Safe and effective percutaneous ethanol injection therapy of 200 thyroid cysts

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Introduction. Ultrasound-guided percutaneous ethanol injection therapy (US-PEIT) is a minimally invasive procedure that may be performed as an alternative to surgery for the treatment of recurrent symptomatic thyroid cysts for which simple aspiration failed. The present study aimed at assessing US-PEIT in a large cohort of patients, identifying factors influencing treatment outcome.


Results. The initial median cyst volume was 8.5 mL [5.5-16.0]; median final volume at 12 months after the completion of therapy was 0.5 mL [0.2-1.3]. A Volume Reduction Rate (VRR) of 95.0% [86.7-98.0] was achieved. For successful US-PEIT, relatively small total amount of ethanol was needed, on average corresponding to 20.0% [16.7-28.6] of the initial cyst volume. VRR positively correlated with the initial cyst volume and negatively with the presence of complex cyst. Multiple regression analysis showed the presence of complex cyst as an independent predictor of treatment efficacy.

Conclusion. US-PEIT of thyroid cysts of all sizes was very successful with using total amounts of ethanol, corresponding to ≈20% of the initial cyst volume.

Key words: thyroid cyst, ultrasound-guided percutaneous ethanol injection therapy, volume reduction rate

INTRODUCTION

According to the 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, the prevalence of palpable nodules is 5% in females and 1% in males living in iodine-sufficient parts of the world. High-resolution ultrasound is able to detect thyroid nodules in 19-68% of a random population, with higher frequencies in females and the elderly. Cystic nodules develop due to hemorrhage or degenerative changes in originally solid nodules. Primary cysts are rare, accounting for approximately 1% of all cysts. Complex nodules with cystic component account for 15-37% of all operated nodules. Based on ultrasound scans, predominantly cystic nodules (complex cysts) are those with the cystic portion accounting for 50-90% of the volume and pure cysts are nodules with the cystic portion accounting for >90% of the nodule volume. Approximately 15-25% of nodules are predominantly cystic or cystic.

The indications for therapy are compressive symptoms or cosmetics complaints. After simple aspiration of the cystic cavity, recurrence is observed in up to 80% of cases, depending on the volume and contents. The standard treatment approach of recurrent cysts represents surgery, either total thyroidectomy or lobectomy. Alternatively, ultrasound-guided percutaneous ethanol injection therapy (US-PEIT) with 96-99% ethanol may be used. Ethanol causes coagulative necrosis in the cyst wall. Subsequently, reactive fibrosis and cyst shrinkage occurs. This method is suitable for patients with a large, solitary cyst or a dominant cyst in a multinodular goiter (other unsuspected nodules less than 1 cm). US-PEIT is performed in cystic lesions with the cystic portion accounting for >60% of the nodule volume.

US-PEIT is considered therapeutically successful if the cyst is reduced by >50% of its initial volume. In published cohorts, the success rate ranges from 68% to 100% (ref.6,8). After 20 years of experience, in 2010, the approach was approved as a full-fledged method in the Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules.

We aimed this study at assessing US-PEIT in a larger cohort (n=200) including large thyroid cysts and identifying factors influencing treatment outcome.

METHODS AND PATIENTS

All patients were provided with explanation of the procedure and signed informed consent forms approved by the University Hospital Olomouc Ethics Committee. The cohort comprised 193 patients (150 females and 43 males) with 200 thyroid cysts (seven female patient having 2 cysts) who were selected for US-PEIT between 2004 and 2018 and completed a follow-up of 12 months. US-PEIT was either performed in patients at increased surgical risk or those refusing surgery; all cysts were symptomatic or recurred after previous simple aspiration (1-4 times). In all
cases, cytology examination was carried out, with benign results being an inclusion criterion (pure cyst Bethesda I and complex cyst Bethesda II). All patients had normal baseline TSH and fT4 levels. The cohort excluded 28/228 patients, when simple aspiration was enough to treat the cyst and over 12 months no recurrence occurred.

For statistical analysis, the cohort was divided into subgroups based on the cyst volume and character of the cystic component. Three size groups were defined as follows: small cysts (3-10 mL; n=112), medium-sized cysts (11-30 mL; n=67) and large cysts (>31 mL; n=21; including 3 extremely large cysts >100 mL). Based on their character, two types of cysts were distinguished, pure and complex. On US scan, a pure cyst (n=49) had anechoic content, smooth internal wall, no septa and a cystic component accounting for more than 90% of the cyst volume (Fig. 1a, b); the drained fluid was clear or pale yellow, without detritus. A complex cyst (n=151) had anechoic or flocculated content, roughened wall or a focally preserved solid part of the nodule and a cystic component accounting for 60-90% of the cyst volume (Fig. 2a, b). The cystic cavity was either separted of irregular shape or multilocular with one dominant cyst and several tiny ones; the drained fluid was brown, viscous-to-gelatinous and often containing detritus.

