Sclerotherapy of simple hepatic cysts by repeated aspiration and alcohol instillation

Feng YAN-HONG, Qian LIN-XUE, Gong HAI-MA, Zhang QING, Gui YU, Hu XIANGDONG

Capital Medical University, Beijing Friendship Hospital, Beijing, P.R. China

Background/aims: The efficacy and safety of traditional alcohol sclerotherapy procedures are controversial in the management of large simple hepatic cysts. In this study, we aimed to develop and evaluate a novel alcohol sclerotherapy procedure, termed repeated aspiration and alcohol instillation sclerotherapy, for the treatment of simple hepatic cysts. Materials and Methods: A prospective, double-blind, randomized study was performed. Sixty-seven patients with large simple hepatic cysts were randomized into two groups to receive either single-session alcohol retention sclerotherapy (alcohol was instilled into the cyst cavity, kept for 20 minutes and aspirated) or repeated aspiration and alcohol instillation sclerotherapy (instillation of 30-70 ml of alcohol and immediate aspiration with repetition 3 to 6 times until the estimated alcohol concentration exceeded 80%). The cyst volume reduction was calculated to compare the efficacy of the two procedures. We evaluated the safety of the procedure by monitoring side effects and assessing blood alcohol concentrations at 0, 0.5, 1, 2 and 3 hours after sclerotherapy. Results: The cyst volume reduction in patients undergoing repeated aspiration and alcohol instillation sclerotherapy was significantly higher than that in those receiving alcohol-retention sclerotherapy. The concentration of alcohol in the last aspirated cyst fluid was correlated with the mean volume reduction in patients undergoing repeated aspiration and alcohol instillation sclerotherapy but not in the alcohol-retention group. Only minor side effects occurred in both groups. Although elevated blood alcohol concentration was noted in all patients, it declined to normal levels within 2-3 hours after treatment. There were no significant differences in blood alcohol concentration between the two groups. Conclusions: Repeated aspiration and alcohol instillation sclerotherapy is superior to single-session alcohol-retention sclerotherapy in the management of large simple hepatic cysts.

Key words: Hepatic cyst, sclerotherapy, alcohol, retention, instillation

Basit hepatik kistlerin tekrarlaylan aspirasyon ve alkol enjeksiyonu ile tedavisi

Amaç: Büyük basit hepatik kistlerin tedavisinde geleneksel alkollü skleroterapisinin etkinliği ve güvenilirliği tartışmalıdır. Bu çalışmada, basit hepatik kistlerin tedavisinde, tekrarlayan aspirasyon ve alkol enjeksiyonu (alcohol kaviteye enjekte edildikten 20 dakika sonra tek seferde aspirasyon uygulanır) ve tekrarlayan aspirasyon ve alkol enjeksiyonu (kist içindeki hesaplanan alkol konsantrasyonunun %80'e ulaşıp kadar kaviteye 30-70 ml alkol enjeksiyonu ve hemen sonda sivi kaviteye enjekte edildikten sonra 2-3 saat boyunca beklenmesi ile tekrarlanır) olarak iki gruba ayrılır. Büyük basit hepatik kist olan 67 hasta tek seferlik aspirasyon-alkol enjeksiyonu (alcohol kaviteye enjekte edildikten sonra 20 dakika sonra tek seferde aspirasyon uygulanır) ve tekrarlayan aspirasyon ve alkol enjeksiyonu (kist içindeki hesaplanan alkol konsantrasyonunun %80'e ulaşıp kadar kaviteye 30-70 ml alkol enjeksiyonu ve hemen sonda sivi kaviteye enjekte edildikten sonra 2-3 saat boyunca beklenmesi ile tekrarlanır) olarak iki gruba ayrılır. Büyük basit hepatik kistlerin tedavisinde, tekrarlayan aspirasyon ve alkol enjeksiyonu ve tek seferlik aspirasyon ve alkol enjeksiyonu prosedürünün geliştirilmesi amaçlanmıştır. 

Gereç ve Yöntem: Araştırma prospektif, çift kör, randomize olarak düzenlenebilir. Büyük basit hepatik kisti olan 67 hasta tek seferlik aspirasyon-alkol enjeksiyonu (alcohol kaviteye enjekte edildikten 20 dakika sonra tek seferde aspirasyon uygulanır) ve tekrarlayan aspirasyon ve alkol enjeksiyonu (instillation of 30-70 ml of alcohol and immediate aspiration with repetition 3 to 6 times until the estimated alcohol concentration exceeded 80%) olarak iki gruba ayrılır. Büyük basit hepatik kisti olan 67 hasta tek seferlik aspirasyon-alkol enjeksiyonu (alcohol kaviteye enjekte edildikten sonra 20 dakika sonra tek seferde aspirasyon uygulanır) ve tekrarlayan aspirasyon ve alkol enjeksiyonu olarak iki gruba ayrılır. Kist hacmindeki küçülme yöntemler arasında etkinliği karşılaştırılır. 

