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Efficacy of percutaneous transhepatic portal vein embolization using gelatin sponge particles and metal coils

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Abstract

Background: Percutaneous transhepatic portal vein embolization (PTPE) can increase the future liver remnant (FLR) volume before extended liver resection; however, there is no current consensus regarding the best embolic material for PTPE.

Purpose: To evaluate the efficacy of PTPE using gelatin sponge particles and coils.

Material and Methods: The medical records of 136 patients who underwent PTPE using gelatin sponge particles and metal coils were retrospectively reviewed. We evaluated the procedural details, liver volume on CT, and clinical status before and after PTPE.

Results: The mean FLR volume increased significantly from 390 ± 147 cm^3 to 508 ± 141 cm^3 ($P < 0.001$). A mean of 22.1 ± 9.4 days after PTPE, the mean increase in the ratio of FLR volume to total liver volume was 9.4 ± 6.5%. Complications related to PTPE occurred in five patients, including arterial damage ($n = 4$) and biloma ($n = 1$). The white blood cell count and C-reactive protein level increased significantly and then returned to baseline within seven days. Aspartate aminotransferase and alanine aminotransferase showed no significant changes. Fever (defined by the Common Terminology Criteria for Adverse Events v4.0) was reported in 74 patients (54%), but it was generally mild (Grade 1/2; $n = 72$). None of the patients experienced severe complications that required cancellation of surgery.

Conclusion: PTPE with gelatin sponge particles and coils may impose low physical stress on patients and is a safe method of inducing a significant increase of FLR.

Keywords
Portal vein, hepatectomy, interventional radiology, embolization

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Introduction

Percutaneous transhepatic portal embolization (PTPE) is an established image-guided procedure for increasing the future liver remnant (FLR) before extended liver resection (1). Hypertrophy of the FLR is considered to convert patients with unresectable disease into candidates for resection by lowering the risk of postoperative hepatic insufficiency and liver failure.

In previous studies, various embolic materials have been used for PTPE, including fibrin glue (2), gelatin sponge particles (3), n-butyl-cyanoacrylate (NBCA) (4), polyvinyl alcohol particles (5), absolute ethanol (6,7),

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sodium tetradecyl sulfate foam (8), and combinations of these materials with metal coils or vascular plugs (9). Thus, there is no current consensus regarding the best embolic material for PTPE (10).

The aim of the present study was to evaluate the effectiveness of gelatin sponge particles and metal coils for PTPE.

Material and Methods

Patients

Our institutional review board approved the retrospective collection of data and data analysis for this study, and the requirement for informed consent from the patients was waived.

From January 2012 to October 2015, 157 consecutive patients scheduled for extended hepatic resection at our hospital underwent PTPE using gelatin sponge particles and metal coils. Data were obtained by review of their medical records. Twenty-one patients were excluded from the study according to the following criteria: other vascular interventions within two weeks of PTPE (transcatheter arterial chemoembolization and hepatic vein embolization) (n = 5); previous liver resection (n = 2); measurement of liver volume by magnetic resonance imaging (MRI) (n = 1); no computed tomography (CT) after PTPE (n = 2); and no data on the liver volume after PTPE in the medical record (n = 11). In these patients, liver volumetry was not performed after PTPE because postprocedural CT scans revealed that an operation was impossible (e.g. distant metastases and/or dissemination).

A total of 136 patients formed the cohort of this study (Table 1). They included 80 men and 56 women with a mean age of 67.2 ± 8.7 years (age range = 35–83 years). Indications for surgery were as follows: hilar cholangiocarcinoma (n = 99); liver metastasis (n = 7); intrahepatic cholangiocarcinoma (n = 6); hepatocellular carcinoma (n = 3); distal bile duct carcinoma (n = 2); gallbladder carcinoma (n = 17); and benign bile duct stricture (n = 2). Six patients had hepatitis virus infection, but none of them showed evidence of cirrhosis. Three patients had received preoperative chemotherapy (S-1 monotherapy in 2 and gemcitabine + cisplatin in 1).

Table 1. Patient characteristics (n = 136).

