of thrombocytopenia and coagulopathy. Patients with counts less than 100×10^9/L were watched closely. In those with counts lower than 70×10^9/L (i.e. severe coagulopathy), recombinant human IL-11 (rhIL-11) (25 μg/kg/day; Northland Biotech, Beijing, China) [29] was administered, usually for 3–5 days, to enhance the ability of the bone marrow to produce platelets.

Evaluation and statistical analysis

All cases of thrombocytopenia in this study were unambiguous; the influence of heparin, immune factors, drugs, sepsis, acute leukemia and internal or external irradiation was excluded [18]. Complications were recorded and classified in accordance with the Common Terminology Criteria of Adverse Events v4.0. Radiographic local tumor control was assessed using image-guided tumor ablation criteria [8]. Abdominal ultrasonography was performed both 1 day and 1 week after treatment. Follow-up ultrasonography was performed at 1 month and then at 3 month intervals. The revised Response Evaluation Criteria in Solid Tumors v1.1 were used to assess the response of the hepatic tumors [6]. The incidences of coagulopathy after ablation of primary and metastatic tumors were compared using the chi square test. Correlations between the incidence of coagulopathy, tumor diameter, pretreatment platelet count and maximal platelet loss were analyzed by linear regression. Differences in maximal platelet loss according to pretreatment platelet count were analyzed by Tukey's multiple comparison test. The statistical significance of correlations and differences was indicated by $P < 0.05$, $P < 0.01$ or $P < 0.001$. All analyses were conducted using GraphPad software (San Diego, CA, USA).

Results

Clinical data

Three hundred and seventy-two patients underwent 525 sessions of hepatic cryoablation; tumor long diameters were <6 cm in 256 patients, 6–10 cm in 79 and >10 cm in 37. One hundred and ninety-seven patients were male and 175 were female and their ages ranged from 29 to 75 years, with a mean of 53 years. Two hundred and forty-five patients were from China and 127 patients were from Southeast Asia. Of these patients, 116 had initially been treated surgically and 194 had been treated with systemic chemotherapy in other centers; 84 patients had thrombocytopenia.

Perioperative outcomes

All percutaneous cryoablations of primary and metastatic hepatic lesions were performed successfully. No severe complications (such as liver rupture or failure, myoglobinuria or acute renal failure) were discovered post-cryoablation. Many mild side effects occurred after cryosurgery, but the affected patients recovered with or without symptomatic treatment. Slight liver hemorrhage occurred after 105 sessions (20%), all cases of which were healed within 5 days by injection of hemostatic agents. Liver capsular rupture was found in 21 patients (4%) but resolved after blood transfusion. In the 84 patients (104 sessions) who had thrombocytopenia before liver cryoablation, the thrombocytopenia had disappeared after 11 sessions and coagulopathy occurred within 4 days after 50 sessions. Transient coagulopathy occurred within 4 days after 96 sessions (18%); 24 patients with severe disease received rhIL-11 and all patients recovered within 1 week. Liver abscess was observed after 32 sessions (6%) at the site of cryoablation, but the patients recovered within 2 weeks with antibiotic and drainage treatment.

Prediction of coagulopathy after liver cryoablation

Coagulopathy occurred after 41 of 241 sessions of cryoablation of primary HCC and 55 of 284 sessions of cryoablation of liver metastasis. According to the chi square test, this difference was not significant ($P = 0.4966$); thus, the 525 sessions could be combined for further analysis. In our therapeutic protocol, the tumor size was comparable between metastatic cancers and HCCs; smaller hepatic tumors (long diameter <6 cm) were treated with a single cryoablation and larger tumors (long diameter 6–10 cm or 10–18 cm) with two or three cryoablations, usually at intervals of 1 week. After each session, the incidence of coagulopathy was 14–22% (long diameter 1–2 cm, 7 of 34 sessions, 20.6%; long diameter

2–3 cm, 20 of 103 sessions, 19%; long diameter 3–4 cm, 43 of 196 sessions, 22%; long diameter 4–5 cm, 26 of 192 sessions, 14%), with no correlation between coagulopathy and tumor diameter ($P = 0.3471$; Fig. 1A). Considering all 525 sessions of liver cryoablation, blood platelet count decreased after 419 sessions, with an average maximal loss of $(66.6 \pm 53.71) \times 10^9$/L ($P_5 = 61.45$, $P_{95} = 71.76$), and increased after 106 sessions, with an average maximal loss of $(42.34 \pm 51.04) \times 10^9$/L ($P_5 = -52.63$, $P_{95} = -32.05$). The overall average platelet loss was $(46.12 \pm 68.13) \times 10^9$/L and there was no correlation between tumor diameter and maximal platelet loss ($P = 0.2933$; Fig. 1B).

