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ORIGINAL ARTICLE

Chemoembolisation of Hepatic Tumours: Changes in Platelet Count, Haemoglobin, and Creatinine Postembolisation

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ABSTRACT

Objective: *To determine the frequency and magnitude of decreases in renal function, haemoglobin levels, and platelet count after chemoembolisation in patients with liver tumours.*

Materials and Methods: *Eighteen patients with a mean age of 59 years (range, 37 to 78 years) were entered in this retrospective study. A total of 28 chemoembolisations were carried out. Eight patients had hepatomas while 10 patients had metastatic disease. Laboratory values for creatinine, platelet count, and haemoglobin were obtained between 3 and 5 days postembolisation (mean 3.2 days), and compared with immediate pre-embolisation values (< 36 hours before). In all instances values were within the normal range pre-embolisation.*

Results: *Creatinine increased by a mean of 51 μmol/L (range, 5 to 326 μmol/L) with values above the normal range in 17/28 embolisations. Platelet count decreased by a mean of 27% (range, -55% to +78%), falling below normal values in 3/28 cases. A mean decrease in haemoglobin of 20 g/L (range, -43 to +8 g/L) was observed, with values below the normal range in 7/28 cases.*

Conclusion: *A significant decrease in renal function, as reflected by increased creatinine levels, was observed ($p < 0.05$). A fall in platelet and haemoglobin levels was encountered frequently in patients postchemoembolisation. All values returned to pre-embolisation levels within 4 weeks of chemoembolisation.*

Key Words: *Creatinine, Disseminated intravascular coagulation, Hemoglobins, Hepatoma, Platelet count, Therapeutic chemoembolization, Tumors*

INTRODUCTION

The past several decades have seen dramatic advances in the development of new techniques for the treatment of unresectable primary and secondary hepatic neoplasms. Among these is the technique of chemoembolisation, which has become widely used internationally. Although its exact place in the treatment armamentarium continues to be debated, chemoembolisation has achieved considerable success in either decreasing tumour size and/or increasing patient survival.[1-8]

Many studies have indicated that properly selected patients generally tolerate the treatment well with only modest morbidity. Adverse events, however, do occur; the complications of this treatment are well known and include gall bladder infarction, oil embolisation to the lungs, abscess formation, hepatic decompensation, and bleeding.[9,10] We observed that over several days postembolisation, many of our patients demonstrated diminution of platelet counts and haemoglobin levels. In many cases creatinine also rose significantly. Apart from a detailed report published by Katsishima et al, which suggests that low-grade disseminated intravascular coagulation (DIC) may occur, we are unaware of any specific studies that have evaluated changes in platelet count.[11] In addition, scattered references to decreases in renal function have appeared in the literature.[2,3] Although overt bleeding postembolisation has also been noted sporadically, little attention has been focused on changes in haemoglobin levels. We report our retrospective observations on a group of patients who have undergone chemoembolisation in our department.

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MATERIALS AND METHODS

A retrospective review was undertaken of 18 patients who underwent chemoembolisation in our institution over a 2-year period. Inclusion criteria for chemoembolisation were normal laboratory values (for our institution): platelet counts > 100,000 x 10^9/L, creatinine < 110 μmol/L, and bilirubin < 25 μmol/L. Haemoglobin was required to be in the normal range (male: 145 g/L; female: 120 g/L). Main portal venous patency was required to be established, either with angiography, CT, or ultrasound within one week prior to embolisation. Patients with leukopenia were excluded, as well as those with uncorrectable coagulopathy (International Normalized Ratio [INR] > 1.6). No patient had concomitant renal disease or diabetes.

Ten patients were male and 8 female, with a mean age of 59 years (range, 37 to 78 years). These patients underwent a total of 28 chemoembolisations (1 to 4 embolisations per patient). Eight patients had hepatomas (3 with cirrhosis Childs A) and 10 patients had metastatic disease (5 colon, 2 carcinoid, 1 melanoma, 1 cholangiocarcinoma, and 1 leiomyosarcoma of jejunum). All patients were non-surgical candidates. Patients with metastatic disease had previously received intravenous chemotherapy, with the exception of 1 patient with cholangiocarcinoma and 1 with colon carcinoma.

After embolisation, all patients were evaluated for the development of fever, right upper quadrant pain, Murphy's sign, nausea and vomiting, cough, shortness of breath, and haematemesis in the first 10 days after chemoembolisation. In addition, creatinine levels, platelet counts, and haemoglobin levels were evaluated in all patients over the same period. Normal values in our institution at the time of the study were as follows: platelet count 125-300 x 10^9/L; haemoglobin: male 145-175 g/L, female 120-160 g/L; creatinine: male 60-110 μmol/L, female 40-100 μmol/L.