To assess the effect of US-PEIT, the Volume Reduction Rate (VRR) was calculated as follows: VRR (%) = initial cyst volume – final cyst volume / initial cyst volume × 100 (ref.13). The therapeutic goal was a reduction in cyst volume >50% and disappearance of the cystic cavity. Complete disappearance of the cystic cavity was the goal in all pure cysts. In case of complex (septated and multilocular) cysts, tiny residual cavities sized less than 5 mm could have remained with no ethanol penetrating inside. In case of cystic cavity recurrence during the 12 months follow-up from the completion of therapy an additional US-PEIT would be performed and follow-up would be rescheduled.

Both US scans and US-PEIT were carried out using the Philips Sonos 5500 and, from 2011, Philips iU22 with 10-MHz probe. For the cyst aspiration, 20-mL syringes of the Philips Sonos 5500 and, from 2011, Philips iU22 with 10-MHz probe. For the cyst aspiration, 20-mL syringes were used. The amount of ethanol used during the first session was 1-2 mL and 3-5 mL for small and medium-sized cysts, respectively. For large cyst the initial volume of ethanol was 5-8 mL and for three extremely large cysts (>100 mL), the maximum single dose was 10 mL (ref.7). During the other sessions, the amount of ethanol was equal to 20% of the residual fluid volume. All analyzed parameters were not normally distributed according to Shapiro-Wilk’s test. Therefore, the median and interquartile range (25th and 75th percentile) were used to express the values. To compare changes at 1, 3, 6 and 12 months after US-PEIT, Friedman’s ANOVA with the Wilcoxon test were used. To determine possible differences in the subgroups, the Mann-Whitney U test and Kruskal-Wallis test were performed for two and three subgroups, respectively. Spearman’s correlation analysis was used to assess relationships between parameters and linear regression analysis was performed to determine independent predictors of treatment. The level of statistical significance was set at P<0.05.

RESULTS

In all 193 patients with 200 cysts, US-PEIT was successful and the therapeutic goal was achieved. At 12 months, the VRR was 95.0% [86.7-98.0] for the entire cohort, 97.5% [95.4-98.7] for pure cysts and 92.3% [83.3-96.7] for complex cysts (for details see Table 1). No patient was indicated for surgery due to method failure.

The patients’ mean age was 49.0 [38.0-67.0] years. The age characteristics of the sample were as follows: the youngest patients – a 17-year-old female and a 22-year-old male; the oldest patients – two 83-year-old females and a 79-year-old male.

Solitary cysts were present in 104 patients. Dominant cysts in a multinodular goiter were found in 96 patients; of those, seven female patients had two cysts in both thyroid lobes (Fig. 3a, b).

The initial cyst volume ranged between 3.0 mL and 170.0 mL. Number of US-PEIT sessions were as follows: 1× in 101 cysts, 2× in 69 cysts, 3× in 22 cysts, 4× in 6 cysts, 5× in 1 cyst and 9× in 1 giant multilocular cyst. The mean number of US-PEIT sessions was 1.72±0.97. The total amount of instilled ethanol was 1–60 mL (median [interquartile range] = 2.0 [1.0-3.0] mL), corresponding to 4.2-66.7% (median [interquartile range] = 20.0 [16.7-28.6] %) of the initial cyst volume. The detailed results for the entire cohort and subgroups by cyst size and type are summarized in Table 1. In both the entire cohort and individual subgroups, the initial cyst volume was significantly reduced as could be seen from the final cyst volume at 12 months after US-PEIT was completed (P<0.001) and the VRR was significantly increasing during the regular checkups at 1, 3, 6 and 12 months (P<0.05). For the entire cohort, significant (P<0.05) negative correlations were
Fig. 1a. An 81-year-old woman with a one month palpable resistance on the neck. US scan prior to PEIT revealed solitary large pure cyst (full arrow), size $66 \times 63 \times 44$ mm and volume 96 mL occupying whole left lobe: smooth wall; anechoic contents; evacuation of yellow liquid; transverse. CCA – common carotid artery, TRA – trachea

Fig. 1b. Twelve months post 3× PEIT. small solid nodule (empty arrow), size $14 \times 11 \times 8$ mm and volume 0.7 mL as residue of cyst: inhomogeneous structure, mostly isoechoic, focally hypoechoic areas, no recurrence of the liquid component; transverse.