The incidence of coagulopathy varied greatly with pretreatment platelet count ($\sim 150 \times 10^9$/L, 50 of 104 sessions, 48.1%; $\sim 200 \times 10^9$/L, 32 of 154 sessions, 20.8%; $\sim 250 \times 10^9$/L, seven of 102 sessions, 6.9%; $\sim 300 \times 10^9$/L, two of 74 sessions, 2.7%; $\sim 350 \times 10^9$/L, one of 47 sessions, 2.1%; $\sim 650 \times 10^9$/L, one of 44 sessions, 2.3%) and the two factors were negatively correlated ($P = 0.0332$, $r = -0.8472$; Fig. 1C). Based on these results, pretreatment platelet count and not tumor diameter predicted coagulopathy. There was no correlation between pretreatment platelet count (mean, $(222.28 \pm 92.18) \times 10^9$/L) and tumor diameter ($P = 0.5188$; Fig. 1D).

To further investigate the correlation between maximal platelet loss and tumor diameter, all 525 sessions were divided into six groups according to pretreatment platelet count. No correlations were found, with the exception of the $200–250 \times 10^9$/L group ($P = 0.0060$, $r = -0.2742$; Fig. 2A). The maximal platelet losses (10^9/L) of the six groups were: 24.58 ± 34.17 for 100–150 ($n = 104$); 36.24 ± 50.75 for 150–200 ($n = 151$); 47.99 ± 59.26 for 200–250 ($n = 99$); 48.14 ± 62.44 for 250–300 ($n = 73$); 67.15 ± 71.97 for 300–350 ($n = 47$); and 121.3 ± 97.13 for 350–650 ($n = 42$). Maximal platelet loss in the $350–650 \times 10^9$/L group was significantly higher than that in the other five groups, and the 300–350 group was significantly higher than 100–150 and 150–200 (Fig. 2B).

Treatment of coagulopathy after liver cryoablation

In our experience, slight coagulopathy (blood platelet count $>70 \times 10^9$/L) can resolve quickly without treatment, whereas severe coagulopathy (blood platelet count $<70 \times 10^9$/L) does not resolve on its own or recovers only slowly; thus, these two types of patient are treated by different methods. By daily monitoring, slight coagulopathy was found to occur after 72 cryosurgery sessions; overall, the platelet count had dropped to $(87.9 \pm 17.8) \times 10^9$/L 2 days after cryosurgery and increased to $(106 \pm 39.9) \times 10^9$/L after 6 days. Severe coagulopathy occurred after 24 sessions; the platelet count was $(77.2 \pm 37.1) \times 10^9$/L after 1 day and $(109.5 \pm 30) \times 10^9$/L after 7 days. The average time to the occurrence of severe coagulopathy was 4 days.

Discussion

Cryosurgery is becoming an attractive technique for nonresectable hepatic tumors. Comprehensive cryoablation of metastatic HCC can prolonged the patient's life to 38.5 months and multiple cryoablations can further improve survival [15]. Multiple cryoablation is an important innovation in the treatment of larger tumors in our hospital. It is difficult to ablate a large tumor thoroughly in a single procedure, and breakage of the tumor may release products into the blood that can cause serious side effects. In the present study, tumors of diameter 6–10 cm were divided into two parts and those of diameter more than 10 cm were divided into three. Based on clinical observations, 1 week rest was usually sufficient for patients to recover their strength and for most tumor breakage products to be metabolized. All of the patients in this study tolerated the treatment and no severe complications were found after cryoablation, demonstrating the safety and efficacy of this technique.

The occurrence of thrombocytopenia after cryosurgery is considered to be related to the volume of tissue frozen [5,20], the