Bulgular: Tek seferlik aspirasyon ve alkol enjeksiyonu grubunda Aspirasyon-alkol enjeksiyonu grubunda sonra aspirasyon sistemi ile 2-3 saat içinde normal değerlerde dönüştü. Kan alkol düzeyinde artışı schlerotherapinin etkinliği ve güvenilirliği tartışlardır. Bu çalışmada, basit hepatik kistlerin tedavisinde, tekrarlayan aspirasyon ve alkol enjeksiyonu (alcohol kaviteye enjekte edildikten sonra 20 dakika sonra tek seferde aspirasyon uygulanır) ve tekrarlayan aspirasyon ve alkol enjeksiyonu (instillation of 30-70 ml of alcohol and immediate aspiration with repetition 3 to 6 times until the estimated alcohol concentration exceeded 80%) olarak iki gruba ayrılır. Büyük basit hepatik kistlerin tedavisinde, tekrarlayan aspirasyon ve alkol enjeksiyonu ve tek seferlik aspirasyon ve alkol enjeksiyonu prosedürünün geliştirilmesi amaçlanmıştır. 

Key words: Hepatic cyst, sclerotherapy, alcohol, retention, instillation

Anahtar kelimeler: Hepatik kist, skleroterapi, alkol, retansiyon, enjeksiyon
INTRODUCTION

Hepatic cysts are common benign hepatic lesions, with a prevalence of 2.5%-7% in the general population (1). Simple hepatic cysts (SHCs) are congenital, arise from aberrant bile duct development (2), and may present as either solitary or multiple lesions. Although the vast majority of SHCs are asymptomatic and require no treatment, they can become large and cause symptoms such as pain, jaundice, nausea, vomiting, and early satiety in rare cases (3). When SHCs become symptomatic or when associated with complications, treatment is often required.

A diverse range of therapies are available for SHC patients with varying clinical outcomes (4-7), including percutaneous drainage, percutaneous drainage in combination with sclerotherapy, open and laparoscopic cyst de-roofing, cyst enucleation, cystojejunostomy, cystectomy, hepatic resection, and liver transplantation. Open surgery provides satisfactory long-term outcomes, but carries a high intraoperative risk (5). Laparoscopic approaches are less invasive than open surgery, but are not usually as effective in terms of recurrence and morbidity rate (3,4). Simple percutaneous aspiration is also minimally invasive but is associated with a high recurrence rate (8). In contrast, percutaneous aspiration demonstrates promising results when it is used in combination with sclerotherapy, offering a valuable alternative to surgical intervention (9,10).

Alcohol sclerotherapy was first described in 1985 by Bean and Rodan (11), who treated six patients with hepatic cysts by percutaneous aspiration and direct injection of 25% replacement volume of 95% alcohol. Alcohol can fix and eliminate the cells lining the cyst cavity in a short period (1-3 minutes [min]), reducing their ability to secrete fluid and thereby controlling cyst growth (11). However, septations, interstices, and debris or clots within the cysts may prevent full destruction of cyst epithelia (10). In addition, because of incomplete aspiration of cyst fluid, the residual cyst fluid markedly dilutes the alcohol concentration, thus affecting its therapeutic efficacy (11). Therefore, there are increasing efforts to improve the outcome of alcohol sclerotherapy, including modulating ethanol concentration and volume, duration of ethanol exposure, and number of sclerotherapy sessions (12-16). For instance, insufficient alcohol concentration, volume, or short contact time with the cyst epithelia tends to result in a high recurrence rate (17), whereas an increased amount of alcohol or a longer exposure period may pose a higher risk of host toxicity (14). We hypothesized that rapid elevation of alcohol to a sufficiently high concentration in a short period may result in a safer and more efficient sclerotherapy procedure with better outcomes. Accordingly, we developed a novel sclerotherapy procedure using repeated aspiration and instillation of high-concentrated alcohol (99%) to treat SHCs. The aim of this study was to demonstrate the efficacy and safety of this novel procedure in the management of large (≥8 cm) SHCs compared to single-session alcohol-retention sclerotherapy.

