Evaluation of patients who underwent percutaneous transhepatic portal vein embolisation by Tc-99m GSA scintigraphy

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Abstract

**Purpose:** To analyse the correlation between the fold change in residual liver volume (RLV) and residual liver uptake at 15 (RLU15) before and after percutaneous transhepatic portal vein embolisation (PTPE).

**Material and methods:** Between August 2010 and December 2016, 20 patients who underwent PTPE were retrospectively selected. Before and three weeks after PTPE, contrast-enhanced computed tomography (CECT) and Tc-99m GSA scintigraphy were performed to analyse the fold changes in RLV and RLU15, respectively, as well as their correlation.

**Results:** After PTPE, a significant increase was observed in the RLV (before: 464 ± 99 ml; after: 573 ± 118 ml, \( p = 0.004 \)) and the RLU15 (before: 11.0 ± 2.9%; after: 17.7 ± 3.8%, \( p = 5 \times 10^{-7} \)). The fold increase of RLV and RLU15 in all patients was 1.25 ± 0.15 and 1.66 ± 0.33, respectively. No significant correlation was observed in the fold increase in both RLV and RLU15 (\( r = 0.14, p = 0.66 \)). In patients no. 3 and 9, who were outliers, the increase in RLV was minimal and RLU15 increased greatly, and these 2 patients underwent radical hepatectomy after PTPE.

**Conclusions:** No correlation was observed between the fold increase in RLV and RLU15 before and after PTPE. In order to accurately evaluate the residual liver function, it should be considered necessary to evaluate not only by morphological CECT volumetry, but also by functional outcome of Tc-99m GSA scintigraphy. Residual liver volume may not necessarily reflect RLF. It may be possible to improve the radical resection rate by detecting the potential increase of RLF with RLU15 of Tc-99m GSA scintigraphy.

**Key words:** PTPE, Tc-99m GSA scintigraphy, LU15, future remnant liver, sinusoidal obstructive syndrome, chemotherapy-associated steatohepatitis.

Introduction

Recently, advances in medical technology have led to active and aggressive major hepatectomies. However, hepatic failure is still a fatal complication and is seen in 2.5% to 12.9% of patients [1-3]. Preoperative percutaneous transhepatic portal vein embolisation (PTPE) is known as an effective means of preventing hepatic failure by functional residual liver hypertrophy and is often performed. However, a variety of hepatic injuries, such as liver cirrhosis, as well as post-systemic chemotherapy, greatly affect the outcomes of PTPE. Although morphological computed tomography (CT) volumetry has been widely used as an easy method of evaluation before and after PTPE, it is not suitable for accurately measuring functional residual liver volume.
To date, the usefulness of Tc-99m galactosyl human serum albumin (GSA) scintigraphy for more accurate evaluation of underlying liver diseases, such as cirrhosis [4,5], during both the preoperative [2,3,6] and peri-PTPE period [7,8], have been reported. A variety of radionuclide parameters can be used for Tc-99m GSA scintigraphy, depending on the institute. Residual liver uptake at 15 minutes (RLU15), which was reported by Koizumi et al., is the cumulative residual liver accumulation rate of a GSA tracer 15 minutes after its injection, and it indicates residual liver function [9]. To safely perform hepatectomies, it has been reported that the RLU15 should theoretically [10] and clinically [2] be 13 or more. A co-author of the present manuscript has already reported the usefulness of using RLU15 to predict liver failure [2]; however, to date, there has been no evaluation of the effectiveness of PTPE using RLU15. We report herein a correlation between morphological residual liver volume (RLV) and RLU15 before and after PTPE in 20 patients, and also compare the rate of increase in RLV and RLU15 between two groups, diagnosed and evaluated as having pathological cirrhosis vs. non-cirrhosis, and post-chemotherapy vs. non-chemotherapy.

**Material and methods**

**Patient characteristics and underlying liver disease**

Patient characteristics are listed in Table 1. Between August 2010 and December 2016, 30 patients underwent preoperative PTPE. Ten of them were excluded because data on either contrast-enhanced computed tomography (CECT) or Tc-99m GSA scintigraphy were missing, and therefore 20 patients (14 men and six women, median age: 72 years, range 42-78 years) were selected as subjects for the present study. Six patients were diagnosed as having pathological cirrhosis and fibrotic grade.
hepatocellular carcinoma (HCC), six were diagnosed as having cholangiocarcinoma, and eight were diagnosed as having metastases from colorectal cancer (MT). Five out of six MT patients underwent systemic chemotherapy before PTPE.

