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Efficacy and safety of ultrasound-guided percutaneous polidocanol sclerotherapy in benign predominantly cystic thyroid nodules: a prospective study

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ABSTRACT

Objective: To evaluate the efficacy and safety of percutaneous polidocanol injection (PPI) in treatment of predominantly cystic thyroid nodules.

Materials and methods: This prospective study included 111 patients with 122 benign predominantly cystic thyroid nodules inducing pressure symptoms or cosmetic problems. The nodules were randomized to a single aspiration with (n = 61) or without (n = 61) subsequent PPI and followed up after 1, 3, 6, and 12 months. Ten patients (12 nodules) declined to follow up after aspiration in group 2. Nodule volumes, symptoms scores, and cosmetic scores were evaluated before and after treatment. The therapeutic success rate and safety of PPI for treatment of predominantly cystic thyroid nodules were also evaluated.

Results: In the PPI group, the nodule volumes were reduced from 13.67 ± 9.90 to 2.60 ± 2.66 (p < .001). Therapeutic success rate (nodule volume reduction >50%) was obtained in 57 of 61 (93.44%) nodules in the PPI group, compared to seven of 49 (14.29%) in the aspiration group (p < .001). In the aspiration group, the nodule volume was not significantly reduced. The reduction in symptom scores was significantly higher in the PPI group (from 3.60 ± 1.65 to 1.60 ± 1.19) than in the aspiration group (from 3.62 ± 1.89 to 3.30 ± 1.06) (p < .001, between groups). The reduction in cosmetic scores showed a significant difference between groups (p < .001). In total, 4.92% of patients (3/61) in the PPI group and 85.71% (42/49) in the aspiration group showed recurrence during the follow-up period. There was a significant difference in the recurrence rate between groups (p < .001). No major side-effects occurred.

Conclusions: US-guided PPI of benign recurrent predominantly cystic thyroid nodules is effective and safe. PPI is an important alternative to benign recurrent predominantly cystic thyroid nodules.

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Polidocanol injection; Ultrasonography; Sclerotherapy; Predominantly cystic thyroid nodules

Introduction

Thyroid nodule is very common in clinical practice, with ultrasound examination showing that 15–25% of thyroid nodules are cystic or predominantly cystic1,2. Simple aspiration is the treatment of choice for diagnostic and therapeutic purposes in symptomatic patients. However, after simple fine-needle aspiration, most cystic lesions (~80%) refill and enlarge over time3. At present, percutaneous ethanol ablation (PEA) is recommended as the first-line therapy in benign recurrent cystic thyroid nodules4. In predominantly cystic nodules, PEA is less effective5,6 and PEA shows a high recurrence rate (range from 26–38.3%)6–8. Therefore, there is a need for novel sclerosants as an alternative to treat predominantly cystic thyroid nodules. Polidocanol injection is a liquid detergent sclerosant developed in 1936 as a topical and local anesthetic. It has been used safely in the treatment of hemangiomas9, varicose veins10, lymphoceles11, renal cysts12, hydroceles13, and hepatic cysts14.

The aim of this study was to assess the efficacy and safety of ultrasound guided percutaneous aspiration and polidocanol sclerotherapy of predominantly cystic thyroid nodules.

Materials and methods

This study was a prospective randomized trial. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. All study participants provided written informed consent before the experiments. The written informed consent was provided by each eligible patient, and the study conformed to the Declaration of Helsinki.

Study design

Between May 2012 and December 2015, a total of 122 predominantly cystic thyroid nodules (proportion of cystic...
component, less than 90% and greater than 50% of the nodule) in 111 patients were included in the prospective study and randomly divided into two groups at the outpatient clinic. Group 1 consisted of 57 patients (36 women and 21 men; mean age = 48.63 years) with 61 predominantly cystic thyroid nodules treated by US-guided percutaneous polidocanol injection (PPI). Of 54 patients with 61 predominantly cystic thyroid nodules in group 2, 10 patients (12 nodules) declined to follow up after aspiration (Figure 1). Group 2 consisted of 44 patients (26 women and 18 men; mean age = 45.21 years) with 49 predominantly cystic thyroid nodules treated by US-guided simple aspiration. All enrolled patients had:

1. Nodules with a cystic portion (proportion of cystic component 50–90% of the nodule);
2. Pressure symptoms or cosmetic problems;
3. Serum thyroid hormone, thyrotropin concentrations, and calcitonin within normal limits;
4. Cytologically confirmed benign nodules after ultrasound-guided fine-needle aspiration (FNA) using 21-gauge needles;
5. No malignant features on ultrasound examination; and
6. All nodules with recurrence of the cystic part after the initial diagnostic aspiration.