MATERIALS AND METHODS

Patients

We conducted a prospective, double-blind, randomized study. The study protocol was approved by the Medical Ethics Committee of Beijing Friendship Hospital (Beijing, China). Written informed consent was obtained from each of the patients upon enrollment. A total of 67 patients with simple, symptomatic, hepatic cysts were included. There were 27 men and 40 women, aged 41-87 years (average, 61.8). All patients were diagnosed using ultrasound and computed tomography (CT) to have a simple cyst of ≥8 cm in diameter. Major complaints included upper abdominal discomfort (n=26), abdominal distension (n=18), and jaundice (n=5). One patient showed elevated direct bilirubin, and two patients had elevated alanine aminotransferase. The remaining patients had normal electrocardiographic results, blood coagulation and liver function tests. All patients underwent a 64-row CT scan to precisely measure initial cyst volume. The initial diameters of the cysts ranged from 8.0 to 13.5 cm (mean, 9.24±1.29 cm), and the volumes ranged from 254.86 to 1251.99 ml (mean, 429.25±205.23 ml). The 67 patients were randomized into two groups: a single-session alcohol retention sclerotherapy group (n=33) or repeated aspiration and alcohol instillation sclerotherapy group (RAAIS, n=34).

Sclerotherapy Procedures

The single-session alcohol sclerotherapy was performed as described by Bean and Rodan (11). Briefly, a cyst puncture was performed using an 18- to 21-gauge fine needle under ultrasound guidance after routine antiseptic preparation and local anesthesia. Then, a 6- to 8-French pigtail catheter
was placed and as much cystic fluid as possible was aspirated. After 10-15 ml of 1% lidocaine was infused, 99% ethanol was instilled. The amount of ethanol injected was approximately 20-30% of the volume of the aspirated cyst fluid but never exceeded 100 ml. The alcohol was kept in place for 20 min and then withdrawn. After completion of sclerotherapy, the catheter was removed and the skin was bandaged.

For RAAIS, the same procedure was performed as above. Based on initial cyst volume and the volume of aspirated cyst fluid, the volume of residual cyst fluid was estimated, which varied from 30 to 50 ml. Then 30-70 ml of alcohol was instilled. Immediately following alcohol instillation, an equal volume of cystic fluid was aspirated. Depending on cyst size, this process was repeated 3 to 6 times. Based on the volume of the initial cyst, aspirated fluid, and alcohol instilled, we estimated the concentration of alcohol in the aspirated cyst fluid. The process was continued until the estimated alcohol concentration exceeded 80%. Finally, all retrievable cystic fluid was drawn and the catheter was removed.

**Measurements and Follow-Up**

The last portion of aspirated cystic fluid from patients undergoing RAAIS was analyzed for alcohol concentration. Blood alcohol concentrations (BACs) were assayed at 0, 0.5, 1, 2, and 3 hours (h) after sclerotherapy. All patients were continuously monitored for 24 h after sclerotherapy. If there was no obvious discomfort, the patient was discharged from the hospital. Routine follow-up included liver function tests, ultrasound examination, and CT scan at 1, 3, 6, 12, and 24 months after the initial sclerotherapy. Final cyst volume was calculated to evaluate the therapeutic efficacy of the two procedures.

**Statistical Analysis**

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 11.5 software package. Numerical data were expressed as mean±standard deviation (SD). Inter-group differences were compared by the Mann-Whitney U test. Linear regression analysis was performed to determine the correlation between the concentration of alcohol in the last aspirated cyst fluid and the mean cyst volume reduction proportion after sclerotherapy. A p value of <0.05 was considered statistically significant.

**RESULTS**

The mean values of the initial volume of cysts, volume of aspirated cyst fluid, volume of injected alcohol, follow-up duration, final volume of cysts, and cyst volume reduction proportion are shown in Table 1. There were no significant differences in the mean initial cyst volumes or aspirated cyst fluid and the mean follow-up duration between the alcohol-retention group and the repeated rapid aspiration/instillation group (all p>0.05). However, significant differences were observed in the mean volume of injected alcohol and final volume of cysts between the two groups (both p<0.05). The mean cyst volume reduction proportion in patients after RAAIS was significantly higher than that in patients undergoing alcohol-retention sclerotherapy (p<0.05). The cyst disappeared completely in 3 patients in the alcohol-retention group and in 6 patients in the repeated rapid aspiration/instillation group. Representative CT images of 2 patients treated using RAAIS are shown in Figures 1 and 2. Patients with normal liver function before sclerotherapy had no obvious changes after treatment. Patients with elevated direct bilirubin or alanine aminotransferase recovered to normal levels after sclerotherapy. Symptom relief (abdominal discomfort, abdominal distension, and jaundice) was achieved in 17 of 21 patients undergoing single-session alcohol retention sclerotherapy and in 21 of 23 patients undergoing RAAIS. Although

