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Review of Methods of Percutaneous Ethanol Injection for Destruction of Thyroid Nodules.

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ABSTRACT

The article discusses about research of the outcomes assessment using sclerotherapy of thyroid nodules by percutaneous ethanol injection in adult patients with benign nodular thyroid neoplasms. Based on the obtained data during the literature search for the primary analysis were separated works meet the criteria of the clinical trial, used the data of the meta-analysis, as well as highlighted publication from not peer-reviewed sources. In the studied literature we found, the conflicting views about the frequency, the amount and the concentration of injected ethanol, indications to the percutaneous ethanol injection, as well as the maximum size of the node, which can be subjected to sclerotherapy. Future research should be aimed at assessing the quality of life after the procedure, the registration of mortality, malignancy, comparing the advantages of minimally invasive procedures with surgery. The main development of the method should be use of the procedure at the level of primary health care organizations.

Keywords: thyroid gland, thyroid nodules, percutaneous ethanol injection, PEI, clinical trials

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INTRODUCTION

The importance of choosing the right tactics of patients' treatment with thyroid nodules caused by the prevalence of disease and the emergence of new therapy methods. The analysis of the medical literature on this issue has shown the lack of consensus among endocrinologists and surgeons on the treatment of benign tumors of the thyroid gland.

Currently, in addition to medical therapy, surgical treatment of benign thyroid neoplasms researchers implemented sclerosis method [1, 2], which has not yet received a comprehensive assessment in the long-term prospective studies. Attitude to sclerotherapy among experts is ambiguous. There are opinions about the possible degeneration of sclerosed nodules, which limits widespread use among endocrinologists this method. According to the literature there are no messages about the long-term effects of sclerotherapy. Therefore, further research is necessary to obtain reliable results on the effectiveness of this type of treatment.

The contents of nodal neoplasms of the thyroid gland may be solid or cystic. According to various studies by 15-30% nodal thyroid neoplasms are cystic or predominantly cystic character [3-7]. Most malignant neoplasms observed in solid and of hypoechogenic nodules, but on its own the character of the detection of cystic node does not preclude its malignancy [5, 7]. Studies have shown that benign cystic neoplasms of the thyroid gland that were treated by the method of simple aspiration provide a high rate of recurrence [8, 9]. Surgical treatment of cystic thyroid nodules is a common method, despite the high risk of complications, such as side effects of general anesthesia, post-operative scarring, nerve damage, hypothyroidism and damage to the parathyroid glands. According to the American and the European Thyroid Association for the treatment of benign tumors of the thyroid gland representing the cystic nodes has to be used conservative (or non-surgical) approach [10].

For the management of patients with benign tumors of the thyroid gland of cystic nature also used radioactive iodine ablation. This non-surgical method of treatment is quite effective, but it requires special equipment [11]. Another option is to apply therapy instillation tetracycline. However, using these methods has not proven statistically significant effects of reducing the size of the thyroid gland nodules [12].

Some experts use suppressive therapy with levothyroxine (LT4) to reduce the number and size of nodules. In addition, as an alternative to surgical intervention in the practical use a minimally invasive procedure such as sclerotherapy of percutaneous ethanol injection (PEI), laser photocoagulation (LP) and microwave frequency (MW), radio frequency ablation (RF) and ablation of high-intensity focused ultrasound (HIFU). The advantages of sclerotherapy of thyroid nodules by PEI presented a number of researchers in small volumes of observations [13]. However, no data on the benefits of the method of ethanol destruction in the treatment of benign nodular thyroid neoplasm were confirmed in large studies [14].

Aim

The aim of our study was to evaluate the outcomes of the sclerotherapy use in thyroid nodules by PEI method in adult patients with benign nodular thyroid neoplasms based on an analysis of published data.

METHODS

Description of the intervention procedure

Preferably blood sampling is performed prior to the intervention to determine the levels of TSH (TSH), free T4 (FT4), thyroid peroxidase antibodies (AbTPO), antibodies to thyroglobulin. The amount of units is calculated in accordance with the recommendations of Brunn et al. [15]. In order to exclude malignancy before starting treatment with the PEI, all patients underwent fine needle aspiration biopsy of nodules. Under ultrasound guidance, without local anesthesia and sedation slowly over 2 minutes entered a sterile 95% ethanol through the needle 23-G. Depending on the size of the nodules, the ethanol dose in each session can vary from 1 to 6 ml. Injected volume of ethanol from 20% to 70% of the volume of aspirated node. In some cases, ethanol administered in a mixed form with the aspirated fluid (in the case of toxic and nontoxic solid components). In such cases, the administered volume of ethanol varied from 20 to 30% of the node volume. PEI sessions are conducted in a single session or a variant depending on the node dynamics. The mean total