Before treatment and at the 12-month evaluation, the patients were asked to rate pressure symptom score on a visual analog scale (0–10 cm) and cosmetic score (1 = no palpable mass; 2 = a palpable mass but no cosmetic problem; 3 = cosmetic problem on swallowing only; 4 = readily detected cosmetic problem). The patients were investigated 1, 3, 6, and 12 months after the treatment. Nodule volumes, symptom score, cosmetic score, therapeutic success rate (nodule volume reduction >50%)5,7, and the complication, as well as thyroid function were investigated during the follow-up. To assess safety, any possible complications both during and immediately after the procedure were evaluated. Major and minor complications were defined by the definitions of the Society of Interventional Radiology16. Procedure-related pain was graded into four categories (grade 0, no pain or mild pain similar to pain during lidocaine injection; grade 1, pain greater than lidocaine injection, but not needing medication; grade 2, pain needing medication; grade 3, PPI procedure incompletely terminated due to severe pain)5.

The volume of each nodule was calculated using the equation volume = \( \pi \frac{abc}{6} \), where \( a \) is the largest diameter, and \( b \) and \( c \) are the other mutually perpendicular diameters.

Recurrence was defined as an increase in nodule volume by >50% relative to the volume recorded by the US previously17,18.

**Procedure**

The procedures were performed in the out-patient clinic. Patients were placed in a supine position with mild neck extension. An 18-gauge needle was inserted into the cystic portion of the thyroid nodule under ultrasound guidance without local anesthesia. The fluid was first completely aspirated. The syringe tube was then replaced with another one containing polidocanol injection while keeping the puncture needle in place. The amount of polidocanol injected was \( \approx 25–33\% \) of the amount of fluid aspirated. Then we
extracted and flushed the injection five times to assure the uniform distribution of the injection and the polidocanol was left in the cysts (Figure 2).

Gentle pressure was applied over the puncture site for 30 min, and the patient was watched for signs of any complications.

Statistical analysis

Results for continuous data are given as Mean ± standard deviation. Within-group changes were assessed by Friedman’s test or by Wilcoxon signed ranks test. A Mann-Whitney test was used to compare data between groups, and Fisher’s exact test was used to analyze differences in outcome. Qualitative variables were evaluated with the Chi-square test. Multivariate analysis was performed with the Statistical Package for Social Sciences (SPSS), version 19.0.

We used a confidence interval of 95% and a significance level of 5%.

Results

Before treatment, there were no significant differences between the PPI and Aspiration groups in any clinical or demographic parameter (Table 1).

The mean nodule volume was 13.67 ± 9.90 (range = 2.46–44.73 mL) in the PPI group and 14.15 ± 10.21 (range = 3.36–52.72 mL) in the Aspiration group. The average nodule volume at 1, 3, 6, and 12 months follow-up US was 6.47 ± 5.48 mL, 4.69 ± 3.98 mL, 2.97 ± 3.17 mL, and 2.60 ± 2.66 mL in the PPI group (p < .001, Figure 3) and 11.98 ± 9.0 mL, 12.92 ± 9.58 mL, 13.02 ± 9.99 mL, and 14.33 ± 10.25 mL in the Aspiration group (p = .43, Figure 3). There was significant difference between the groups (p < .001, Figure 2).

