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ORIGINAL ARTICLE

EVALUATION OF THE EARLY RESULTS OF PERCUTANEOUS ETHANOL ABLATION IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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Abstract. *Percutaneous ethanol ablation (PEA) is an alternative non-surgical method for the treatment of patients with primary hyperparathyroidism (PHPT), suitable in cases with comorbidities and high surgical risk. The* ***aim*** *of the present study was to evaluate the results of PEA in patients with PHPT at the early stages of follow-up.* ***Materials and methods:*** *The study included 35 patients (30 women and 5 men, mean age 59.7 ± 12.4 years) with biochemical and hormonal data of PHPT and localized parathyroid adenoma (PTA) by ultrasound, nuclear scan, FNB with cytology and evaluation of PTH in the needle washout. All patients were at high surgical risk or refused surgical treatment. PEA was applied and changes in the PTA volume and calcium-phosphate metabolism were monitored at the third (M3) and sixth (M6) months after the procedure.* ***Results:*** *Normocalcaemia was achieved in 26 patients (74.3%) at M3 and persisted at M6 in 22 of them. A second course of PEA was administered in 11 patients with persistent hypercalcaemia at M3 and M6, respectively. Compared to the baseline, the mean PTA volume decreased significantly by 53% at M3 and 67% at M6 ($p < 0.001$). Side effects including local pain, edema and dysphonia were observed in 5 patients (14.3%).* ***Conclusion:*** *PEA is an efficient and safe treatment modality for the management of PHPT. A significant reduction in PTA volume and a normalization of serum calcium and PTH levels were observed at the early stages of follow-up.*

Key words: *percutaneous ethanol ablation, primary hyperparathyroidism, parathyroid adenoma, hypercalcemia*

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia. It is the result of chronic overproduction of parathyroid hormone (PTH), most often (80-90%) from a single benign adenoma in one of the parathyroid glands (PTG). Less commonly (10%), the cause is hyperplasia or multiple adenomas, typical of familial forms of PHPT or parathyroid carcinoma which is responsible for less than 1% of the cases. The disease is three times more common in women than in men. The incidence increases with age, peaking in the fifth or sixth decade [1].

Parathyroidectomy is the standard treatment modality of PHPT, with over 95% probability of a complete return of calcium-phosphate metabolism to normal and an increase in bone mineral density (BMD) [2, 3]. However, advanced age and concomitant diseases increase the surgical risk [4]. Moreover, many patients with asymptomatic forms of PHPT decline surgery because they experience few or no symptoms at all.

Percutaneous ethanol ablation (PEA) is an alternative non-surgical method for the treatment of patients with PHPT. It is suitable in cases with comorbidities and high surgical risk. The procedure consists of ultrasound-guided application of 95-99% ethanol to the target area. Ethanol causes thrombosis of the small vessels and direct coagulation necrosis, followed by fibrosis, contraction and reduction in the volume of the treated lesion. PEA has been used for more than 30 years in the treatment of benign solid and cystic thyroid nodules, toxic adenomas, papillary thyroid microcarcinomas, metastatic lymph nodes from papillary thyroid carcinoma, hepatocellular carcinoma and metastases in the liver [5-8].

PEA was first described as an alternative non-surgical treatment of PTG hyperplasia in drug-resistant patients by Solbiati et al. in 1985 [9]. The procedure was used mainly in cases of secondary and tertiary hyperparathyroidism [10-12]. In 1987, a team from Mayo Clinic reported successful treatment of persistent PHPT with PEA [13]. Later, Herman et al. summarized 4 main indications for PEA in PHPT: 1) concomitant diseases that increase the surgical risk; 2) patient's choice; 3) technical difficulties in performing surgery and 4) partial ablation of the remaining PTG after surgery for multiple hyperplasia [14].

In recent years, other mini- and non-invasive methods for PTG ablation have been increasingly used, such as high-intensity focused ultrasound, radiofrequency and microwave thermal ablation [15-18]. The advantages of PEA over these procedures are its accessibility and low cost, combined with minimal invasiveness and good efficiency.

The aim of the present study was to evaluate the short-term results of PEA in patients with PHPT – at the third (M3) and sixth (M6) months following the procedure.