Chemoembolisation Procedure

Prior to embolisation, normal saline 150 mL/hour was administered for at least 6 hours, to ensure adequate hydration. This was continued throughout the procedure, and for at least 4 hours afterwards. Patients were cautioned to avoid non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 days before the procedure, to avoid compromising renal function.

All patients underwent selective hepatic angiography. The patients were embolised with one of the following 2 mixtures:

1. For hepatoma and non-colorectal metastases: Lipiodol (Therapex/E-Z-EM Canada Inc, Montreal, Quebec) 20 mL emulsified with adriamycin (doxorubicin) 60 mg and 10 mL of Optiray® (ioversol) [Mallinkrodt Medical Inc, Pointe-Claire, Quebec]; or
2. For colorectal metastases: 5-fluorouracil 1 g and mitomycin C 10 mg emulsified with 20 mL of Lipiodol. Gelatin foam slurry (Gelfoam®, Pharmacia & Upjohn Co, Kalamazoo, Michigan) was then embolised until vascular stasis was achieved. In no instance was more than 89 mL of Isovue® (iopamidol) 320 utilised (range, 25 to 89 mL; mean 51 mL) for the purposes of angiography, including the volume used in the embolisation mixture. The minimum liver volume that encompassed the whole of the tumor to be treated was embolised; no more than one lobe was embolised at a single session.

Patients were evaluated in the first 5 days (range, 3 to 5 days; mean 3.2) postembolisation to determine whether decreases in haemoglobin or platelet counts, or increases in creatinine level, had occurred. These were defined as follows — haemoglobin: fall of ≥ 20 g/L; platelets: fall of ≥ 20%; creatinine: increase of ≥ 20 μmol/L — as compared to a baseline value obtained ≤ 2 days prior to embolisation. Statistical analysis for comparison of preprocedural and postembolisation values was performed using Student's t-test.

RESULTS

Signs and Symptoms

Among the 28 patients, low-grade fever was demonstrated in 27, right upper quadrant pain in 26, nausea and vomiting in 14, cough in 3, shortness of breath in 2, and haematemesis in 1. Murphy's sign developed in 5 patients, in no instance more than once in the same patient. In 3 cases, ultrasound was performed and showed distension of the gallbladder and thickening with small amounts of pericholecystic fluid consistent with infarction/ischaemia. All of these cases settled with conservative therapy. Patient data are summarised in Table 1.

Creatinine

Creatinine values demonstrated a mean increase of 51 μmol/L (range, 5 to 326 μmol/L) per procedure. Two patients required temporary dialysis (creatinine levels of 296 and 326 μmol/L), in both cases for less than 2 weeks. An increase in creatinine level of 20 μmol/L or more occurred in 21 of the 28 embolisations (7 of the

Table 1. Postembolisation changes.

	Change in value		
	Range	Mean	
Creatinine (μmol/L)	+5 to +326	+51	Increase ≥ 20 μmol/L in 21/28 (7/11 hepatoma, 14/17 metastasis)
Platelet count (% change)	-55 to +78	-27	Decrease ≥ 20% in 22/28 (11/11 hepatoma, 14/17 metastasis)
Haemoglobin (g/L)	-43 to +8	-20	Decrease ≥ 20 g/L in 15/28 (7/11 hepatoma, 4/17 metastasis)

11 hepatoma and 14 of the 17 metastatic cases). In 17 of the 28 patients creatinine values were abnormally elevated.

Platelet Count

There was a mean decrease of 27% in platelet count (range, -55% to +78%). A single instance of an increase in platelet count was observed, with all other patients showing a decrease. A reduction in platelet count of ≥ 20% occurred in 22 of 28 embolisations (all 11 patients with hepatoma and 14 of 17 metastatic cases). In 14 of the 28 patients counts were below the normal range, with 2 less than 50,000 x 10^9/L.

Haemoglobin

A mean decrease in haemoglobin level of 20 g/L was observed (range, -43 g/L to +8 g/L). A decrease of ≥ 20 g/L occurred in 15 of 28 embolisations (7 of 11 hepatomas and 4 of 17 metastatic cases). The patient with haematemesis showed a decrease in haemoglobin level of only 3 g/L. In 7 of the 28 patients, haemoglobin values were lower than normal postembolisation.

Statistical comparison of immediate preprocedural vs postprocedural values showed the differences to be significant at $p < 0.05$ for all 3 laboratory parameters. In patients with multiple chemoembolisation sessions, no correlation between severity of laboratory value changes in the first session and in subsequent chemoembolisations was observed. Patients were evaluated again between 3 and 4 weeks postembolisation. All patients showed recovery of creatinine and platelet levels into the preembolization range. In 3 cases (those with the greatest decrease), haemoglobin values remained lower than normal.