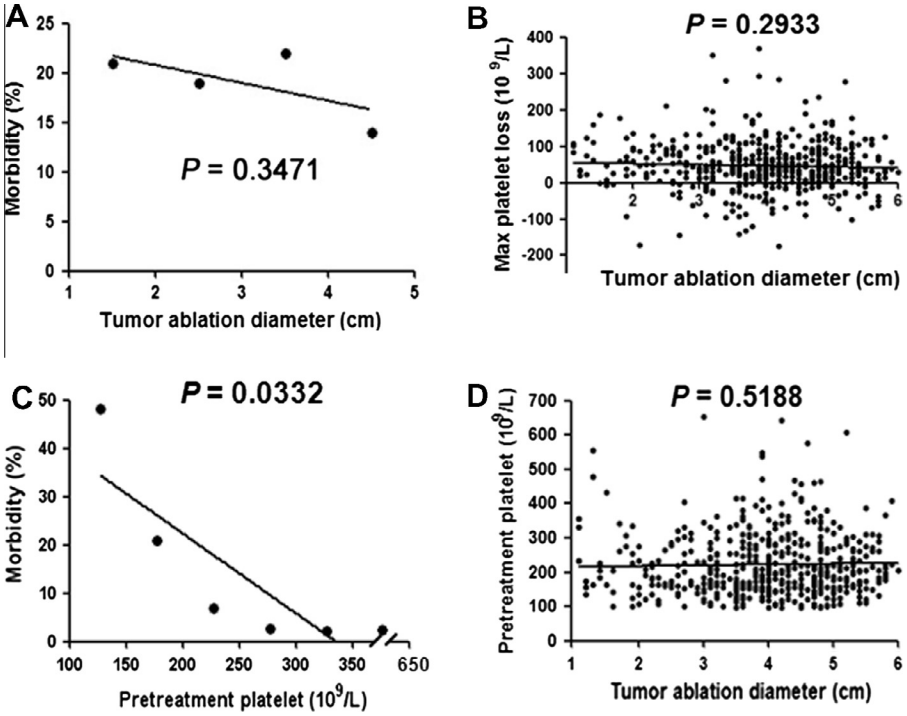

Fig. 1. Correlations among the incidence of coagulopathy, tumor diameter and blood platelet count were analyzed by linear regression. (A) Incidence of coagulopathy and tumor diameter; (B) tumor diameter and maximal platelet loss; (C) incidence of coagulopathy and pretreatment platelet count; (D) tumor diameter and pretreatment platelet count.

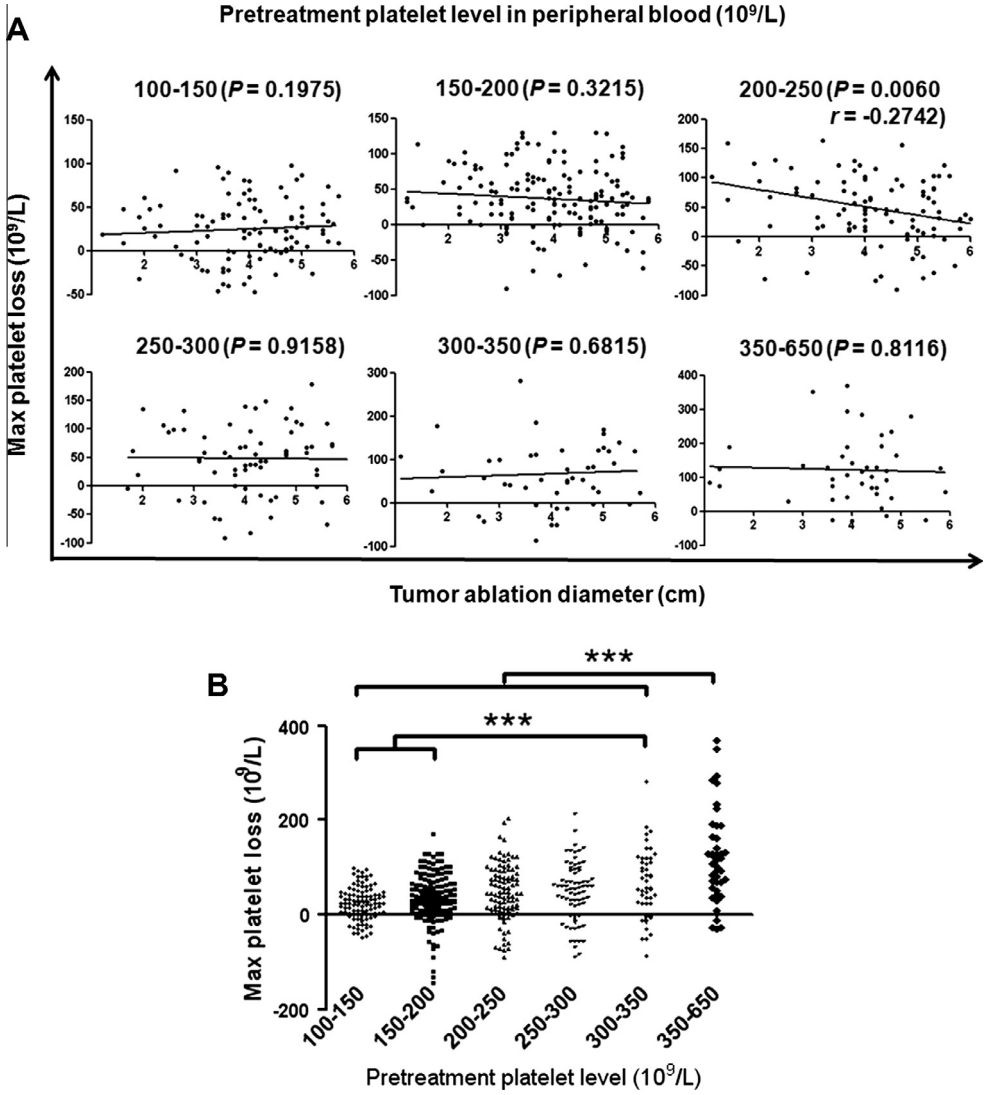

Fig. 2. Relationship between pretreatment platelet count and maximal platelet loss. (A) Correlations between maximal platelet loss and tumor diameter according to pretreatment platelet count. All correlations were analyzed by linear regression. (B) Maximal platelet losses compared according to pretreatment platelet count. All differences were analyzed by Tukey's multiple comparison test. $^{***}P < 0.001$.