Characteristic	Value
Age (years), median (range)	67.2 (35–83)
Sex (man), n (%)	80 (59)
Diagnosis, n (%)	
Hilar cholangiocarcinoma	99 (73)
Liver metastasis	7 (5)
Intrahepatic cholangiocarcinoma	6 (4)
Hepatocellular carcinoma	3 (2)
Distal bile duct carcinoma	2 (2)
Gallbladder carcinoma	17 (13)
Benign bile duct stricture	2 (2)
Percutaneous portal vein embolization	
Targeted portal veins for embolization, n (%)	
Right poral vein	71 (52)
Right anterior and left poral vein	38 (28)
Right portal vein and branches to segment IV	18 (13)
Right anterior portal vein	9 (7)
Complete embolization at the end of PTPE, n (%)	136 (100)
Complications, n (%)	5 (3.7)
Hepatic artery damage	3 (2.2)
Hemothorax	1 (0.7)
Subcapsular biloma	1 (0.7)
Recanalization of targeted portal vein, n (%)	2 (1.5)
Time from PTPE to CT scans (days), median ± SD	22.1 ± 9.4
Pre-PTPE FLR (cm^3), median ± SD	390 ± 147
Post- PTPE FLR (cm^3), median ± SD	508 ± 141
Mean increase in the ratio of FLR volume to total liver volume (%), median ± SD	9.4 ± 6.5
Pre-PTPE KICG of FLR (cm^3), median ± SD	0.053 ± 0.014
Post-PTPE KICG of FLR (cm^3), median ± SD	0.070 ± 0.017
Fever after PTPE (CTVAE v4.0), n (%)	
Grade 1	56 (41)
Grade 2	16 (12)
Grade 3	2 (2)
Grade 4 or 5	0 (0)

PTPE, percutaneous portal vein embolization; FLR, future liver remnant; KICG, the plasma clearance (k) of indocyanine green (ICG).

Technique

Before PTPE, 15 mg of pentazocine and 0.5 mg of atropine sulfate were administered intravenously as premedication. After local anesthesia, the ipsilateral intrahepatic portal vein was punctured with an 18-G needle (PTCD needle; Create Medic Co., Kanagawa, Japan) under ultrasound guidance. A 0.035-inch guide wire was inserted into the portal vein though the needle, followed by a 5-Fr sheath introducer. After a 4-Fr shepherd hook catheter was inserted, direct portography was performed to evaluate the anatomy (Fig. 1a). Then, portal vein embolization was done as follows. A 4-Fr shepherd hook catheter was inserted into a segmental or subsegmental branch of the portal vein. First, gelatin sponge particles mixed with iodine contrast medium were infused to occlude the portal branch vein until blood flow in the branch was weak or

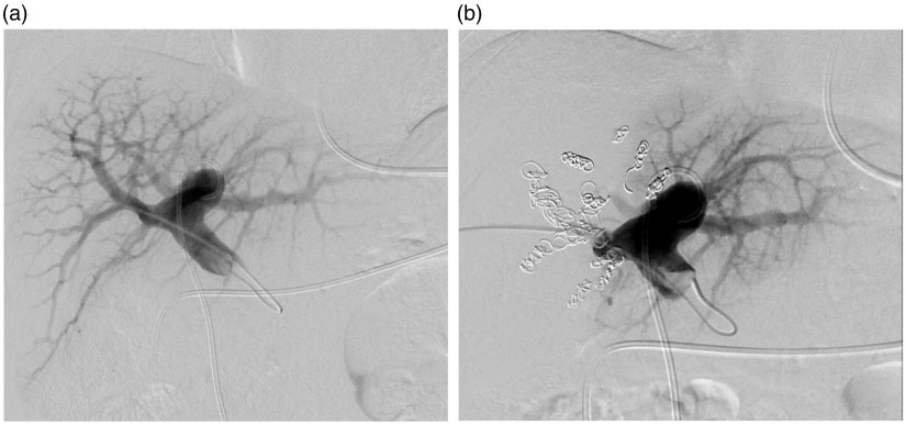

Fig. 1. A 67-year-old man with hilar cholangiocarcinoma underwent PTPE with gelatin sponge particles and metal coils before right trisectionectomy. (a) Direct portography before PTPE shows the ipsilateral approach to the portal vein. There are a number of portal vein branches in segment IV that need to be embolized. (b) Direct portography shows occlusion of the right portal vein and the portal vein branches in segment IV.