dose is 0.68 ml of ethanol (in the range of 0,43-0,91 ml) per milliliter of nodal volume. The alcohol is introduced by an average of 2.92 (ranging from 2 to 4 times) on outpatient techniques. Ethanol deposited at the node and gradually absorbed without any discomfort for the patient during the next 24 to 48 hours. The injection causes permanent tissue ablation with local thrombosis and necrosis of small vessels intrasite. Control with the ultrasonic testing is required to perform the procedure because the technique can be considered safe only in the hands of a professional [16].

Another variant of the PEI method has been proposed by Bennedbaek et al..They aspirated subtotal cysts, washing with ethanol and then aspirating liquid through the full two minutes (without removing the needle) under ultrasound guidance [17]. According to the study of this method complications were noted only in 18% of participants. Such persons are subsequently subjected hemithyroidectomy.

In most cases, the subsequent follow-up after the protocol of tactics choice includes a medical examination to determine the degree of compression symptoms, ultrasound measurement and evaluation of TSH, FT4, AbTPO and ATG. The subsequent examination after the effect is carried out annually. Clinically significant effect is considered to be $\geq 50\%$ reduction in unit sizes with respect to the initial volume before treatment. With respect to toxic components, achieving complete success is considered normal TSH and FT4 levels at 4 weeks following the PEI, and then during follow-up without thyreostatic therapy [15].

Criteria for consideration of studies in review

Research types

We planned to include a wide range of controlled comparative studies: RCTs, controlled clinical trials, controlled before and after studies and intervention studies of time series. In the absence of such experimental studies, we included observational studies, if in the course of performing their authors have compared the results with a control group. We have examined the results of studies published in all languages in the databases available on request or obtained directly from the researchers.

Research participants

Participants in the study were identified in the report all adult patients of both sexes with a verified diagnosis of benign nodular thyroid neoplasms.

Types of intervention

The review included all studies that evaluated the effectiveness of sclerotherapy of thyroid nodules by percutaneous ethanol injection (PEI).

Types of outcome measurement

Primary outcomes

Primary outcomes were mortality, reduction of the size of the node more than 50% after the intervention, the registered ultrasound method and quality of life (measured by a validated scale or instrument to assess quality of life).

Secondary outcomes

Secondary outcomes included: normalization of TSH, FT4, aTPO and ATG, reducing compression symptoms (dysphagia, respiratory disorders, feeling of "lump in the throat") and lack of cosmetic complaints. Adverse effects of the intervention include: local pain, node malignancy.

Searching methods

Electronic search

The target list included all studies carried out prior to January 2016, registered in the major databases: The Cochrane Library, MEDLINE, EMBASE, and "gray" literature.

We have the following search terms were used: percutaneous ethanol injection thyroid nodule OR PEI thyroid nodule OR PEI TN OR sclerotherapy thyroid nodule OR thyroid sclerotherapy OR alcohol ablation thyroid nodule OR ethanol ablation thyroid nodule OR noninvasive treatment thyroid nodule. Searches were combined in the following search terms and adapt your search terms in each of the bases.

Overview of the search strategy used to work with each of the bases, presented in the table 1.

Table 1: Search strategy and the number of the results

Source	Strategy	Selected sources
Medline (Ovid SP)	1 thyroid\$.mp. 2 nodule\$.mp. 3 percutaneous ethanol injection thyroid nodule/ 4 PEI thyroid nodule/ 5 PEI TN/ 6 sclerotherapy thyroid nodule/ 7 alcohol ablation thyroid nodule/ 8 ethanol ablation thyroid nodule/ 9 noninvasive treatment thyroid nodule/ 10 percutaneous ethanol injection thyroid nodule.mp. 11 PEI thyroid nodule.mp. 12 PEI TN.mp. 13 sclerotherapy thyroid nodule.mp. 14 alcohol ablation thyroid nodule.mp. 15 ethanol ablation thyroid nodule.mp. 16 noninvasive treatment thyroid nodule.mp. 17 thyroid sclerotherap\$.mp. 18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 19 randomized controlled trial.pt. 20 controlled clinical trial.pt. 21 randomized.ab. 22 randomly.ab. 23 trial.ab. 24 groups.ab. 25 survey\$.tw. 26 evaluat\$.tw. 27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28 humans.sh. 29 27 and 28	138
Embase (Ovid SP)	1 thyroid\$.mp. 2 nodule\$.mp. 3 percutaneous ethanol injection thyroid nodule/ 4 PEI thyroid nodule/ 5 PEI TN/ 6 sclerotherapy thyroid nodule/ 7 alcohol ablation thyroid nodule/ 8 ethanol ablation thyroid nodule/ 9 noninvasive treatment thyroid nodule/ 10 percutaneous ethanol injection thyroid nodule.mp.	138