Interventional radiology devices and embolic agents

A 6-Fr long sheath and a J-curved and loop-shaped 5.5-Fr balloon catheter (Selecon MP catheter II, Terumo, Tokyo, Japan) were used in every procedure (Figure 1). Absolute ethanol (Absolute Ethanol™, FUSO Pharmaceutical Industries, Ltd., Osaka, Japan) was used as an embolic material in all cases and was also used for the ethanol-lipiodol mixture, which contained 2 ml of ethiodised oil (Lipiodol™, Guerbet Japan, Tokyo, Japan) and 8 ml of ethanol. The maximum dose of ethanol was decided to be less than 0.2 ml/kg of body weight, which was considered a safe dose. Gelatine sponges (GS, Serescue™ Nippon Kayaku Co., Ltd., Tokyo, Japan) were used for approach tract embolisation.

PTPE procedure

A routine method by which we perform embolisation of the portal vein branch of the right hepatic lobe is described below, which is similar to the PTPE outline using absolute ethanol reported by Satake et al. [11]. In all cases, the percutaneous transhepatic and ipsilateral approach was used. The portal vein of segment no. 5 (P5) or P6 was usually punctured with a 21-G needle under ultrasound guidance. A 6-Fr long sheath and a 5.5-Fr loop-shaped balloon catheter was coaxially inserted and advanced to the main trunk of the portal vein. Digital subtraction angiography (DSA) was performed, and whole portal vein images were confirmed (Figure 2A). A loop was made at the tip of the balloon catheter within the splenic vein. The tip of the catheter was inserted into the anterior branch of the portal vein and the balloon was inflated at the beginning of the anterior branch. Selective DSA was performed from this point (Figure 2B), which was also a test injection. The ethanol and lipiodol mixture was carefully and slowly injected to avoid backflow, particularly back into the left portal branch (Figure 2C). The dose of the embolic material was set at approximately the same as that of the test injection. Next, a 10-minute wait was necessary, until the endothelium of the portal vein became damaged and an embolic effect appeared. The balloon catheter was removed, DSA was performed from the sheath, and we confirmed that the embolised anterior branch of the portal vein was not displayed on the image. Next, the other J-curved balloon catheter was inserted into the portal vein trunk, and the tip of the balloon was placed on the beginning of the posterior branch as distally as possible because this makes portal vein reconstruction easier for the surgeon during hepatectomy. Selective DSA (test injection) was performed during balloon occlusion (Figure 2D). The ethanol-lipiodol mixture was injected from the sheath at the same dose as the test injection (Figure 2E). Finally, access tract embolisation was necessary to prevent bleeding from the puncture site (Figure 3). A GS was cut into equal-sized thin strips, which were rounded into a cylindrical shape (Figure 3C). A second sheath was prepared and cut at approximately 5 cm intervals (Figure 3D), and the cylindrical shaped GS was put into the cylindrical cut sheath. The cut sheath within the GS was inserted from behind of the first sheath, and the GS was pushed into the tract by the inner cylinder with a guidewire from behind the first sheath, and the tract was packed with GS in the form of a mould (Figure 3E).

Parameters and evaluation items

Before and approximately three weeks after PTPE, CECT and Tc-99m GSA scintigraphy were performed. The RLV and the RLU15 were used as the main parameter. CT volumetry, including RLV, was calculated by Synapse Vincent (Fujifilm Holdings Corporation, Tokyo, Japan). Liver uptake at 15 minutes (LU15) is the ratio of cumulative liver uptake from 15 to 16 minutes after GSA administration divided by the total GSA dose, and its formula is as below [9].

\[
LU15 = \frac{\int_{15}^{16} C(t) \, dt}{\text{total injected dose}} \times 100 \%
\]

C(t) is the time-activity curves in which the region of interest is set in the liver in a continuous image taken from the anterior surface. RLU15 is the value obtained by multiplying LU15 by the residual count ratio calculated from single-photon emission computed tomography.
When evaluating residual liver function before hepatectomy, the desirable RLU15 value is reported to be more than 13 [10].