interrupted under fluoroscopy. The gelatin sponge particles were obtained by cutting a 2.5×5 cm gelatin sponge sheet (Serescue or Spongel; Astellas, Tokyo, Japan) into approximately 1- to 2-mm squares. Subsequently, 0.035-inch metal coils (MReye Embolization Coil; Cook Inc., Bloomington, IN, USA) were used to occlude the origin of the targeted portal vein branch. When it was difficult to select the portal vein branch with a 4-Fr catheter to inject coils safely, a 2.0- to 2.3-Fr microcatheter was advanced through the 4-Fr catheter and 0.018-inch metal coils (Tornedo Embolization Coil; Cook Inc., Bloomington, IN, USA) were injected, especially for portal vein branches in segment IV. After repeating embolization until all targeted portal vein branches were occluded, direct portography was performed to confirm the final results (Fig. 1b). On completion of the procedure, the access tract was embolized with 0.035-inch metal coils (3–5 mm in diameter).

CT volumetry and liver function index

The FLR volume and total liver volume were calculated from CT scans before and after PTPE. FLR volume and total liver volume data used in this study were obtained from the medical records. Liver volumetry was performed by the referring surgeons at our hospital using CT scans with a slice thickness of 0.5 mm or 2 mm. The intrahepatic tumor volume was also measured and was subtracted from the total liver volume. The percent increase of the FLR after PTPE (% increase FLR) was calculated according to the following formula:

$$\%\,\mathrm{FLR} = \frac{\text{FLR volume}}{\text{Total liver volume}} \times 100$$

$$\%\,\text{increase FLR} = \frac{\%\,\mathrm{FLR}_{\text{post-PTPE}} - \%\,\mathrm{FLR}_{\text{pre-PTPE}}}{\%\,\mathrm{FLR}_{\text{pre-PTPE}}} \times 100$$

We used the indocyanine green (ICG) test as an index of liver function, and an ICG test was performed before and after PTPE in 131 patients. In brief, ICG was administered via a peripheral vein, with venous blood samples being collected before and 5, 10, and 15 min after injection. Then the ICG concentration in the specimens was determined by measuring the absorbance at 805 nm. The plasma clearance rate of ICG (KICG) was calculated by linear regression analysis of the plasma ICG concentration data, after which KICG for the FLR was determined according to the following formula:

$$\text{KICC of FLR} = \text{KICG} \times \%\,\text{FLR}$$

Follow-up examinations

Changes of laboratory values were evaluated by comparing data before PTPE and data from zero (approximately 2 h after PTPE) to seven days after PTPE, including the white blood cell (WBC) count and the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), total bilirubin (T-Bil), lactic dehydrogenase (LDH), and C-reactive protein (CRP). Fever was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Recanalization of embolized portal vein branches and non-target embolization were evaluated on CT scans after PTPE.

Study endpoints and definitions

The primary endpoint for technical success was defined as occlusion of the targeted portal veins with patency of the non-targeted portal veins on final angiography at the end of PTPE. The secondary technical endpoint was defined as occlusion of the targeted portal veins on CT scans after PTPE. We also assessed changes of the FLR and KICG of FLR, changes of biochemical parameters, fever, complications of PTPE, and the clinical outcome.

Statistical analysis

Data were expressed as the mean ± SD. Statistical analysis was performed with the SPSS software package (SPSS Statistics 24; IBM, Armonk, NY, USA). Comparisons between two groups were done with a non-parametric matched-paired test (Wilcoxon signed rank test). Analyses of the changes of biochemical parameters over time were performed with Friedman's test and Scheffe's test. Differences were considered statistically significant at $P < 0.05$.

Results

The primary technical endpoint of PTPE was achieved in all 136 patients, with the following portal branches being embolized: the right portal vein in 71 patients, the right anterior and left portal veins in 38 patients, and the right portal vein and the branches to segment IV in 18 patients. Nine patients who were scheduled for left trisectionectomy, underwent only embolization of the right anterior branch because the left portal vein was occluded by tumor invasion.