	11 PEI thyroid nodule.mp. 12 PEI TN.mp. 13 sclerotherapy thyroid nodule.mp. 14 alcohol ablation thyroid nodule.mp. 15 ethanol ablation thyroid nodule.mp. 16 noninvasive treatment thyroid nodule.mp. 17 thyroid sclerotherap\$.mp. 18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 19 randomized controlled trial.pt. 20 controlled clinical trial.pt. 21 randomized.ab. 22 randomly.ab. 23 trial.ab. 24 groups.ab. 25 survey\$.tw. 26 evaluat\$.tw. 27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28 humans.sh. 29 27 and 28	
The Cochrane Library	1 "percutaneous ethanol injection thyroid nodule" (In All Text) 2 "sclerotherapy thyroid nodule" (In All Text) 3 "thyroid sclerotherapy" (In All Text) 4 "alcohol ablation thyroid nodule" (In All Text) 5 "ethanol ablation thyroid nodule" (In All Text)	5

Search other sources

Also, we have attempted to contact experts in this field to identify for any further test data, which were not found in the main search. In addition, reference lists and collections of conferences have been tested by the above methods.

RESULTS

We analyzed 987sources, 256 of them were found in databases, including Cochrane Library. The part of the publications were not indexed in special repositories and have been obtained from a search in the Google Scholar; ISTP (<http://portal.isiknowledge.com/portal.cgi>) (Index to Scientific and Technical Proceedings); INSIDE (BL database of Conference Proceedings and Journals); Index to Theses (formerly ASLIB) (<http://www.theses.com/>) (UK and Ireland theses).

Among all the analyzed works in clinical trials (clinical trials), only 4 studies were classified. Fifth publication included in our review was presented a meta-analysis, some of which affected related to the purpose of this study research questions.

Percutaneous ethanol injection (PEI) under ultrasound guidance is the least invasive therapeutic procedure proposed for the non-surgical management of benign nodular thyroid neoplasms. PEI was firstly proposed in 1990 as a possible alternative to surgical methods of therapy with radioactive iodine for the treatment of autonomously functioning thyroid nodules in ambulatory patients [18-20]. Also, some authors described satisfactory results of PEI (43% reduction in unit volume) for the treatment of solid thyroid nodules in patients with symptoms of compression or cosmetic complaints, refused surgery or surgical risk [21]. When analyzing the data in the literature, we were allocated the results of studies on the behavior of the 607 randomized patients, 337 different intervention and 270 comparison group. Clinical tests were conducted to compare PEI clinical efficacy using different doses of ethanol [22], introduction NaCl [17], levothyroxine LT4 [23], percutaneously hydrochloric acid [1], only aspiration [16, 24] and radiofrequency ablation [25]. One study conducted in Denmark has been devoted over injecting tetracycline hydrochloride with NaCl [12]. Participants

in the trials were euthyroid women with complaints of local compression of the neck due to cystic nodules in age from 18 to 85 years.

The study Jayesh S.R. et al., 2009 was aimed to assess the efficacy and safety of ultrasound controlled ethanol sclerotherapy of cystic thyroid nodules. As a result of the study, 16 of 54 patients were mostly cystic nodules detected. 15 patients were included in the study. After the ethanol sclerotherapy, four of 15 patients (26.6%) showed complete disappearance of cysts and nine (60%) showed significant decrease in cyst volume (i.e., volume reduction of cysts $\geq 50\%$ of the initial volume). Only two patients showed a significant volume reduction of cysts; Both of these patients had nodules with an initial volume of ≥ 20 cc. During the observation period had no complications related to injecting ethanol. Thus, the researchers concluded that sclerotherapy with ethanol is an effective and safe treatment of benign cystic thyroid nodules with volumes < 20 cm. For the treatment of cystic nodules with volume > 20 cc may need a larger amount of ethanol injection and longer observation period [10].