### Table 1. Comparison of the treatment outcomes between the alcohol-retention group and the RAAIS group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alcohol-retention group (n = 33)</th>
<th>RAAIS group (n = 34)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial volume of cysts (ml)</td>
<td>466.25±256.76</td>
<td>393.33±132.71</td>
<td>0.821</td>
</tr>
<tr>
<td>Volume of aspirated cyst fluid (ml)</td>
<td>389.09±291.96</td>
<td>325.06±112.83</td>
<td>0.518</td>
</tr>
<tr>
<td>Volume of injected alcohol (ml)</td>
<td>86.97±9.51</td>
<td>179.12±64.36</td>
<td>0.000</td>
</tr>
<tr>
<td>Final volume of cysts (ml)</td>
<td>22.19±36.78</td>
<td>2.43±7.33</td>
<td>0.016</td>
</tr>
<tr>
<td>Cyst reduction rate (%)</td>
<td>93.64±11.76</td>
<td>98.90±18.3</td>
<td>0.043</td>
</tr>
<tr>
<td>Follow-up duration (months)</td>
<td>30.36±4.48</td>
<td>29.56±4.05</td>
<td>0.668</td>
</tr>
</tbody>
</table>

Note: Data are expressed as mean ± SD; *Mann-Whitney test
the percentage of patients achieving symptom relief was higher in the repeated rapid aspiration/instillation group than in the alcohol-retention group, there was no statistical difference in this percentage between the two groups (91.3% vs. 80.9%, p>0.05).

The concentrations of alcohol in the last aspirated cyst fluid ranged from 26.67% to 86.25% (mean, 50.81%±13.49%) in the alcohol-retention group and from 78.73% to 99.62% (mean, 95.47%±4.52%) in the RAAIS group. Linear regression analysis showed that the concentration of alcohol in the last aspirated cystic fluid was not correlated with mean cyst volume reduction proportion in the alcohol-retention group (p>0.05). In contrast, a significant positive correlation was found in the RAAIS group (r = 0.847; p<0.01).

No deaths or major complications were encountered after alcohol-retention sclerotherapy or RAAIS. Symptoms and signs of drunkenness occurred in 16 patients in the alcohol-retention group, of which 12 complained of headaches, 9 showed flushing, and 3 had nausea. Symptoms and signs of drunkenness were noted in 18 patients undergoing the RAAIS procedure, of which 15 complained of headaches, 12 showed flushing, and 2 had nausea. All symptoms and signs of drunkenness disappeared after sclerotherapy. There was
no significant difference in the incidence of complications between the two groups (p>0.05).

BAC was elevated in every patient regardless of the type of procedure. The dynamic changes in mean BACs after alcohol sclerotherapy are shown in Figure 3. No significant differences were noted in mean BAC at all time points between the two groups (all p>0.05). The BACs in individual patients ranged from 0 to 57.48 mg/dl in the alcohol-retention group and from 0 to 73.19 mg/dl in the RAAIS group. In both groups, the mean BAC peaked at 30 min and then began to decline. Three hours after the last sclerotherapy, mean BAC had declined to 4.02 ± 4.93 and 5.66 ± 5.37 mg/dl in the alcohol-retention group and the RAAIS group, respectively.

DISCUSSION

As the trend in the management of hepatic cysts continues to move towards minimally invasive approaches, alcohol sclerotherapy has been advocated as the first-line treatment for SHCs (18). Previous studies have suggested that multiple-session alcohol sclerotherapy can result in low recurrence rates, but it is associated with a higher risk of complications, whereas the single-session procedure is less risky but linked to a high recurrence rate (19). In the present study, by combining the advantages of multiple- and single-session alcohol sclerotherapy procedures, we developed the RAAIS procedure to treat large hepatic cysts and compared its efficacy and safety with that of the alcohol-retention procedure. Compared to traditional alcohol sclerotherapy procedures, this novel procedure had several characteristic features. First, a high alcohol concentration (99%) was used. Second, alcohol instillation was administered repeatedly. The repeat times depended on cyst size. Third, cyst aspiration was performed immediately after alcohol instillation. Repeated instillation of high concentrations of alcohol resulted in a rapid elevation of alcohol to a sufficiently high concentration within the cysts with a short duration of ethanol exposure, ensuring that alcohol sclerotherapy is both safe and efficient.