Complications related to PTPE occurred in 5/136 patients. Hepatic artery damage occurred when puncturing portal vein under ultrasound guidance in three patients, who required transcatheter arterial embolization. Hemothorax due to intercostal artery damage occurred when puncturing portal vein in one patient and was treated by drainage of the pleural cavity. Subcapsular biloma occurred in one patient who required drainage. None of the patients experienced severe complications requiring cancellation of surgery. Our patients did not complain of pain during embolization, so additional analgesia was not needed.

On CT scans after PTPE, none of the patients showed non-target portal vein occlusion. Recanalization of the right posterior branch was noted in two patients who required additional PTPE because they did not have sufficient FLR for extended hepatectomy. The secondary technical endpoint was achieved in 99% of the patients (134/136 patients).

Volumetric CT was performed at 22.1 ± 9.4 days after PTPE. The mean FLR volume increased from 390 ± 147 cm^3 to 508 ± 141 cm^3 after PTPE, and this increase was significant ($P < 0.001$) (Fig. 2a). The mean ratio of FLR volume to the total liver volume was 34.1 ± 7.5% before PTPE and 43.5 ± 7.7% after PTPE. Thus, the mean increase in the ratio of FLR volume to total liver volume was 9.4 ± 6.5%, and this increase was also significant ($P < 0.001$). The mean % increase FLR was 30.7 ± 25.6%.

KICG was 0.157 ± 0.030 before PTPE and 0.160 ± 0.028 after PTPE, showing no significant difference ($P = 0.181$). KICG of FLR was 0.053 ± 0.014 before PTPE vs. 0.070 ± 0.017 after PTPE and this increase was significant ($P < 0.001$) (Fig. 2b).

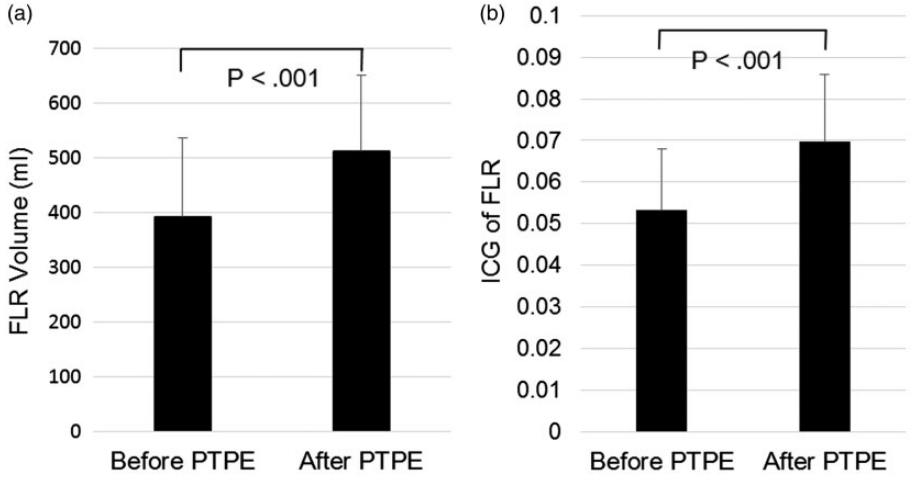

Fig. 2. FLR volume and ICG of FLR before and after PTPE. Data are expressed as the mean ± standard deviation (SD). (a) The mean FLR volume increased from 390 ± 147 cm^3 before PTPE to 508 ± 141 cm^3 after PTPE, which was a significant increase ($P < 0.001$). (b) KICG of FLR was 0.053 ± 0.014 before PTPE and 0.070 ± 0.017 after PTPE, showing a significant increase ($P < 0.001$).

The changes of laboratory data after PTPE are summarized in Fig. 3. The WBC count increased significantly from zero to three days after PTPE and returned to baseline by four days (Fig. 3a). CRP increased significantly from one to six days after PTPE and returned to baseline by seven days (Fig. 3b). There were no significant changes of AST, ALT, γ-GTP, ALP, T-Bil, and LDH after PTPE.

After PTPE, fever (defined by CTVAE v4.0) was reported in 74 patients (54%): Grade 1 in 56 patients (41%); Grade 2 in 16 patients (12%); and Grade 3 in 2 patients (1%). No patient had Grade 4 or 5 fever.