Two studies have been devoted for the therapy of solid nodules (the liquid content less than 10%) [18, 23]. The authors determined the characteristics of nodules using ultrasound and the diagnosis was confirmed by the purity of the process of aspiration needle biopsy and cytology, as well as evaluated thyroid function. Study participants with suspicious or positive results of FNAB of follow-up were excluded.

In the paper of Bennedbæk F.N. the purpose of the study was to evaluate the effect on the frequency of recurrent relapses benign thyroid cysts in a double blind randomized study after sclerotherapy ethanol as compared to administration of isotonic saline and subsequent complete emptying of the node. Sixty-six patients with recurrent benign (control based on ultrasound biopsy) thyroid cysts ($> \text{or} = 2$ ml) were randomly assigned to either a group subtotal cyst aspiration washing with 99% ethanol and subsequent complete fluid aspiration ($n = 33$) or a group with cysts washing procedure isotonic saline followed by aspiration of the liquid ($n = 33$). In case of relapse (defined as the amount of cysts after treatment of > 1 mL) at a monthly assessment, the procedure was repeated, but no more than three times. Manipulations were performed under ultrasound guidance. Patients were followed up for 6 months. Groups were similar in age and sex, and clinical-laboratory data prior to the intervention. The effect of treatment (defined as the amount of cysts $< \text{or} = 1$ ml at the end of the observation period) was obtained in 27 of 33 [82%; 95% (CI), 65-93] in patients treated with ethanol, and 16 of 33 (48%; 95% (CI), 31-66), patients treated with saline ($P = 0.006$). In the group of ethanol, 21 of 33 (64%) patients were cured after only a single session compared with six of the 33 (18%) in saline group ($p = 0.002$). The number of previous procedures, administration of the drug (the $P = 0.005$) and the base volume cysts ($p = 0.005$) also influenced the result, there is a chance of success decreased with the number of previous administrations and to the increase in cysts. Seven patients (21%) treated with ethanol experienced the pain of moderate to severe (average duration of 5 min, 95% (CI), 2-10), one was marked by transient dysphonia. Thus, the authors concluded that the treatment of recurrent thyroid cysts ethanol exceeds simple aspiration and washing with brine. Sclerotherapy with ethanol devoid of serious side effects and is clinically relevant alternative to non-surgical treatment of recurrent thyroid cysts.

Also these researchers were conducted in another study (Bennedbæk, F.N. et al.) In order to estimate the effect of the two alternative methods of medical treatment, percutaneous ethanol injection therapy, and L-T4, to single cold benign thyroid nodules. These prospective randomized trial of 50 patients with single hypothyroid solid colloidal nodes causing local discomfort or are allocated to one group of intranodular injection of sterile 98% ethanol ($n = 25$) or to a group receiving suppressive dose of L-T4 ($n = 25$). The dose of ethanol was 20-50% of the initial volume prior to the treatment site. The initial daily dose of L-T4 was 1.5 μg / kg body weight and adjusted monthly during the first six months in order to reduce the concentration of serum TSH to subnormal levels (< 0.40 IU / L). Displacement nodules and total thyroid were assessed by ultrasound, thyroid function determined by routine tests before and during observation. Clinical symptoms (feeling of compression, cosmetic symptoms) were assessed at baseline and after 12 months. The average dose of ethanol was 21% [95% (CI), 18; 25] of the original volume prior to treatment sites. In this group the median size of nodulation reduction was 47% (95% (CI) 33; 57; $P < 0.0001$) versus 9% (95% (CI) -7; 22; $P = 0.09$) group, treated with L-T4. The differences between the two treatment regimens were statistically significant ($P < 0.0001$). Median of perinodular thyroid volume reduction was 20% (95% (CI) 11; 31; $P = 0.03$) in the group of L-T4, while no change was observed in ethanol sclerotherapy group (-2.5% 95% (CI) -18, 11; $P = 0.9$). Fourteen out of 25 (56%) of patients receiving injections of ethanol and 8 out of 25 (32%) treated with L-T4 had complete relief of symptoms within 12 months of follow-up ($P = 0.09$). No major adverse effects were

noted in either group. As a result of the study, the authors concluded that percutaneous ethanol injection administered in the form of a single-mode lead to a satisfactory clinical response at ~ 50% of patients in the form of a reduction in units of volume in half, and the effect of treatment of L-T4 is insignificant [23].

In the trial carried out [26] of the excluded observations and cases of toxic multinodular goiter.