In earlier reports, various parameters, such as cyst disappearance, symptom relief, recurrence rate, and reduction in mean cyst diameter, were used to evaluate the efficacy of alcohol sclerotherapy for hepatic cysts, which makes it difficult to compare the efficacy of different sclerotherapy procedures. In recent years, researchers have compared mean cyst volume reduction proportion to evaluate the efficacy of alcohol sclerotherapy. In the present study, we showed that the mean cyst volume reduction proportion was significantly higher in patients undergoing RAAIS than in those undergoing alcohol-retention sclerotherapy (98.90% vs. 93.64%). Moreover, this value is higher or comparable to those reported by Zerem et al. (90.2%) (1), Larssen et al. (95%) (13) and Yang et al. (98.3%) (14). These data clearly indicate that the RAAIS procedure has better efficacy than alcohol-retention sclerotherapy in the management of large SHCs.

The present study also demonstrated that the concentration of alcohol in the last aspirated cystic fluid was positively correlated with mean proportion of cyst volume reduction in the RAAIS group. This observation provided indirect evidence for the existence of a large dilution effect of residual cystic fluid on alcohol and supported our initial hypothesis that RAAIS may improve efficacy by elevating the effective concentration of alcohol for sclerotherapy. In contrast, no significant correlation was noted in the alcohol-retention group. This may be due to the fact that the low alcohol concentration in the alcohol-retention procedure had low efficacy and could only kill a portion of cyst epithelial cells. As a result, cyst reduction proportion depends more on the individual cyst than the alcohol concentration used. However, the exact mechanisms contributing to such differences between the alcohol-retention procedure and the RAAIS procedure remain to be elucidated.

Most patients were symptom-free or only had mild symptoms at their last follow-up visit and requi-
red no additional therapy. Compatible with the observation that patients undergoing RAAIS had a higher mean cyst volume reduction proportion than those undergoing alcohol-retention sclerotherapy, the percentage of patients achieving symptom relief was higher in the repeated rapid aspiration/instillation group than in the alcohol-retention group. However, this difference was not statistically significant. Because symptoms associated with large hepatic cysts result from pressure effects, we surmise that a certain amount of decrease in cyst volume will result in symptom relief. Thus, it is not surprising to observe that the alcohol-retention procedure was comparable to the RAAIS procedure in relieving symptoms in patients with large hepatic cysts.

Previous reports have documented many complications associated with alcohol sclerotherapy, such as dizziness, nausea, headache, vomiting, flushing, deep sleep, and drops in blood pressure (14). In the present series, some symptoms and signs of drunkenness were also noted following the repeated rapid aspiration/instillation sclerotherapy. However, these complications were mild and disappeared spontaneously several hours after sclerotherapy. Kairaluoma et al. (9) first used BAC to evaluate the safety of alcohol sclerotherapy. They demonstrated that the highest BAC after alcohol-retention sclerotherapy was 102 mg/dl. Tikkakoski et al. (12) showed that the maximum BAC after single-session alcohol-retention sclerotherapy was also 102 mg/dl. Studies of Yang et al. (14) indicated that as much as 200 ml of alcohol was used in alcohol sclerotherapy, and the highest BACs ranged from 60 to 199 mg/dl in individual patients. Due to a larger amount of alcohol used and a longer exposure, the patients developed severe complications. In our series, the maximum BAC in patients undergoing RAAIS was approximately 18.92 mg/dl, slightly higher than that in patients undergoing alcohol-retention sclerotherapy, but significantly lower than values previously reported.

In conclusion, the RAAIS procedure has several advantages over the traditional single-session alcohol sclerotherapy procedures, showing a better efficacy and safety profile. Although RAAIS can cause some symptoms and signs of drunkenness, these complications are not severe and do not require special treatment. The elevated BAC induced by the procedure declines to normal levels within 2-3 h after sclerotherapy. As the procedure can be performed on an outpatient basis, hospital admission is not required. For these reasons, we recommend the repeated rapid aspiration and alcohol instillation procedure as the preferred therapeutic option in patients with large, symptomatic SHCs.

Acknowledgements: This work was supported by a grant (No: 2006-23) from the Scientific Foundation of Beijing Friendship Hospital. We thank Jing Zhao and other members of our team for technical assistance. We also thank Professor Chen-Hong Yin for enlightening discussions and Professor Su Shen for technical assistance.

REFERENCES