Table 1. Characteristics of the two treatment groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PPI treatment</th>
<th>Aspiration</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.63 ± 12.73 (20–76)</td>
<td>45.21 ± 11.18 (18–72)</td>
<td>.68</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>36/21</td>
<td>26/18</td>
<td>.20</td>
</tr>
<tr>
<td>No. nODULES</td>
<td>61</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>NODULE volume, baseline (ml)</td>
<td>13.67 ± 9.90 (2.46–44.73)</td>
<td>14.15 ± 10.21 (3.36–52.72)</td>
<td>.81</td>
</tr>
<tr>
<td>Cyst volume (ml)</td>
<td>10.46 ± 7.79 (2.0–35)</td>
<td>10.73 ± 7.93 (3–40)</td>
<td>.86</td>
</tr>
<tr>
<td>Symptoms score</td>
<td>3.60 ± 1.65 (1–8)</td>
<td>3.62 ± 1.89 (0–8)</td>
<td>.83</td>
</tr>
<tr>
<td>Cosmetic grade</td>
<td>3.37 ± 1.00 (1–4)</td>
<td>3.48 ± 0.85 (1–4)</td>
<td>.42</td>
</tr>
<tr>
<td>Biochemical measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (normal, 0.34–5.60 mIU/L)</td>
<td>2.40 ± 1.22 (0.79–4.76)</td>
<td>2.47 ± 1.27 (0.69–4.48)</td>
<td>.66</td>
</tr>
<tr>
<td>FT3 (normal, 3.8–6.0 pmol/L)</td>
<td>4.68 ± 0.69 (3.35–5.87)</td>
<td>4.62 ± 0.62 (3.82–5.81)</td>
<td>.69</td>
</tr>
<tr>
<td>FT4 (normal, 7.86–14.41 pmol/L)</td>
<td>11.54 ± 1.72 (8.28–14.28)</td>
<td>11.91 ± 1.78 (8.97–14.21)</td>
<td>.90</td>
</tr>
</tbody>
</table>

PPI: percutaneous polidocanol injection; F: female; M: male.
A progressive decline in nodule volume was noted in the PPI group \((p < .001, \text{Figure 3})\).

At 12 months follow-up, the volume reduction ratio from baseline was 81.10 ± 14.79\% (range ¼ 22–91\%) in the PPI group and 4.50 ± 22.48\% (range ¼ 0–67\%) in the Aspiration group \((p < .001, \text{Figure 4})\).

PPI resulted in significant improvements in cosmetic scores \((p < .001, \text{Table 2})\) and symptom scores \((p < .001)\). Neither cosmetic scores (from 3.48 ± 0.85 to 3.30 ± 1.06; \(p = .41, \text{Table 2}\)) nor symptom scores (from 3.62 ± 1.89 to 3.23 ± 1.76; \(p = .55, \text{Table 2}\)) were not significantly reduced in the Aspiration group. Also, the mean symptom scores and cosmetic scores showed a significant difference between the two groups at the 12 months follow-up \((p < .001, \text{Table 2})\).

In the PPI group, 93.44\% of patients achieved therapeutic success, and 14.29\% of patients in the Aspiration group achieved therapeutic success at 12 months \((p < .001, \text{Table 2})\). There were three recurrences of 61 nodules (4.92\%) in the PPI group during the follow-up period. There was a high recurrence rate of up to 85.71\% in the Aspiration group. Also, the recurrence rate showed a significant difference between the two groups at the 12 months follow-up \((p < .001, \text{Table 2})\).

Nine patients (15.79\%) in the PPI group experienced slight localized pain for 1–5 days after treatment. Six patients (10.52\%) had a fever of 37.5–39.3 °C, and four of them required paracetamol or non-steroidal anti-inflammatory analgesics. There were no major complications, such as voice change, infection, hematoma, esophageal injury, or tracheal injury, either during the procedure or in the follow-up period.