Eight single-center studies have been carried out in Denmark [12, 17, 22, 23], Italy [16, 24], South Korea [25] and Taiwan [1]. Their number has described the work of the research team Bennedbæk, F.N. et al..The great interest were the results of studies of the Italian thyroidologists. Valcavi R. and Frasoldati A. in 2004 published data on the US-controlled study of percutaneous ethanol injection therapy of cystic thyroid nodules [16].

The study was a controlled, randomized, pre data trial involving 281 patients (221 women and 60 men, aged 18 to 85 years) with benign cystic thyroid nodules. Inclusion criteria was local discomfort or cosmetic complaints, cystic volume of 2 ml, 50% or > liquid component, goodness, confirmed by cytology samples obtained in the US-controlled of FNAB, and euthyroidism. After randomization, 138 patients were subjected to a simple aspiration of nodules and 143 to PEI. The amount of ethanol was assigned from 50% to 70% of the volume of liquid extracted from the aspiration site.

During one year of observation, the volume of nodules in the ethanol sclerotherapy group were reduced to a size of 5.5 +/- 11.7 mL vs. 16.4 +/- 13.7 mL ($p < 0.001$) in the simple aspiration, an average of 85, 6% and 7.3% respectively of the original volume ($p < 0.001$). Compression and cosmetic symptoms disappeared in 74.8% and 80.0% of patients treated with PEI compared with 24.4% and 37.4% of patients undergoing simple aspiration, respectively ($p < 0.001$). Side effects were minor in PEI.

Another paper presented the Italian team of researchers Verde G., Papini E. et al. For 10 years before Valcavi R. study [24] also showed the effectiveness of PEI in the treatment of cystic thyroid nodules. The first operation unit characterized randomized study that one month after the treatment, a decrease of nodules in the PEI group was significantly higher than in the group after aspiration of fluid without ethanol injection ($p < 0.01$). Reducing the volume of nodes more than 50% compared with the basic dimensions of 8 (80%) patients in group PEI, and 3 (30%) patients in group simple aspiration ($p < 0,01$).

The second block of their work representing the data of a prospective study. There were obtained the following results: a significant decrease in volume units ($p < 0,01$ compared to pre) in the observation after 1 and 12 months after percutaneous ethanol injection (initial size (before treatment) Median - 14.5 Range 1.5 - 65.8 ml; 1 month: the median - 3.5, range 0.4-38.9 mL; 12 months: the median - 2.5, range 0.4-34.5 mL). Reduced volume of nodules more than 50% was observed in 24 (80%) patients. At the same time, as well as the absence of significant side effects have been reported in previous studies. Thus, the authors concluded that the ultrasound controlled PEI in treating cystic thyroid nodules is safe, inexpensive and effective therapeutic approach in patients with cystic benign thyroid nodules.

Similar data were also obtained by other researchers, such as the Korean researchers Sung J.Y. et al. [25], 2010. They were conducted a prospective randomized study of the use of PEI versus radiofrequency ablation in the treatment of cystic thyroid nodules. The average decrease in volume units amounted to 96.9% and 93.3% PEI in radiofrequency ablation ($n = 21$ each) (the difference 3.6%), thus demonstrating the therapeutic effect of the identity of treatments. All patients demonstrated a significant therapeutic success ($p > 0.99$). The average level of symptoms and cosmetic evaluation showed no significant differences in both groups ($p = 0.806$ and $p = 0.682$ respectively). Also, the two intervention did not give any serious complications ($p > 0.99$). Thus, the authors concluded that PEI is not less effective, but cost significantly less costly procedure for the treatment of benign cystic thyroid nodules.

The study of Taiwanese scientists Chu S.N. et al., also dedicated ethanol sclerotherapy thyroid nodules with cystic contents mainly focused on the effect of c PEI compared to administration nodes after aspiration of a weak solution of hydrochloric acid (pH 1.0).As a result, a group of PEI had a significantly higher percentage of extinction units than the group with the introduction of hydrochloric acid (90% vs. 37,5%, $p = 0,023$) and the disappearance of complaints after the first treatment (90% vs. 44.4%, $p = 0.038$). In this paper, it was rejected

the hypothesis about the possibility of the use of hydrochloric acid solution with a low pH as a sclerosing substance and once again confirmed the high efficiency of PEI [1].