Fig. 2a. A 53-year-old woman with two years palpable resistance on the neck. US scan prior to PEIT showed multinodular goiter with dominant large complex septated cyst (full arrow), size $58 \times 42 \times 27$ mm and volume 35 mL in the right lobe (fluid recurrence after three evacuations of brownish liquid): hyperechoic focally thick wall, anechoic contents with one tiny colloid clot and “comet tail”, thick transverse septum and another thin septa et periphery, tiny complex nodules in the left lobe; transverse.

Fig. 2b. Twelve months post 3× PEIT. small solid nodule (empty arrow), size $14 \times 11 \times 7$ mm and volume 0.6 mL as residue of cyst: inhomogeneous structure, mostly hypoechoic, tiny punctuations of fibrosis, no recurrence of the liquid component; transverse.

found between the VRR at 12 months and with the complex type of cyst ($\rho=-0.37, P<0.05$), number of US-PEIT sessions ($\rho=-0.24, P<0.05$) and amount of instilled ethanol ($\rho=-0.21, P<0.05$). No significant correlation were found with age and the initial cyst volume. Multivariate regression analysis also showed the presence of a complex cyst (beta=$-0.30, P<0.001$), number of US-PEIT sessions (beta=$0.84, P<0.001$), and amount of instilled ethanol (beta=$-0.32, P<0.001$), to be independent predictors for the VRR at 12 months.

When considering the cyst size, statistical differences were found in the success rate of US-PEIT and amount of instilled ethanol (larger cysts required higher rate of US-PEIT and amount of instilled ethanol, although the ratio ethanol amount to initial cyst volume was significantly lower). VRR at all months was significantly higher in large cysts compared to small cysts although final cyst volume remained higher in large than in small cysts.

Comparison of complex and pure cysts showed that US-PEIT was more successful (according to VRR at all months) in pure cysts. Although less ethanol amount was used, fewer US-PEIT sessions and smaller amounts of ethanol relative to the initial cyst volumes were needed (see Table 1). Figure 4 shows the increase of VRR after repeated injection in pure and complex cysts.

In our study we observed only minor complications of the procedure; transient mild local pain was most frequently observed (58/200, ≈29%), usually disappearing within several hours but no later than three days after the procedure. Local anesthesia was not needed. Another typical complaint, particularly noted in elderly patients, was a short-lasting dizziness occurring immediately after
the procedure; most likely resulting from the head being tilted back for about 10-15 min during the US examination and PEIT (dizziness is typically seen even after normal fine-needle aspiration biopsy). Two patients (2/200, 1%) with a large complex cysts experienced dysphonia lasting for 7–14 days after repeated US-PEIT, subsiding spontaneously without need for further specialized examination. No permanent dysphonia was noted. Also, no patient developed thyrotoxicosis or subsequent hypothyroidism. No life-threatening complications were observed in the patients undergoing US-PEIT.

**DISCUSSION**

It has been repeatedly confirmed, that a simple aspiration is mostly unsuccessful in treatment of thyroid cysts. The high recurrence rates from 58% to 80%, depended on the initial cyst volume, density of the fluid and number of previous aspirations. After a simple evacuation we registered even \( \approx 88\% \) of recurrence in >3 mL cyst.

US-PEIT for thyroid cysts is a successful alternative to surgery. At 12 months after the completion of US-PEIT (a non-aspiration approach), the VRR was 95.0% for the entire cohort (n = 200), with no recurrence being observed. Presence of a complex cyst was an independent predictor of treatment efficacy. In the complex cyst we observed lower VRR particularly after the first ethanol injection; however after repeated US-PEIT the final success rate increased. During all the monitored months of follow up the VRR differed statistically significantly in between the pure and complex cysts (Fig. 4).

The superiority of US-PEIT over placebo (isotonic saline) in the treatment of cysts was reported by Bennedbaek and Hegedüs (n=33/33, therapeutic success in 82% vs. 48%) or by Antonelli et al. (n=26/44, therapeutic success in 77% vs. 36%) or Zingrillo et al. or Del Prete et al. were successful at using US-PEIT for large cysts ≥40 mL (n=20, n=43, n=98) (ref.16-18). In large cohorts reported in 2005 by Lee and Ahn (n=432) and del Prete et al. (n=98), the VRR ranged between 73% and 93% (ref.11,18). Kim DW et al. compared two approaches to US-PEIT, non-aspiration (leaving ethanol in the cyst; n=30) and aspiration (removal of ethanol from the cyst after 10 min; n=30). Both approaches were equally successful (96.7% vs. 93.3%) but there was a considerable difference in the total procedure time (≈17 vs. ≈31 min). Moreover, the aspiration approach required another puncture of the cyst, resulting in increased risk of intracystic hemorrhage during the procedure (3% vs. 23%) (ref.7). These days, the aspiration approach is less common; it was initially developed to avoid undesirable ethanol leakage into the surroundings and further development of periglandular fibrosis that could impair potential surgery in case of US-PEIT failure and persistence of symptomatic cyst.