MATERIALS AND METHODS

From January 2018 to May 2021, 312 patients with PHPT were admitted at the inpatient Department of Thyroid and Metabolic Bone Diseases of the University Hospital of Endocrinology "Acad. Ivan Penchev". Thirty-five of them (30 women and 5 men, mean age 59.7 years) with localized parathyroid adenoma that were identified as high-risk surgical candidates or refused surgery, were considered for PEA. Patients with multiple adenomas, familial forms of PHPT and genetically proven multiple endocrine neoplasia (MEN) were not included in the study. The diagnostic procedures and the subsequent monitoring of the treatment effect were performed in the hospital and all patients signed a standard informed consent before the procedures.

The diagnosis of PHPT was based on the combination of elevated serum PTH and calcium (Ca), with or without decreased levels of inorganic phosphates (PO4). The intact PTH was determined by immunoradiometric method (IRMA, CisBio Bioassays, ref. range 1.6-6.9 pmol/L). Serum Ca, PO4 and calcium excretion in 24-hour urine (uCa) were measured by enzymatic colorimetric method (Roche Diagnostics, F. Hoffmann-La Roche Ltd.). The reference ranges were as follows: serum Ca – 2.12-2.62 mmol/L, serum PO4 – 0.87-1.45 mmol/L and uCa – 2-8 mmol/24 h. Serum 25(OH)D was measured by radioimmunoassay (RIA, DIA Source, ref. range > 30 ng/ml).

The PTA was localized by neck ultrasound, using Aloka devices Prosound Alpha 6 and Alpha 7, with a linear transducer of 7-13.3 MHz frequency range. The adenoma size was measured and the volume (V) was determined by the formula for ellipsoid: $V = \pi/6 \times (a \times b \times c)$, where a, b and c represent the three perpendicular diameters of the PTA.

Ultrasound-guided fine-needle biopsy (FNB) with cytology and evaluation of PTH in the needle washout were performed in all patients to confirm the parathyroid origin of the lesion, found on ultrasound examination. Additionally, conjugated nuclear scan with 99mTc-MIBI and single-photon emission computed tomography (SPECT-CT) were performed to exclude the presence of other parathyroid lesions outside the neck region.

Percutaneous ethanol ablation under ultrasound guidance

After skin disinfection, 95% ethanol was injected into the lesion under continuous ultrasound control. A 25G/25 mm needle was used. The injected ethanol amount was 50-100% of the calculated adenoma volume. The number of applications varied from 1 to 5 at 24 to 48-hour intervals, depending on the ultrasound-assessed changes in the volume, structure, borders and vascularity of the PTA, as well as the patient's feeling of pain. The disappearance of the Doppler blood flow signals was a criterion for completing the PEA course.

Follow-up after the PEA

Serum Ca, PO4, PTH, 25(OH)D and uCa were measured and neck ultrasound was performed to determine the size and vascularity of the treated PTA at M3 and

M6 after the procedure. The relative change in PTA volume was calculated by the formula: [(V0 – VM3/M6) × 100]/V0, where V0 is the PTA volume before PEA and VM3/M6 is the PTA volume at M3 and M6, respectively.

A second course of PEA was administered in the patients with elevated serum Ca and/or persisting vascularity of the treated PTA at M3 follow-up. Those participants were excluded from further analysis.

Statistical analysis

The data was processed and analyzed using IBM SPSS Statistics for Windows, Version 19.0 Armonk, NY: IBM Corp. Numerical variables were presented as mean and standard deviation or median and IQ range according to the type of data distribution. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify the normality of the data distribution. The category variables were presented as proportions and 95% confidence interval. Parametric (Student t-test) and non-parametric analysis (Mann-Whitney U test, χ^2 test) were used to explore the differences between groups in continuous variables. Hypothesis testing was performed at a pre-fixed significance level $p \leq 0.05$ at a 95% confidence interval. The change in the studied parameters was presented with graphics.

RESULTS

The baseline characteristics of the treated patients are presented in Table 1.

Overall, 19 (54.3%) patients underwent three consecutive ethanol applications, 6 (17.1%) – four applications, 4 (11.4%) – five applications, 5 (14.3%) – two applications. In one patient the procedure was discontinued after the first application due to side effects.

A follow-up of all patients was carried out at M3 after PEA. A second course of PEA was administered in 9 patients because of persisting elevated serum Ca at M3. Two participants did not show up for the visit at M6. Thus, 24 patients remained in the analysis group at M6.

The PTA volume decreased by 53.3% at M3 compared to baseline ($p < 0.001$). There was no volume change in 4 (11.4%) patients (Fig. 1a). The reduction of PTA volume reached 67.9% at M6 ($p < 0.001$), including two patients who had not responded with volume decrease at M3. The other two patients were excluded from the analysis because of a second course of PEA (Table 2).