All tests were performed on an outpatient basis with the participation of primary care physicians or specialists from clinics specializing in diseases of the thyroid gland. Seven studies originally conducted aspiration thyroid content node followed by ethanol, and the corresponding effect of the ablation assembly walls. The volume of ethanol ranged from 21% [1] and 70% of the volume of aspirated fluid [16]. For therapy of solid test nodes using PEI median volume of ethanol administered ranged from 21% to 25% of the volume of fluid aspirated node [18, 23]. The resistance during the introduction of the ethanol or severe pain were the reasons for the termination procedure.

In one study was devoted the study of comparing the use of tetracycline hydrochloride and NaCl in thyroid cysts unit with volume of about 2 ml of [12]. Under ultrasound guidance first fluid is then aspirated or injected 2 ml tetracycline hydrochloride and 2 ml of sodium chloride solution, and then aspirated to five times to achieve the complete emptying of the cyst.

Evaluation of intervention outcomes [14]

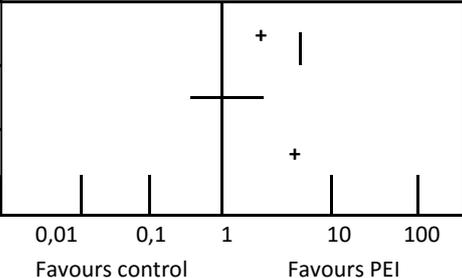
Primary outcomes

Symptoms of compression and cosmetic symptoms

Five studies evaluated the complaints and symptoms of compression of the cosmetic symptoms. Valcavi 2004 using questionnaire-based questionnaire, interviewing with the use of direct answers to the questions "yes / no" has been applied in the work Bennedbaek 2003 graded questions and visual analogue scale were described in Bennedbaek 1998-1999 research and Sung 2013.

Signs of improvement in symptoms after compression studies have been demonstrated in three trials of 370 participants in the range of observation by 6 months after the PEI and 12 months follow 145/187 (78%) and 70/183 (38%) in the study using for sclerotherapy alternative substance. The relative risk (RR) in the range from 1.0 to 3.06 in favor of PEI meta-analysis to assess the effects of works of levothyroxine compared with minimally invasive therapies nodal thyroid tumors was calculated [14] (Table 2).

Table 2: Results of a meta-analysis of works on the assessment of effects of levothyroxine and minimally invasive treatments for nodular thyroid tumors [14]

Comparison of Percutaneous ethanol instillation versus control (cyst aspiration, isotonic saline, levothyroxine, radiofrequency ablation), Outcome I Improvement of pressure symptoms (end of study)							
Review: Levothyroxine or minimally invasive therapies for benign thyroid nodules							
Comparison: 2 Percutaneous ethanol instillation versus control (cyst aspiration, isotonic saline, levothyroxine, radiofrequency ablation)							
Outcome: I Improvement of pressure symptoms (end of study).							
Study or subgroup	PEI	Control	Risk Ratio M-		Risk Ratio M-		
	n/N	n/N	H, Random, 95% CI		H, Random, 95% CI		
PEI Bennedbaek 1998	17/22	11/22			1,55	(0,96, 2,49)	
PEI Bennedbaek 1999	27/30	27/30			1,00	(0,84, 1,18)	
PEI Valcavi 2004	101/35	32/131			3,06	(2,23, 4,20)	
			0,01	0,1	1	10	100
			Favours control		Favours PEI		

The dynamics of the symptoms of compression and cosmetic discomfort did not show statistically significant differences in the trials comparing PEI method of treatment radiofrequency ablation [25].

Reduction unit volume by 50% or more [14]

In all studies it has achieved a statistically significant reduction in unit sizes up to $\geq 50\%$ of the original volume.

Side effects [14]

In all we analyzed studies reported side effects in the form of pain of mild to moderate degree and a burning sensation. Two studies reported on serious side effects, such as dysphonia, permanent nerve palsy, perinodular tissue fibrosis [22], transient laryngeal dysfunction for a period of two months [16]. These effects varied depending on the dose of ethanol.

Secondary outcomes [14]

The degree of pain was also assessed as an indicator of portability PEI. The use of local anesthetic in the treatment of cystic thyroid nodules tend not described [1, 12, 17, 24, 25], in contrast to the studies that were treated solid components injections ethanol, where there was the need for a local anesthetic and analgesic agents [22, 23]. All studies except three [1, 16, 25] reported in the minutes of the dynamics of the levels of thyroid hormones during the observation. Bennedbaek 1999 conclusions about the cost-effectiveness of PEI have been made, but details were not provided. Two studies on the necessity and the importance of verifying the absence of malignancy of the process in the long term [1, 16]. Neither test is not assessed all-cause mortality or health-related quality of life.