Numerous studies concluded that the initial cyst volume was the only factor influencing the success of US-PEIT. Cho et al. (n=22), Lee and Ahn (n=432) or Verde et al. (n=32) reported significantly more successful treatment for larger cysts of >10 mL (ref.12,14). Reverter et al. showed a higher VRR in cysts >15 mL (ref.21). By contrast, Bennedbaek and Hegedüs (n=33) were more successful at treating small cysts; there was no difference in the outcome between pure and complex cysts identified by ultrasound. Similarly, Yasuda et al. (n=61) and Kim YJ et al. (n=217) showed a greater success rate and fewer recurrences for cysts <10 mL (ref.12,20). Cho et al. found a correlation between the total amount of injected ethanol and the VRR, irrespective of whether the cyst was pure
Fig. 4. Comparison of VRRs of complex and pure cysts at different months of follow up. Volume Reduction Rate (VRR) was calculated as follows: VRR (%) = initial cyst volume – final cyst volume / initial cyst volume × 100. VRR 1 – after one month, VRR 3 – after 3 months, VRR 6 – after 6 months, VRR after 12 months of follow up. Level of difference *** ~ P<0.001.

Table 1. US–PEIT of thyroid cysts study: results for the entire cohort, three subgroups by cyst volume and two subgroups by character of the cystic component.

<table>
<thead>
<tr>
<th>Cyst/number</th>
<th>Total cysts/200</th>
<th>Small cysts/112</th>
<th>Medium cysts/67</th>
<th>Large cysts/21</th>
<th>Pure cysts/49</th>
<th>Complex cysts/151</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M</td>
<td>157F/43M</td>
<td>91F/21M</td>
<td>52F/15M</td>
<td>14F/7M</td>
<td>39F/10M</td>
<td>118F/33M</td>
</tr>
<tr>
<td>Age (y)</td>
<td>[38–67]</td>
<td>[38–66]</td>
<td>[37–64]</td>
<td>[42–74.0]</td>
<td>[35–59]</td>
<td>[39–68]</td>
</tr>
<tr>
<td>Initial cyst volume (mL)</td>
<td>[5.5–16.0]</td>
<td>[5.0–7.0]</td>
<td>[12.0–20.0]</td>
<td>[39.0–70.0]</td>
<td>[5.0–15.0]</td>
<td>[6.0–16.0]</td>
</tr>
<tr>
<td>VRR (%) at 1 month</td>
<td>[78.6–94.0]</td>
<td>[77.3–93.3]</td>
<td>[77.3–94.7]</td>
<td>[88.8–97.4]</td>
<td>[90.0–97.0]</td>
<td>[75.7–91.9]***</td>
</tr>
<tr>
<td>VRR (%) at 3 months</td>
<td>[85.0–96.7]</td>
<td>[83.7–96.0]</td>
<td>[85.5–97.0]</td>
<td>[93.0–98.2]</td>
<td>[94.6–98.0]</td>
<td>[81.3–95.3]***</td>
</tr>
<tr>
<td>VRR (%) at 6 months</td>
<td>[86.5–97.5]</td>
<td>[85.4–96.8]</td>
<td>[86.4–98.2]</td>
<td>[94.1–99.0]</td>
<td>[95.0–98.6]</td>
<td>[83.3–96.7]***</td>
</tr>
<tr>
<td>VRR (%) at 12 months</td>
<td>[86.7–98.0]</td>
<td>[85.7–97.5]</td>
<td>[86.4–98.3]</td>
<td>[94.1–99.0]</td>
<td>[95.5–98.7]</td>
<td>[83.3–96.7]***</td>
</tr>
<tr>
<td>Final cyst volume (mL)</td>
<td>[0.2–1.3]</td>
<td>[0.1–0.8]</td>
<td>[0.3–2.0]</td>
<td>[0.6–2.5]</td>
<td>[0.1–0.4]</td>
<td>[0.2–1.5]***</td>
</tr>
<tr>
<td>US–PEIT×</td>
<td>[1.0–2.0]</td>
<td>[1.0–2.0]</td>
<td>[1.0–2.0]</td>
<td>[2.0–3.0]</td>
<td>[1.0–2.0]</td>
<td>[2.0–3.0]**</td>
</tr>
<tr>
<td>Ethanol (mL)</td>
<td>[1.0–3.0]</td>
<td>[1.0–2.0]</td>
<td>[2.0–4.0]</td>
<td>[3.0–10.0]</td>
<td>[1.0–3.0]</td>
<td>[1.0–3.0]**</td>
</tr>
<tr>
<td>Ethanol vs. initial cyst volume (%)</td>
<td>[16.7–28.6]</td>
<td>[20.0–33.3]</td>
<td>[15.4–25.0]</td>
<td>[9.1–20.9]</td>
<td>[13.3–20.0]</td>
<td>[16.7–33.3]**</td>
</tr>
</tbody>
</table>