Discussion

Gelatin sponge is a water-insoluble hemostatic agent that is absorbed by phagocytes within 4–6 weeks after injection, so it is widely recognized as a temporary embolic agent (11). Tranchart et al. reported that PTPE using gelatin sponge powder without metal

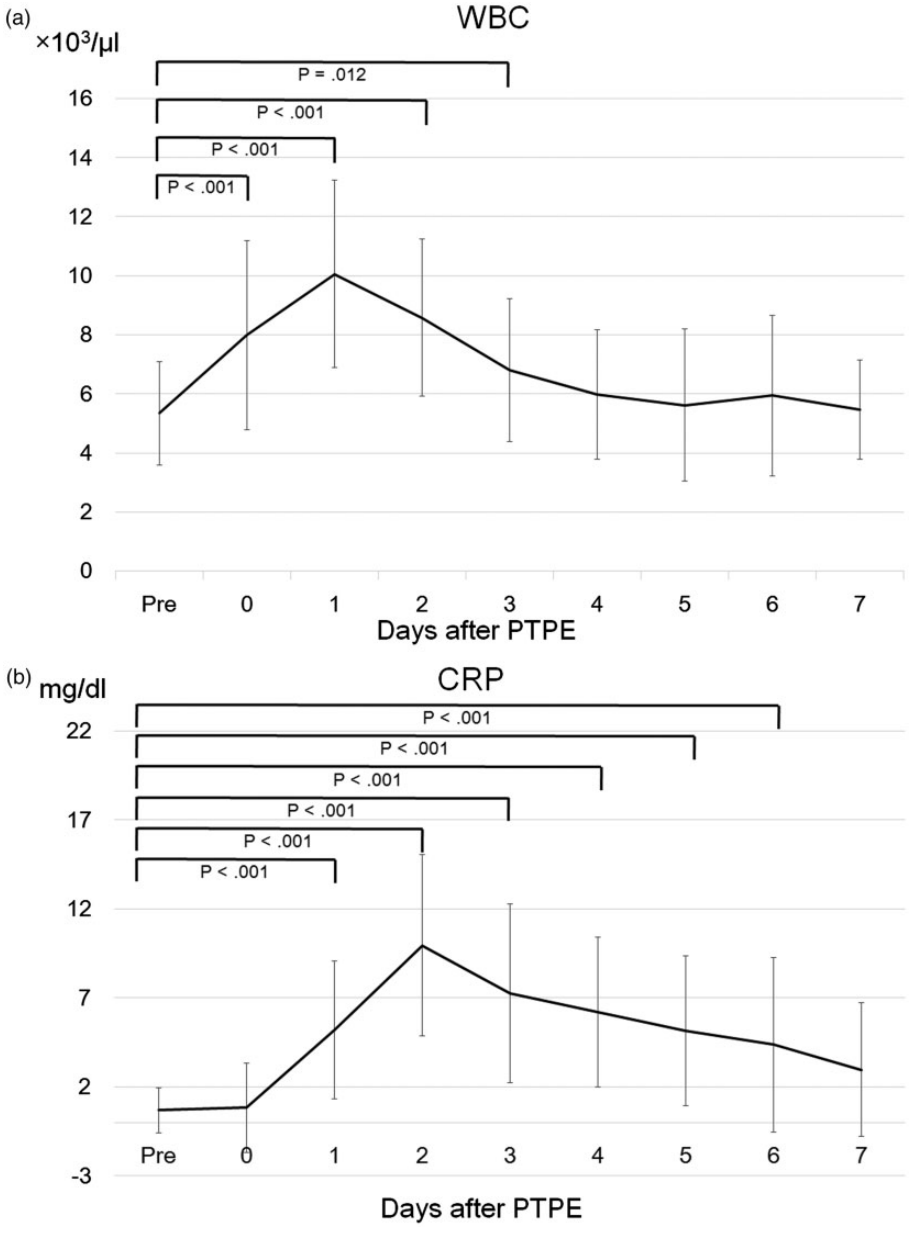

Fig. 3. Laboratory parameters before and after PTPE. Data are expressed as the mean ± standard deviation (SD). (a) The WBC count increased significantly from zero to three days after PTPE and returned to baseline by four days. (b) CRP increased significantly from one to six days after PTPE and returned to baseline by seven days.