The research results of non-clinical or simple randomized clinical trials

As noted above, the most pronounced effect observed for clinical sclerotherapy cystic nodes. According to the results Papiny E. et al. 1998 [27], over 85% of these units can be fully cured only with PEI. Lee S.J. et al. [28] analyzed the effect of sclerotherapy in 432 patients with benign nodular neoplasms of cystic nature. The effect of treatment was assessed by the authors on the degree of reduction of the volume of units: 1) the full effect – a decrease of more than 90% compared to the initial volume of the node; 2) partial effect - a reduction of 50% to 90%; 3) lack of effect - a decrease less than 50%. Full effect was observed in 19% of cases, partial - in 60.4%, and its absence - in 20.6%. According to other researchers reduced the size of cystic sclerotherapy nodes more than 50% at 80% [24] and 94% of patients [29].

Zingrillo M. et al. [30] conducted hardening large cystic benign tumors in patients in whom surgery was planned due to the presence of compression symptoms and no effect after two simple aspirations of the liquid contents of cystic nodes. After 6 months post-treatment the sizes of nodes decreased more than 90% – 85% of patients by 50 – 90%, no effect was observed in only 5% of patients. After 1.5 – 2 years of further clinical observation node size does not change significantly. These same researchers in his other work [31] reported a decrease in large cystic nodes after administration of ethanol at 91.9% in 93% of patients. Clinical monitoring of these patients over 5 years the authors found that the components have reached the maximum decrease of about 2 years after PEI and not further increased.

However, it should be noted that in some cases the treatment with ethanol cystic changed nodes may prevent two points. The first of them - is getting enough cellular material for cytology at two diagnostic FNAB [29]. As noted above, cytological confirmation of high quality of these components is a necessary condition for the start of formal therapeutic introduction of ethanol [32, 33]. Unfortunately, the percentage of non-informative results of needle biopsy of benign nodes predominantly cystic component is high enough, according to different authors, as well as their own research it reaches 30% [34]. The absence of a convincing double cytological confirmation of purity of such formations is a formal obstacle for the PEI, with little information of FNAB [35], such as the "colloid", "cystic fluid", "isolated group of follicular epithelial cells" are considered inconclusive.

The second point – is the presence in the cystic cavities nodes thick viscous colloid - liquid gel that is extremely difficult to give in aspiration through a needle puncture. According to some researchers, such formations sclerotherapy is ineffective [36]. According to the results Zingrillo M. et al. [31], the colloidal units are approximately one-third of cystic formations. In order to reduce the density of colloid ethanol sclerotherapy of these nodes the researchers began with the introduction of the primary alcohol without liquid aspiration. After 1 - 2 weeks carried attempt to aspirate the contents of the cystic cavity. If it was possible, the patient further was held 1 - 4 PEI sessions. The paper Zielenik W. et al. [37] also shows this method. In the first phase introduced a small amount of alcohol. According to the observations of the authors, for two weeks reduced the viscosity of the colloid. The second stage was done by PEI. According to the researchers, the effectiveness of methods was 91.7%.

In the Tarantino L. et al. [38] evaluated the efficacy of PEI large independently functioning nodules with capacity from 33 to 90 ml. According to the authors, after 3 months of treatment the size of nodules was decreased by 30 - 50% in 9 months - by 40 - 80%. It was recorded during the next 2 years of clinical observation of relapse of hyperthyroidism. According to another work of these researchers [38], the full therapeutic effect of sclerotherapy autonomous adenomas was 92.7%. According to the results Mazzeo S. et al. [39] this type of sclerosing tumors led to complete clinical effect in 81% of patients, partial - 16%, no effect was observed in only 3% of patients, with all components decreased by more than 50%. In cases of partial response or no re-treatment cycle sclerotherapy authors recommend spending in 15 months. Similar results are given in [20, 40, 41], where the authors noted that the use of sclerotherapy leads to a complete clinical effect in 64 - 85% of patients with toxic adenomas, and 80 - 100% with non-toxic (pretoxic) autonomous units. Solbiati L. et al. [42] used PEI in toxic adenomas and performed it under the control using ultrasound color Doppler system by which they are determined most vascularization area of neoplasms. Exactly in these zone authors injected ethanol. According to the results of research, the overall effect was achieved in 85% of cases, no longer observed at this increased vascularization nodes had before. Similar results were obtained Cerbone G. et al. [43, 44], who with the help of color Doppler ultrasonography was performed aiming sclerotherapy with ethanol autonomous adenomas with a view to the destruction of their main afferent intranodular vessels. Significant obstacles dual cytological confirmation of the soundness of these tumors necessary for the PEI. According to our results, as well as other researchers it can be achieved more than 80% of patients [45, 46].