Similarly, serum Ca and PTH decreased significantly at M3 and M6 (Fig. 1b, c).

Table 1. Characteristics of patients with PHPT before PEA

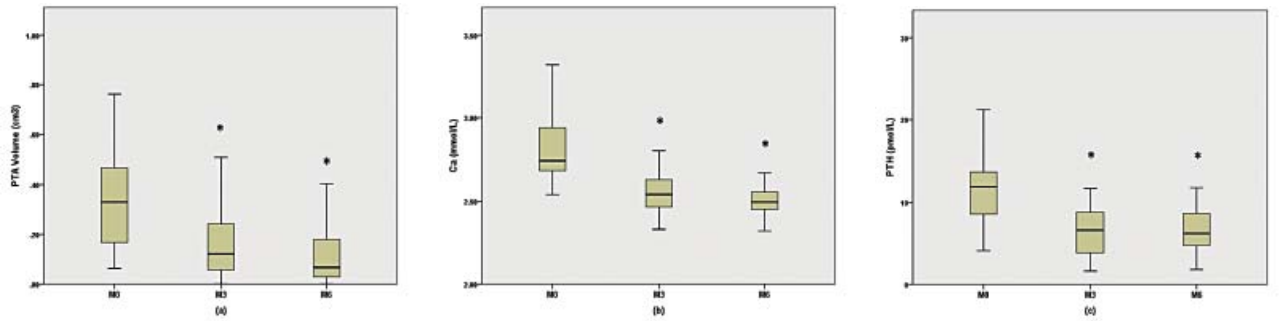
Age (y)	**59.7 ± 12.4**
Gender n (%) Female Male	 30 (85.7) 5 (14.3)
BMI (kg/m^2)	25.4 (22.8-30.8)
Ca (mmol/L)	2.74 (2.68-2.95)
PO4 (mmol/L)	0.92 ± 0.14
PTH (pmol/L)	11.9 (8.2-13.9)
25(OH)D (ng/ml)	22.87 ± 9.39
uCa (mmol/24 h)	5.69 (3.30-8.97)
PTA volume (cm^3)	0.33 (0.17-0.48)
Ethanol volume (cm^3)	0.29 ± 0.11
Number of ethanol applications per gland	3.2 (1-5)

Data are presented as mean ± SD or median (IQ range) according to the type of data distribution. **Abbr.:** BMI – body mass index; Ca – calcium; PO4 – inorganic phosphates; PTH – parathyroid hormone; 25(OH)D – 25-hydroxy-vitamin D; uCa – calcium excretion in 24-hour urine; PTA – parathyroid adenoma

Table 2. Changes in serum Ca, PTH and PTA volume at M3 and M6 follow-up

Parameters	**M0 (35)**	**M3 (35)**	**M6 (24)**	**p**
Ca (mmol/L)	2.76 (2.68-2.89)	2.54 (2.46-2.63)	2.49 (2.45-2.56)	P < 0.001
PTH (pmol/L)	11.9 (8.2-13.9)	6.6 (3.8-9.4)	6.1 (4.3-8.7)	P < 0.001
PTA volume (cm^3)	0.33 (0.13-0.60)	0.12 (0.06-0.26)	0.07 (0.02-0.18)	p < 0.001

Data are presented as median (IQ range). Abbr.: p – compared with baseline value before PEA; M0 – before PEA; M3 – three months after PEA; M6 – six months after PEA; Ca – calcium; PTH – parathyroid hormone; PTA – parathyroid adenoma



Abbr.: M0 – before PEA; M3 – three months after PEA; M6 – six months after PEA; (*) – p < 0.001 compared with baseline value before PEA

Fig. 1. Changes in the PTA volume (a), serum Ca (b) and PTH (c) after PEA

Normocalcaemia was achieved in 26 patients (74.3%) at M3 and their serum Ca before PEA was significantly lower than in patients with persistent hypercalcaemia (Table 3).

The baseline PTA volume was significantly smaller in the normocalcaemic patients than in the hypercalcaemic ones (p = 0.02) and the difference remained significant at M3 (p = 0.004). There was no difference in the serum PTH both at baseline and at M3, in either group (Table 3). The serum Ca and PTH and the PTA volume decreased significantly at M3 in patients who achieved normocalcaemia and no difference was found in the group of still hypercalcaemic patients.

At M6, 22 (91.7%) of the 24 subjects remained normocalcaemic, which is 62.8% of the whole treated group. Serum Ca increased compared to M3 levels in 2 patients who were switched to second course of PEA.