As the primary endpoint, RLV, RLU15, the fold change in RLV (ΔRLV), the fold change in RLU15 (ΔRLU15), and correlation between ΔRLV and ΔRLU15 were obtained. ΔRLV and ΔRLU15 were calculated as follows:

\[
\Delta RLV = \frac{\text{after RLV}}{\text{before RLV}} \quad \Delta RLU15 = \frac{\text{after RLU15}}{\text{before RLU15}}
\]

The samples of 16 patients who underwent radical hepatectomy were histopathologically evaluated. The liver cirrhosis group was defined as cases of fibrosis grade (F) 3 or F4 pathologically diagnosed according to the classification reported by Desmet et al. [12].

Sinusoidal obstructive syndrome (SOS) and chemotherapy-associated steatohepatitis (CASH) are well-known hepatic impairments caused by systemic chemotherapy for colorectal cancer, and they were evaluated...
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Based on the scores reported by Rubbia-Brandt et al. [13]. ΔRLV and ΔRLU15 were compared between the two groups, i.e. the cirrhosis group (n = 3) vs. the non-cirrhosis group (n = 13), and the chemotherapy group (n = 5) vs. the non-chemotherapy group (n = 15).

As a secondary endpoint, % future remnant liver (FRL) change rates (increase %FRL) were calculated using the following formulas:

\[
\%\text{FRL} = \frac{\text{FRLV} - \text{future remnant liver volume}}{\text{TLV} - \text{total liver volume}} \times 100%
\]

\[
\Delta\%\text{FRL} = \frac{\text{after } \%\text{FRL} - \text{before } \%\text{FRL}}{\text{before } \%\text{FRL}}
\]

(FRLV – future remnant liver volume; TLV – total liver volume; TV – tumour volume)

Adverse events were evaluated using CTCAE v4.0 software.

**Statistical analysis**

Ratios were expressed as means and standard deviations. For the differences in increases in RLV and RLU15 before and after PTPE, Student's t-test was used. For two-group
In comparisons, Wilcoxon’s rank sum test was used. A p-value less than 0.05 was considered to indicate a significant difference between two groups.

Results

The median amount of ethanol used was 7.5 (3.67–10.0) ml. The embolic areas were the right lobe in 16 patients and the three segments in four patients. Of these four patients, three were embolised in the left lobe and anterior segment, and one was embolised in the right lobe and segment 4. The median intervals from PTPE to CECT, to Tc-99m GSA scintigraphy, and to surgery were 21 (7–52) days, 21 (13–48) days, and 31 (20–56) days, respectively. Radical resection was performed in 16 patients (curative hepatectomy rate: 80%), and these patients were pathologically evaluated. In the other four patients (nos. 15, 17, 18, and 19), hepatectomy was not performed because the progression of the original disease was seen (Table 2).

Primary endpoint

Total liver volume before and after PTPE were 1304 ± 278 ml and 1249 ± 254 ml, respectively, and no significant difference was seen (p = 0.53). A significant increase was observed in the RLV (464 ± 99 ml and 573 ± 118 ml, p = 0.004, Figure 4) before and after PTPE. ARLV in all cases was 1.25 ± 0.15. Total liver LU15 before and after PTPE were 28.8 ± 4.9% and 27.3 ± 4.9%, respectively, which indicated no significant difference (p = 0.35). The RLU 15 before and after PTPE were 11.0 ± 2.9% and 17.7 ± 3.8%, respectively, with a significant increase (p = 5 × 10^-7, Figure 4). ARLU15 in all cases was 1.66 ± 0.33. No significant correlation was observed in either RLV or RLU15 before and after PTPE (r = 0.14, p = 0.66, Figure 5A), although both RLV and RLU15 were significantly increased. Outliers were patients nos. 3, 9, and 16, and after these patients were excluded, the correlation coefficient increased to 0.76 (p = 0.005, Figure 5B). The results