DISCUSSION

Major clinical sequelae postchemoembolisation are well recognised, and fortunately infrequent.[12-19] In suitably selected patients, morbidity is relatively minimal and well controlled, while mortality is low and restricted mainly to patients with borderline hepatic reserve, such as those with extensive portal venous thrombosis.[18] In our patients we observed transient thrombocytopenia and elevated creatinine. This phenomenon has been recognised by a number of other authors.[2,3,8,11,20] In our patient series a fall in haemoglobin levels was observed, and this finding has been noted less frequently in the literature. Katsushima et al commented that, with careful scrutiny, low-grade DIC with platelet and fibrinogen consumption could be observed in a large number of patients postchemoembolisation.[11] Prothrombin time was also prolonged in their study. This observation is of concern because of the potential predisposition to bleeding complications. The increased creatinine levels were certainly greater than would be expected simply from the contrast load, if patients were kept well hydrated prior to, during, and following the procedure, as we did. The fall in haemoglobin level is also greater than would be expected from chemotherapy, and suggests possible occult bleeding. Chung et al, in their series of 942 chemoembolisations, noted only 10 cases of clinically apparent gastrointestinal bleeding, 4 of whom were patients with known varices.[12] One patient with lobar portal vein thrombosis experienced lobar infarction, with subsequent coagulopathy and full-blown DIC, but recovered with treatment. The mechanism of development of low-grade DIC-like changes seen in patients previously reported is unclear, although release of cellular products with necrosis likely plays a role.[11] Presumably, thrombocytopenia is in part related to occult bleeding, reflecting consumption of platelets in an effort to maintain haemostasis in haemorrhagic areas.

Diminution in renal function may be due to various factors.[2,3,20] Following chemoembolisation, tumour necrosis occurs, with release of nucleic acids and proteins by the necrotic tumour. In combination with the presence of contrast media and nephrotoxic chemotherapeutic agents, transient diminution in renal function may occur. There have been rare reports of acute tumour lysis syndrome after chemoembolisation of large hepatomas.[21] This event was sufficiently severe as to necessitate temporary dialysis in 2 of our patients. Since patients were kept well hydrated before and after the procedure, dehydration is unlikely to have contributed to an elevation in creatinine. Rose et al

reviewed 78 embolisation procedures, and encountered 3 cases of deterioration in renal function.[8] Two of these required no treatment, and 1 was diagnosed as acute tubular necrosis, necessitating dialysis for several weeks with subsequent return of normal renal function.

Of note in our series was a significant fall in haemoglobin level in many patients. The rapid decrease cannot be accounted for by a myelosuppressive effect of the chemotherapy, as it occurred almost immediately. A haemodilution effect may have partially contributed to the measured decline in haemoglobin; however, hydration was well maintained throughout the procedure as well as before and after — it is, however, difficult to determine accurately how much fluid was given intraprocedurally for each patient. A number of patients underwent either CT or ultrasound, which in several cases demonstrated subcapsular haematomas in patients with tumour extending to the capsular surface, as well as irregular areas of haemorrhage within the chemoembolised tumours. Presumably the fall in haemoglobin was due at least in part to occult internal bleeding in and around the embolisation site.

Our results can be contrasted with those of Lopez et al, who studied 15 patients who underwent 23 chemoembolisations.[15] In their group of patients, no significant impact on renal function, platelet count, or haematocrit was apparent in over a month of follow-up. Their embolisation protocol, however, was different from our own, using less adriamycin but adding cisplatin. The volume of iodinated oil used was not specified in their report, and they used polyvinylalcohol particles rather than Gelfoam to achieve vascular stasis.

This study has a number of significant limitations. Only a small number of patients were evaluated. Changes in clotting parameters such as prothrombin time, partial thromboplastin time, and INR were not evaluated, and could possibly have been altered by the chemoembolisation procedure, thereby contributing to occult, unrecognised internal bleeding. In addition, fibrin/fibrinogen degradation products were not measured; such measurements would have been helpful in comparing our results with those of Katsushima et al.[11] Comparison with other reports is difficult due to differing chemoembolisation protocols and the sparse details provided regarding complications.

We conclude that significant deterioration in renal function, as well as decreases in haemoglobin and platelet counts, may attend chemoembolisation procedures. In most instances these changes are not clinically evident and are only detected by laboratory evaluation. Radiologists and clinicians should be aware of this phenomenon, which appears to be common. The mechanism may involve DIC in combination with a subclinical tumour necrosis syndrome. Efforts should made to minimise these abnormalities by measures such as vigorous hydration and avoidance of the use of intravenous contrast, if at all possible, in the immediate postchemoembolisation period. These findings also emphasise the importance of preprocedural screening.

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