In the work of Bartos M. et al. [47] was analyzed the effect of PEI of tissue nodes size from 7 to 60 mm in 2 years after treatment. The authors obtained the following results: 1) The complete disappearance of nodes observed in 37% of cases; 2) decrease to less than 0.5 cm – 25%; 3) reduction of more than 50% of the initial volume – 17.5%; 4) reduction of less than 50% of the initial volume of – 20%. Categories 1 and 2, the researchers assessed how the full effect, 3 –as a partial and 4 – a lack of effect.

Results of data studies in the countries of the Commonwealth of Independent States (other clinical trials)

Most of the studies in the domestic literature on the use of sclerotherapy in the treatment of thyroid nodules based on an analysis of the effectiveness of the use of ethanol [48-50]. In Russia, the first reports on the introduction of ethanol for the treatment of thyroid nodules under ultrasound guidance were published by A.N. Bubnov et al. (1996, 1997), and other clinics in the Commonwealth Independent Countries [51-56].

In general, the results of the St. Petersburg scientists indicates the presence of a large group of professionals and supported by a large number of studies in this direction. Thus, the results of the study Fedotov Y.N. et al. in 2010 showed that ethanol sclerotherapy is highly effective in reducing the size of the nodes in 80.8% of cases in the treatment of cystic transformed thyroid nodules, and treatment of solid components in 53.3% of cases [57].

One of the works of the same school showed the presence of the effectiveness of sclerotherapy in a group of elderly people. There was obtained a relief thyrotoxicosis 87.5% of cases [58].

Along with the use of sclerotherapy in adult and elderly age groups in the analysis of data in the literature we have found works of the Ekaterinburg clinicians that demonstrated the effectiveness of the method with the introduction of 95% ethanol solution for the treatment of children and adolescents with nodular thyroid disease [59].

There were also reports of successful treatment of hyperthyroidism relapse of thyroid gland at the remains of a small mass of tissue destruction left by ethanol under control sonography [60].

After the introduction of alcohol in patients with hyperfunctioning sites and phenomena thyrotoxicosis authors noted absorption recovery radionuclide surrounding tissue, and disappearance of the signs of hyperthyroidism.

There are different views on the number and courses destruction of the ethanol to obtain a positive effect. Most researchers noted improvement in treatment outcomes after repeated courses of alcohol injection [60, 50]. However, the timing of the repeated courses were different.

For objectification of the effectiveness of treatment, most authors find it necessary to use the results of ultrasound [61, 62]. However, ultrasound allows to determine only change the size of the node and is not able to assess the change in its function.

Interesting data on the use of ethanol sclera therapy were obtained by A.S. Tolstokorov et al. in 2010. This research group was monitored the effect of sclerotherapy on clinical and morphological picture, and as perinodular sclerosed tissue around the nodes [63].

An alternative to use of 96% ethanol was suggested the use of 70% solution in the work of Ukrainian researchers. After sclerotherapy of nodules 70% ethanol in the same place was introduced 1/3 of the evacuated content. The control of efficacy was performed for 2 days, 2 weeks, and at 1, 3, 6 and 12 months after the procedure. Full replacement node connective tissue as a result of this study was observed in 98.4% of cases [64-65].

CONCLUSIONS

In the studied literature there are conflicting views about the frequency and the amount and concentration of administered ethanol, the indications of the PEI, as well as the maximum size of the node, which can be subjected to sclerotherapy. It requires also study the question of choosing the most simple method of the ethanol destruction monitoring.

None of the studies have not evaluated the end point such an outcome is all-cause mortality, health-related quality of life or the data on the development of thyroid cancer. Key observations were in the range of six months to five years, the average follow-up was 12 months. Reduction of nodes as colloidal and solid nature was achieved in all studies. However, the clinical significance of this measurement result is highly questionable. Future research should be aimed at assessing the patient-oriented outcomes, especially, the quality of life after sclerotherapy, prolonged observation after the procedure (at least 10 years), registration of mortality, malignancy, comparing the advantages of minimally invasive procedures with surgery.

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