Table 2. Morphological and functional parameters obtained from PTPE, PTPE complications, and follow-up

| Patient no. | Before PTPE | After PTPE | ∆RLV | Before PTPE | After PTPE | ∆RLU15 | Complications | Radical resection* | Reason that radical resection could not be performed |
|-------------|-------------|-----------|------|-------------|-----------|--------|---------------|-------------------|---------------------|
| 1           | 418         | 516       | 1.23 | 8.5         | 14.2      | 1.67   | —             | Yes               | —                   |
| 2           | 501         | 598       | 1.19 | 9.8         | 17.6      | 1.80   | —             | Yes               | —                   |
| 3           | 378         | 360       | 0.95 | 5.9         | 11.4      | 1.93   | —             | Yes               | —                   |
| 4           | 541         | 693       | 1.28 | 11.0        | 19.4      | 1.76   | —             | Yes               | —                   |
| 5           | 459         | 562       | 1.22 | 4.3         | 7.6       | 1.77   | —             | Yes               | —                   |
| 6           | 481         | 675       | 1.40 | 10.6        | 16.8      | 1.58   | —             | Yes               | —                   |
| 7           | 519         | 625       | 1.20 | 16.5        | 22.9      | 1.39   | —             | Yes               | —                   |
| 8           | 313         | 470       | 1.50 | 7.5         | 18.0      | 2.40   | —             | Yes               | —                   |
| 9           | 553         | 633       | 1.14 | 10.3        | 22.9      | 2.22   | —             | Yes               | —                   |
| 10          | 558         | 748       | 1.36 | 10.9        | 17.2      | 1.58   | ALT and AST elevation (grade 4) | Yes               | —                   |
| 11          | 612         | 637       | 1.04 | 13.6        | 17.3      | 1.27   | —             | Yes               | —                   |
| 12          | 687         | 845       | 1.23 | 10.3        | 18.6      | 1.61   | —             | Yes               | —                   |
| 13          | 495         | 616       | 1.24 | 11.0        | 22.0      | 1.69   | —             | Yes               | —                   |
| 14          | 445         | 609       | 1.37 | 12.2        | 22.0      | 1.80   | —             | No Multiple dissemination | —                   |
| 15          | 406         | 484       | 1.19 | 13.0        | 16.7      | 1.28   | —             | Yes               | —                   |
| 16          | 391         | 592       | 1.51 | 14.7        | 15.0      | 1.02   | Cholangitis (grade 3) | No Tumour progression | —                   |
| 17          | 509         | 492       | 0.97 | 12.7        | 15.2      | 1.20   | —             | No Tumour progression | —                   |
| 18          | 358         | 456       | 1.27 | 14.8        | 21.9      | 1.48   | —             | No Tumour progression | —                   |
| 19          | 297         | 411       | 1.38 | 10.1        | 18.8      | 1.86   | —             | Yes               | —                   |
| 20          | 348         | 437       | 1.26 | 11.9        | 23.9      | 1.93   | —             | Yes               | —                   |
| Mean        | 464 ± 99    | 573 ± 118 | 1.25 ± 0.15 | 11.0 ± 2.9 | 17.7 ± 3.8 | 1.66 ± 0.33 | —             | —                   | —                   |

PTPE – percutaneous transhepatic portal vein embolisation; RLV – residual liver volume; RLU15 – residual liver uptake at 15 minutes
of these three outliers are shown in Table 3. In patients nos. 3 and 9 there was a minimal increase in RLV and a large increase in RLU15, and these two patients were able to undergo radical hepatectomy after PTPE. Patient no. 16 showed a large increase in RLV and a small increase in RLU15, and radical hepatectomy could not be completed because of tumour progression. The outcomes of the two-group comparisons are listed in Table 4. Pathological cirrhosis was observed in patients nos. 5, 7, and 14 (Figure 6A), and the other 13 patients, including those with
Table 4. Outcomes of patients with cirrhotic liver vs. non-cirrhotic liver and patients undergoing systemic chemotherapy vs. no systemic chemotherapy before PTPE

|                | Cirrhotic (3) vs. non-cirrhotic (13) | p-value | Chemo (5) vs. no chemo (15) | p-value |
|----------------|-------------------------------------|---------|-----------------------------|---------|
| ΔRLV           | 1.28 vs. 1.22                       | 0.12    | 1.26 vs. 1.23               | 0.76    |
| ΔRLU15         | 1.69 vs. 1.77                       | 0.59    | 1.58 vs. 1.69               | 0.97    |