number of freeze–thaw cycles and the number of cryoprobes used [22]. Systemic thrombocytopenia may develop to coagulopathy (platelet count $\leqslant 100 \times 10^9$/L), which will seriously threaten patients life if it was not closely monitorred and promptly found [10]. In this study, using tumor long diameter to represent the frozen tissue volume, we found no correlation between tumor long diameter and coagulopathy (Fig. 1A) or between tumor diameter and maximal platelet loss (Fig. 1B). In some cases, platelet count increased after cryoablation (Fig. 2A). This is an interesting finding in discord with previous research. Other studies have demonstrated local platelet trapping and destruction within the margin of cryolesions [10,13,20]. More work is needed to elucidate the differences between studies. In the present study, we found that blood platelet count before cryoablation was significantly correlated with coagulopathy (Fig. 1C), but there was no correlation between tumor diameter and pretreatment platelet count (Fig. 1D). Patients in the $100–150 \times 10^9$/L group were the most susceptible to coagulopathy, they should be monitored more closely, and preventative action should be given before cryosurgery.

To analyze platelet changes in susceptible and less susceptible patients, 525 sessions of cryoablation were divided into six groups according to pretreatment platelet count, with the following findings: (1) maximal platelet loss in each group was unrelated to or significantly negatively correlated with tumor diameter (Fig. 2A); (2) elevated platelet counts immediately after cryoablation were found in some patients in every group (Fig. 2A); (3) maximal platelet losses in the high platelet count groups (300–350 and 350–650) were higher than those in the low platelet count groups (100–150 and 150–200), as shown in Fig. 2B. These phenomena may be associated with differing compensatory abilities of bone marrow and better organ function, though the causes and detailed mechanisms need to be confirmed.

Coagulopathy caused by liver cryoablation and that due to chemotherapy have different mechanisms, but both – alone or in combination – can cause a serious bleeding risk (e.g. ecchymosis under the skin, gingival bleeding, visceral bleeding) [14]. Many therapies have been found to be effective in relieving coagulopathy, including the following. (1) Aprotinin, a serine protease inhibitor, prevents platelet trapping, reduces recruitment of leukocytes and permits a more uniform cryolesion with complete parenchymal cell destruction [13]. (2) Plasma infusions have been shown to be effective in early/mild cases [3,4]. (3) Platelet transfusion should

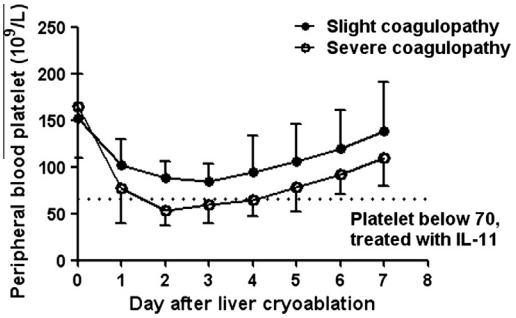

Fig. 3. Recovery of peripheral blood platelet count in patients with coagulopathy. Horizontal dotted line represents platelet count of 70×10^9/L.

be used with caution because of the risk of inducing microvascular platelet deposition [7]. (4) rhIL-11 is the only agent currently approved by the US Food and Drug Administration for coagulopathy induced by chemotherapy [28].

Based on the characteristics of cancer patients (most of whom are in a state of increased blood coagulation [2,12,27]), therapeutic drugs (increase platelets slowly; usually 3 days or more before a significant effect [3,4,28]) and platelet transfusion (substantial risk of alloimmunization against HLA antigens and/or platelet glycoproteins [25]), we treated patients with severe coagulopathy with rhIL-11 only. According to retrospective analysis, almost all patients with coagulopathy, whether slight or severe, can resume their normal activities within 1 week (Fig. 3). Thus, daily monitoring of platelet count and treatment when necessary can effectively alleviate coagulopathy. Once the patient's platelet count to less than 70×10^9/L, IL-11 treatment should be given immediately and continuously, until the platelet count remount to 100×10^9/L again.

In summary, this study showed that low platelet count before cryoablation was the most important risk factor for coagulopathy. With symptomatic treatment based on severity, patients with coagulopathy can recover within 1 week. However, these findings were based on observations of patients in a single center, and the specific mechanisms of action require further investigation.

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