PTH levels at M3 returned to normal in 19 (54.3%) patients. PTA volume, serum Ca and 25(OH)D, both at baseline and at M3, did not differ between patients with normal PTH and those with elevated PTH at M3 (Table 4).

Table 3. Comparison of serum Ca, PTH and PTA volume at baseline and at M3 between normocalcemic and hypercalcemic subjects at M3

Parameters / M3 groups	M0			M3		
	Ca (mmol/L)	PTH (pmol/L)	PTA volume (cm^3)	Ca (mmol/L)	PTH (pmol/L)	PTA volume (cm^3)
Normocalcemic (26)	2.70 (2.66-2.85)	12.4 (9.6-15.1)	0.31 (0.14-0.41)	2.48 (2.44-2.56)	6.3 (4.1-7.9)	0.08 (0.05-0.19)
Hypercalcemic (9)	2.95 (2.79-3.05)	8.90 (4.8-12.0)	0.64 (0.28-0.91)	2.78 (2.65-2.99)	8.2 (3.1-24.5)	0.26 (0.15-0.94)
p	p = 0.007	NS	p = 0.02	p < 0.001	NS	p = 0.004

Data are presented as median (IQ range). NS – not significant (p > 0.05). **Abbr.:** Ca – calcium; PTH – parathyroid hormone; PTA – parathyroid adenoma; M0 – before PEA; M3 – three months after PEA

Table 4. Comparison of serum Ca, 25(OH)D and PTA volume at baseline and at M3 between patients with normal and persistently high PTH at M3

Parameters / M3 groups	M0			M3		
	Ca (mmol/L)	25(OH)D (ng/ml)	PTA volume (cm^3)	Ca (mmol/L)	25(OH)D (ng/ml)	PTA volume (cm^3)
Normal PTH (19)	2.78 (2.65-2.95)	21.6 (14.1-30.9)	0.31 (0.15-0.39)	2.47 (2.41-2.63)	25.9 (20.5-30.1)	0.08 (0.04-0.22)
High PTH (16)	2.72 (2.68-2.99)	22.0 (19.5-26.9)	0.42 (0.17-0.88)	2.56 (2.49-2.66)	22.8 (19.1-32.3)	0.17 (0.08-0.44)
p	NS	NS	NS	NS	NS	NS

Data are presented as median (IQ range). NS – not significant (p > 0.05). Abbr.: Ca – calcium; PTH – parathyroid hormone; 25(OH)D – 25-hydroxy-vitamin D; PTA – parathyroid adenoma; M0 – before PEA; M3 – three months after PEA

Normal PTH was found in 15 (62.5%) of the 24 patients at M6. In 3 cases, PTH rose after normalization at M3.

Adverse effects of PEA

Mild and transient adverse effects during and after PEA were reported by 5 (14.3%) patients. Local pain and subcutaneous edema after the second ethanol application were observed in 4 of them, which led to interruption of the treatment. The symptoms disappeared completely within 1 to 4 weeks. Voice change, neck discomfort and pain were reported in one patient after the first ethanol application. Intramuscular methylprednisolone (40 mg/day) was applied for 3 consecutive days, followed by oral prednisolone for 2 weeks. Complete voice recovery was registered after 4 months. In all patients with adverse effects, the treated PTA originated from an inferior PTG (in 4 patients – left inferior and in one patient – right inferior gland). The PTA volume was less than 1 cm^3 in 4 patients and over 1 cm^3 – in one patient. The baseline PTA volume and the amount of applied ethanol in patients with adverse effects did not differ significantly from those in the other patients. Symptomatic hypocalcaemia was not observed in our group.