HCC, had no obvious fibrosis. There were no significant differences between cirrhotic and non-cirrhotic groups regarding both ΔRLV (1.28 vs. 1.22, \( p = 0.12 \)) and ΔRLU15 (1.69 vs. 1.77, \( p = 0.59 \)). Five patients (nos. 7, 8, 10, 11, and 20) underwent two to six courses of systemic chemotherapy before PTPE. Oxaliplatin-based chemotherapy was performed in these five patients. Only one patient (no. 8) switched to irinotecan-based chemotherapy because of an allergy to oxaliplatin (Table 1). No significant differences were observed between chemotherapy and non-chemotherapy groups in both ΔRLV (1.26 vs. 1.23, \( p = 0.76 \)) and ΔRLU15 (1.58 vs. 1.69, \( p = 0.97 \)).

**Secondary endpoint**

The % FRL increase was 34.4 ± 25.2%. At the time of injection of ethanol, local abdominal pain was recognised in all patients; however, it was under self-control by the administration of analgesics. Major adverse events are listed in Table 2. Grade 3 cholangitis, which requires endoscopic retrograde biliary drainage (ERBD), was found in one patient. Grade 4 alanine aminotransferase (ALT) and aspartate transaminase (AST) elevation were observed in one patient, grade 3 ALT elevation in 10 patients, grade 3 AST elevation in seven patients, grade 3 bilirubin elevation in one patient, and grade 3 thrombocytopenia in one patient; however, these symptoms were adequately treated by conservative treatments. Regarding postembolic syndromes, grade 1 fever was observed in five patients, grade 2 nausea in five patients, and grade 1 vomiting in one patient.

**Discussion**

Some studies have compared morphological RLV with residual liver function (RLF), which is another radionu-
clide parameter that is different from RLU15 obtained from Tc-99m GSA scintigraphy, before and after PTPE [7,8,14]. The fold change in RLV and RLF were 1.28 to 1.32 and 1.63 to 1.7, respectively, and generally, the increase in the rate of change in RLF is known to be much greater than that of RLV [3,6,8,15]. In the present study, the fold changes in RLV and RLU15 were 1.25 ± 0.15 and 1.66 ± 0.33, respectively, which is equivalent to those of previous reports. No correlation was seen between the fold change in RLV and RLU15 in all patients. Kono et al. reported that no correlation was observed between morphological RLV and residual liver R max (a radionuclide parameter) before and after PTPE in all patients (r = 0.105, p = 0.803) [8]. A good correlation between these parameters was observed when the patients were narrowed down to the good response group that showed a large increase in R max (r = 0.826, p = 0.037). Nanashima et al. found a good correlation between CT volumetry before PTPE and RI volumetry (r = 0.69); however, a very weak correlation was found between CT volumetry and RI volumetry after PTPE (r = 0.03) [15]. From these previous reports, it is suggested that although PTPE increases both RLV and RLF, these parameters may not be simply well correlated. Therefore, it is clinically important and desirable to analyse both parameters for more accurate evaluation of liver function. We divided the outliers into two types. Type A, comprising two of the three outliers, showed a small increase in RLV but a large increase in RLU15 (Table 3A). Type B, comprising one of the three outliers, showed a large increase in RLV but a small increase in RLU15 (Table 3B). Compared with morphological RLV, RLF values obtained from GSA scintigraphy are known to be better correlated with postoperative albumin level [15], prothrombin time [10], total bilirubin [10,15], preoperative indocyanine green retention rate at 15 min (ICGR 15) [9,10], and postoperative indocyanine green [6,15]. Therefore, in patients of type A, even if only a small increase in RLV is observed, a large increase in RLU15 is likely to indicate sufficient regeneration of the residual liver. As a result, we were able to perform surgery on all type A patients. On the other hand, in type B, two hypotheses were clinically inferred. The first hypothesis was that the underlying liver disease was much worse, and liver regeneration might take a comparatively long time. The remnant liver is known to continue to undergo hypertrophy after PTPE and postoperatively [3,15]. The second hypothesis was that there was rapid progression of the present liver disease and that regeneration itself was poor. In the case of patient no. 16, the latter hypothesis was thought to be true because progression of the present disease was found during surgery and hence curative operation was not performed. Many studies have reported that sufficient RLV and RLF increases in patients with liver cirrhosis may not be observed after PTPE [3,16-19]. In the present study, the fold change in RLV appeared to be good (1.28), but the RLU15 remained at 1.69. In the case of cirrhotic patients, Kono et al. speculated that an increase in RLV reflects not an increase in the number of functional hepatocytes but instead an increase in the interstitial area [8]. This hypothesis suggests that in patients with liver cirrhosis, even if a good increase in RLV is observed, careful evaluation is required. To our knowledge, there are few studies comparing RLF in post-chemotherapy and non-chemotherapy groups before and after PTPE. Patients undergoing systemic chemotherapy after PTPE did not show a significant decrease in the rate of increase in RLV compared with the non-chemotherapy group [17,20,21]. On the other hand, de Baere et al. found that the rate of increase in RLV significantly decreased in the patient group, using the platinum formulation [22]. Narita et al. reported that the rate of increase in RLV significantly decreased in the SOS group (16.8 ± 24.0 vs. 55.6 ± 32.5, p < 0.001) [23]. The median number of chemotherapy cycles was 10 (range, 2-44), and the grades of SOS were mild in five patients, moderate in four patients, and severe in two patients. Ninety percent of the patients with SOS received more than six cycles of chemotherapy and/or underwent oxaliplatin-based chemotherapy. In the present study, the chemotherapy group had equivalent outcomes in both RLV and RLU15 compared with the non-chemotherapy group, and consequently, curative hepatectomy was performed. Five cases in the chemotherapy group were pathologically evaluated, as follows: Moderate SOS was found in patients nos. 11 and 20, mild SOS in patient no. 8, moderate CASH was seen in patient no. 10, and mild CASH was seen in patient no. 7. No severe cases of both SOS and CASH were observed. An insufficient increase in RLU15 was observed only in patient no. 11. Thus, for up to six cycles of chemotherapy, it seems that systemic chemotherapy before PTPE might not affect increases in RLV and RLU15.