F – females, M – males, initial cyst volume – volume of the cyst before sclerotherapy, VRR – volume reduction rate at intervals after the completion of sclerotherapy, final cyst volume – volume of the cyst at 12 months after the completion of sclerotherapy, US–PEIT× – the mean number of sclerotherapy sessions per cyst, ethanol – the total amount of instilled ethanol per cyst, ethanol vs. initial cyst volume – proportion of the total amount of ethanol to the initial cyst volume

Significant difference P<0.05 at least – * vs. small cysts; † vs. medium cysts; ‡ vs. large cysts.

* ~ P<0.05, ** ~ P<0.01, *** ~ P<0.001 ... statistical significance level of difference
or complex. A study by Raggiunti et al. (n=109) showed a statistically significant correlation between the initial cyst volume and the number of US-PEIT sessions. The present study showed no statistically significant differences in the VRR between cyst volume subgroups. Medium-sized and large cysts required more ethanol and US-PEIT sessions than small cysts (not statistically significant). At 12 months, the final VRR was not statistically different for all cyst volumes. Consistently with other studies, no significant correlations were found with age or gender.

We performed multiple regression analysis and found the presence of complex cyst to be an independent predictor of treatment success. Approx VRR, the overall value was 95.0%; VRR of pure and complex cysts differed statistically significantly (97.5% and 92.3%, P<0.001).

The latter were less successfully treated, in particular with the first ethanol injection. Similar results were reported by Basu et al. (n=60; pure/complex cysts 42/18), with the VRR being 92.8% for pure cysts and only 44.4% for complex cysts. Significantly better treatment response was observed in pure cysts (P<0.001) while complex cysts were associated with higher recurrence rates and need for repeated treatment. When treating complex, medium-sized and large cysts, more US-PEIT sessions and ethanol were needed. Additionally, higher amounts of ethanol relative to the initial cyst volume were needed to treat complex cysts.

Generally, there are no exact recommendations regarding the amount of ethanol injected during a single US-PEIT session, intervals between US-PEIT sessions or use of local anesthesia. In particular, considerably different amounts of ethanol have been reported by various authors. In the present study, small amounts of ethanol were used initially due to the concerns for potential local side effects. Our first experiences with US-PEIT were reported by Basu et al. (n=60; pure/complex cysts 42/18), with the VRR being 92.8% for pure cysts and only 44.4% for complex cysts. Significantly better treatment response was observed in pure cysts (P<0.001) while complex cysts were associated with higher recurrence rates and need for repeated treatment. When treating complex, medium-sized and large cysts, more US-PEIT sessions and ethanol were needed. Additionally, higher amounts of ethanol relative to the initial cyst volume were needed to treat complex cysts.

We assessed that the small amount of ethanol is sufficient to necrotize the collapsed cystic wall and possess lower risk of ethanol leakage into surrounding tissues. Therefore, US-PEIT for thyroid cysts with relatively small total amounts of ethanol is safe and successful alternative to surgery. Carefully selected patients warrant by relevant ultrasound findings should benefit from this method. We observed recurrence (another new cystic cavity >3mL) in a period longer than 12 months. In each case, the cystic cavity that recurred was smaller than the original one and was treated by another US-PEIT session, without a need for surgery.

For successful US-PEIT of thyroid cysts of all sizes, it is sufficient to use relatively small total amounts of ethanol, corresponding to 20% of the initial cyst volume.

CONCLUSION

We assessed that the small amount of ethanol is sufficient to necrotize the collapsed cystic wall and possess lower risk of ethanol leakage into surrounding tissues. Therefore, US-PEIT for thyroid cysts with relatively small total amounts of ethanol is safe and successful alternative to surgery. Carefully selected patients warrant by relevant ultrasound findings should benefit from this method.

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