DISCUSSION

In our study, we evaluated the changes in serum Ca, PTH and PTA volume as measures of the early results of PEA in patients with PHPT. We found a significant reduction in serum Ca three months after the procedure, with normal levels achieved in 74.3% of the treated patients. The effect persisted at M6, with normal serum Ca achieved in 91.7% of the patients in the follow-up at M6, which is 62.8% of the whole treated group. Our results do not differ significantly from those of previously published studies though the exact implementation of the procedure and the observed efficacy vary to some extent. Cercuel et al. reported normalization of both serum Ca and PTH in 56% of the treated patients [19]. In another 33% of patients, they achieved normal or slightly increased serum Ca levels, but the serum PTH remained elevated. Stratigis et al. reported that 89.5% of the patients became normocalcemic at M6 and remained so for a mean follow-up of 21 months [20]. They defined as responders to treatment patients with PTH within the normal range at M6. According to this criterion, the authors reported a treatment success in 65% of the patients. In contrast to our results, the patients with normal PTH at M6 in their series had lower baseline PTH levels and baseline PTA volume. There was no difference in baseline Ca levels between patients with normal and elevated PTH. In our study, we observed a normalization of PTH in 54.3% of the cases at M3 and in 62.5% at M6, which reaffirms the hypothesis of a continuous PEA effect. We measured the levels of 25(OH)D as a possible confounder in the evaluation of PTH. The lack of difference between the 25(OH)D levels at baseline and at M3 both in the groups with normal and with persistently high PTH, justifies the conclusion that the vitamin D level doesn't influence the outcome of the PEA treatment.

In the follow-up we used the upper normal value of serum Ca (≤ 2.62 mmol/L) as a main criterion for the efficiency of PEA. Patients who were normocalcemic at M3 had lower baseline serum Ca than patients with persistent hypercalcaemia. These data suggest a predictive role of baseline Ca for the therapeutic effect. The baseline PTA volume, which was significantly higher in the patients with hypercalcaemia at M3, is another predictive factor. The limited ethanol exposure mainly along the needle way might be a reason for a lower PEA efficacy in larger PTAs. As a technical difference, we used a standard sharp-tip needle for the procedure unlike other teams who perform PEA with a 21G blind-tip needle with three lateral holes [20].

At the M6 follow-up normocalcaemia persisted in 91.7% of the cases with normal serum Ca at M3. Therefore, the normalization of serum Ca at M3 may predict the treatment results at M6. These data suggest that the decision to perform a second PEA should be based on an incomplete effect at M3.



Fig. 2. Ultrasound image of PTA from the right inferior PTG. (**a**) before PEA – well vascularized PTA with volume of 0.76 cm^3; (**b**) three months after PEA – 93.4% volume reduction of PTA, without vascularity; (**c**) six months after PEA – 97.4% volume reduction and no vascularity

In two cases the serum Ca increased at M6 after normalization at M3. This fact could be explained with the incomplete necrosis of the PTA and subsequent hyperplasia of the residual functional tissue [22].

We achieved a 67.9% median reduction in PTA volume at M6. Yazdani et al. reported volume decrease of PTA from 1.87 ± 6.45 cm^3 to 0.38 ± 0.48 cm^3 one month after PEA [21]. In our study, in 2 cases we observed the first volume reduction at M6, which is probably due to the latent effect of PEA.

Compared with surgery, PEA is less invasive and cheaper, does not require general anesthesia and is associated with fewer side effects. Moreover, PEA does not adversely affect the outcome of subsequent surgery in cases of insufficient cure results [20, 22]. However, PEA has some disadvantages including partial effect of ethanol on the PTA parenchyma, temporary dysfunction of the recurrent laryngeal nerve, transient hypocalcemia and fibrosis of the surrounding tissues [20, 22-25]. In our study, side effects occurred in 14.3% of the cases. All of them were transient and resolved within four months of the procedure. According to published data, the main factor for complications in PEA is the amount of applied ethanol [13, 23, 24]. Our data didn't show a significant difference in the amount of injected ethanol between the patients with and without adverse effects. Currently there is no standardized technique for performing PEA. The time interval between the applications and the ethanol volume vary among the different published studies – the patients have been injected at 24-48-hour, weekly or monthly intervals in amount between 50% and 100% of the PTA volume [19-21, 26]. In the present study, the quantity of injected ethanol varied between 50% and 100% of the PTA volume and was applied at 24-hour intervals. The number of consecutive applications was determined individually depending on the vascular flow inside the PTA. We chose this approach because it allows the administration of a higher total amount of ethanol at relatively low single doses without increasing the risk of complications.

This study has some limitations. The number of patients with PHPT who were treated with PEA was small, though comparable to those in most published studies. The follow-up was relatively short to assess the overall efficacy. Larger studies with longer follow-up are needed to estimate the long-term effect of PEA. Finally, we did not have a control group of patients with PHPT who were treated surgically to compare the efficiency and safety of the two therapeutic methods.

In conclusion, the results of our study show that PEA is an effective and safe method for the treatment of patients with PHPT and increased surgical risk. A significant reduction in PTA volume, serum Ca and PTH levels was observed in the short-term follow-up. An early decrease of serum Ca to normal range is a prognostic factor for the treatment efficiency.

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