According to a systematic review of PTPE, % FRL was used for calculating the hypertrophy response of residual liver in 68.2% of reported studies [17]. The average and width of % FRL volume increase were used in 37.9 ± 0.1% and 20.5% to 69.4%, respectively, Sakuhara et al. reported that, in a study of 143 patients who underwent PTPE using ethanol, the % FRL volume increase and resection rate were 33.6% and 84%, respectively [24]. In the present study, the % FRL volume increase and resection rate were 34.4 ± 25.2% and 80%, respectively, using ethanol, the % FRL volume increase and resection rate were 33.6% and 84%, respectively [24]. In the present study, the % FRL volume increase and resection rate were 34.4 ± 25.2% and 80%, respectively, which were similar to the previous study. The rate of PTPE complications was reported as 2.2% to 15% [25-27]. As a mild complication that is specific to the use of ethanol, pain at the time of injection may be reported. However, in our present study, most cases of pain were relieved within a few minutes with or without analgesics, similarly to a previous publication [24]. Pneumothorax, cholangitis, PVT, etc. were reported as major complications [25-27]. Rare but fatal cases of pulmonary embolism and cholangitis after PTPE have been reported [28]. In the present study, patient no. 16 had cholangitis on day 12 after PTPE, and although ERPB had been performed 14 days before PTPE, it was...
performed again. Radical hepatectomy was attempted after two months; however, the tumour was unresectable due to tumour progression. A serious complication after PTPE was only observed in this patient.

**Limitations**

This study has several limitations. Firstly, it is a retrospective study with only a few patients. All pathological specimens were obtained after surgery, and therefore they were affected by both PTPE and surgery. As hypertrophy of the residual liver continues even after hepatectomy, the final postoperative residual liver function was not evaluated. The outcomes after hepatectomy appear to most greatly affect the patients’ prognosis; however, the success rate of the operation depends not only on residual liver function but also on operation time, amount of bleeding, and whether or not vascular reconstruction was performed. In the present study, the effect of pure PTPE was evaluated.

**Conclusions**

No correlation was found between rates of changes in RLV and RLU15 both before and after PTPE. Outliers in which RLU15 increased despite a small increase in RLV suggested that these may be cases in which to consider surgery. Severe liver injury did not occur upon systemic chemotherapy for up to six cycles, and the effects of PTPE were similar to those in patients with liver cancer, who did not receive chemotherapy.

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**Conflict of interest**

The authors report no conflict of interest.

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