**Discussion**

PEA as a first-line treatment is debatable for predominantly cystic thyroid nodules because one of the major limitations is a high recurrence rate. A recent study showed that the recurrence rate is >50\% in these nodules with solid components of >20\%. Side-effects of ethanol instillation into cystic thyroid nodules seem to be few. Some studies reported pain/"burning sensation" radiating to the ear or neck in 12–21\% of the treatment sessions. A higher rate (71\%) was observed in patients treated with larger thyroid cysts. There are other side-effects including transient vocal cord palsy, respiratory distress and emergency surgical treatment, periglandular fibrosis, making the surgical procedure more difficult, and venous thrombosis in sporadic cases.
Although Radiofrequency ablation (RFA) is effective in thyroid nodules, regardless of their solid component, RFA has several disadvantages compared with EA, including high cost and technical difficulty.

Polidocanol is an effective sclerosing agent consisting of 95% hydroxypolyethyleneoxide decane and 5% ethyl alcohol. The Food and Drug Administration (FDA) has approved polidocanol as a medicinal sclerosing agent in the US, as has its equivalents in European countries. Polidocanol has been widely applied in sclerotherapy of all kinds of hemangioma, venous malformations, varicosity, and cyst disease. Some studies showed that Polidocanol is a safe and effective sclerosant for hepatic and renal cysts, with lower complication rates than ethanol. Brunken et al. reported that, over a mean period of 25.8 months, 118 patients with 132 cysts were followed up. In 56% of the cysts treated the cystic cavity disappeared completely, and in 30% the remaining volume was less than 10% of the initial volume, without the need for repeated interventions associated with sclerotherapy performed with ethanol.

In the literature, few studies have examined polidocanol as a sclerosing agent for thyroid nodules. Belcaro et al. evaluated the long-term efficacy of the sclerosing agent polidocanol in the treatment of benign cystic nodules. After 5 years in the group treated with the sclerosing agent, 93% of the cysts had completely disappeared. At 10 years more than 90% of the original, sclerosed target cysts were not visible, and no side-effects were noted. Chen et al. found polidocanol treatment is effective and safe for treatment of benign cystic thyroid nodules. Therapeutic success was achieved in 82 of the 97 cysts (82.83%) and only 2/97 (2%) patients suffered mind pain and mild fever. The mechanism of treating a cyst is probably destroying endothelial cells of the capsule wall which occurs with aseptic inflammation, thus the endothelial tissue atrophies and cyst cavity adheres and occludes. Otherwise, injection of polidocanol causes protein death and denaturation in which an aggregation of detergent molecules forms a lipid bilayer that induces disruption of cell surface membrane in a concentration dependent manner, activates cellular calcium signaling and nitric oxide pathways, and produces endothelial cell death. The results of a rabbit Model histopathologic evaluation revealed that inflammation and fibrosis were significantly increased. This finding shows polidocanol can be effectively used to treat thyroid nodules by means of fibrosis. Excess adhesions were found after sclerosing agent induction, but there were no adhesion related complications in the observation period.

In our study, we tested PPI in a randomized prospective study in recurrent benign predominantly cystic thyroid nodules. The therapeutic success rate was highly significantly better than with aspiration alone, and was not lower than that obtained with PEA. A randomized study showed the therapeutic success rate of RFA (100%) is superior to that of EA, but RAF is more expensive and complex. Our study showed that the recurrence rate (4.91%) of polidocanol sclerotherapy in predominantly cystic thyroid nodules was low during the follow-up period. Also, symptoms scores and cosmetic scores vanished in the vast majority. No major complications were observed after PPI, showing that it is a safe procedure. Also, it can be left in the cyst cavity without reaspiration to achieve a complete adhesion with only a one-step application.

The present study had some limitations. We didn’t compare PPI treatment with a control group treated with EA because we couldn’t obtain absolute ethanol. Secondly, the patients were followed up only for 1 year. Further studies with larger patient samples are needed to confirm these findings.

The findings of this study indicate that PPI is a safe, effective, and rapid treatment that can be performed on an outpatient basis. The cost of PPI treatment for benign predominant cystic thyroid nodule is $600 RMB ($93.41). If long-term data confirm safety, the high remission rate, and relief of pressure symptoms and cosmetic problems, PPI should be added to the therapy algorithm for predominant cystic thyroid nodules.

Transparency

Declaration of funding

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Declaration of financial/other relationships

The authors have declared that no conflicts of interest exist. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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