coils achieved adequate hypertrophy of the FLR (3). On the other hand, use of gelatin sponge without metal coils frequently results in recanalization after PTPE, and fails to induce effective compensatory hypertrophy of the non-embolized lobe (12). Shin et al. reported that the gelatin sponge with metal coils was more effective than gelatin sponge alone for induction of compensatory hypertrophy (13). Therefore, we used gelatin sponge particles combined with metal coils. Though we used metal coils for tight embolism, recanalization of posterior branches occurred in two cases after PTPE and was treated by additional embolization with direct infusion of absolute ethanol. The reason for recanalization was thought to be injection of an insufficient amount of gelatin sponge particles.

In the present study, marked FLR hypertrophy was achieved after PTPE with gelatin sponge particles and metal coils. The mean FLR volume increased from 390 ± 147 cm^3 to 508 ± 141 cm^3 after PTPE, the mean increase in the ratio of FLR volume to total liver volume was $9.4 \pm 6.5\%$, and the mean % increase FLR was $30.7 \pm 25.6\%$. Tsuda et al. reported the mean % increase FLR was $28.2 \pm 1.62\%$ after PTPE with gelatin sponge particles and metal coils (9). Lienden et al. performed a systematic literature analysis and reported that the % increase FLR was $37.9 \pm 0.1\%$ (range = 20.5–69.4%) in 1791 patients after PTPE using various embolic materials (14). Our results showed equivalent efficacy compared with the previous large cohort study. Nagino et al. reported that the mortality rate after surgery for advanced biliary cancer was higher in patients with a KICG of FLR was <0.05 than in those with a KICG of FLR ≥ 0.05 (15). In the present study, KICG of FLR increased from 0.053 ± 0.014 before PTPE to 0.070 ± 0.017 after PTPE in 131 patients. Surgery might have been performed more safely in our patients because of this increase in the KICG of FLR. Recently, Edeline et al. reported that radioembolization induced a significant increase of FLR in cirrhosis patients. This technique may be another option for PTPE (16).

Hepatobiliary enzymes showed no significant changes after PTPE with gelatin sponge particles and metal coils. It was reported that AST and ALT reach peak levels at 1–3 days after PTPE with ethanol, usually rising to less than three times the baseline values (6,7,17). Tsuda et al. also found no transient increases of liver enzyme levels after PTPE with gelatin sponge particles and metal coils (9). Therefore, embolization with gelatin sponge particles and metal coils causes relatively less damage to the liver. Also, most of our patients had no fever (n = 62; 46%) or only slight fever (Grade1/2 n = 72; 53%) after PTPE. Sakuhara et al. reported fever (38–39°C) in 47/151 (31.1%) patients after performing PTPE with ethanol (6). They also reported that most of their patients complained of pain immediately after ethanol injection and sometimes needed additional analgesia for severe pain. Our patients did not need additional analgesia. Therefore, PTPE with gelatin sponge particles and metal coils may place a smaller burden on the patient than use of ethanol and could shorten the hospital stay.

Migration of embolic materials to non-target portal veins is one of the complications of PTPE, especially when using liquid embolic materials like ethanol and NBCA (17–20). If an occlusion balloon catheter is employed to avoid reflux of liquid materials, it may become difficult to select small and tortuous portal vein branches, such as the veins of segment IV, and this can result in technical failure of PTPE (21,22). It is also difficult to place a plug in these branches because it is necessary to insert a large bore catheter. On the other hand, gelatin sponge particles and metal coils can be injected through a microcatheter, which may make it easier to select difficult target vessels.

Our study had several limitations. First, it was a retrospective single-center investigation. Second, it was not randomized and lacked comparison with other embolic materials. Finally, embolization procedures varied (targeting the right portal vein, the right anterior and left portal veins, and the right portal vein and the branches to segment IV), which could have hampered interpretation of our data.

In conclusion, PTPE with gelatin sponge particles and metal coils may impose low physical stress on patients and is a safe procedure that induces significant FLR hypertrophy, which can be important in expanding the indications for major hepatectomy.

Declaration of conflicting interests

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