



Hypo-Coagulated Patients and Ultrasound Guided Fine-Needle Aspiration of Thyroid Nodules: A Worry?

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Abstract

Thyroid Ultra Sound guided Fine-Needle Aspiration (US-FNA) is the gold standard for thyroid nodules diagnosis. Many patients are under anticoagulation or antiplatelet medication. Haemorrhagic complications of US-FNA are rare. It is not clear if performing thyroid US-FNA in hypo-coagulated patients increase risk of complications or if this medication should be stopped before the procedure. Additionally, influence that anticoagulated state may have on number of non-diagnostic cytological results is unknown. It is our purpose to assess haemorrhagic risk and impact on non-diagnostic results of thyroid US-FNA, performed in patients under anticoagulation/antiplatelet therapy.

Methods: Retrospective study of 278 thyroid US-FNA performed during 18 months. Patients were divided into two groups according to whether doing or not anticoagulation/antiplatelet medication. None of patients stopped that medication before the procedure, which was made by the same radiologist. In each group was evaluated the prevalence of haemorrhagic and non-haemorrhagic complications and the number of non-diagnostic results. Statistical analysis was performed using SPSS with significance index $p < 0,05$.

Results: 278 thyroid US-FNA were analysed. Majority of patients were female (55,5%) with a medium age of 66,8 years. 71,7% of patients were included on Control Group (without medication) and 28,3% on Hypo-coagulated Group (under anticoagulation/antiplatelet medication). This last group comprise 67,5% of patients doing antiplatelet medication, 25,6% of patients undergoing direct oral anticoagulant agents (DOAC) and 6,7% under vitamin K inhibitors. Prevalence of haemorrhagic complications on the Hypo-coagulated Group was 1,35% ($p=0,11$). Non-haemorrhagic complications were reported in 1,96% on control group and

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in 2,7% on hypo-coagulated group ($p=0,71$). Non-diagnostic cytological results were found in 2,5% of the total US-FNA performed, without statistical significance between groups (1,47% on control group and 5,4% on hypo-coagulated group, $p=0,07$).

Conclusions: Haemorrhagic complications after thyroid US-FNA are minimal and without severity. We conclude that haemorrhagic risk in hypo-coagulated patients is not significantly increased.

Introduction

Nodular thyroid disease is very common in clinical practice and its diagnosis has increased with the performance of imaging tests, such as ultrasound [1]. Thyroid Fine-Needle Aspiration (FNA) is the most cost-effective and diagnostic method for thyroid nodules, with high sensitivity and specificity (76-98% and 71-100%, respectively) [1,2]. FNA can be performed by thyroid palpation or, more often, guided by ultrasound. Studies have shown that ultrasound-guided FNA (US-FNA) allows a lower rate of false positives and fewer non-diagnostic samples, comparing to FNA by palpation [1,3]. However, the effectiveness of US-FNA still depends on the experience of the operator [1]. Although rare, the most frequent complications of US-FNA reported are pain or cervical discomfort caused by the procedure itself, and bleeding, in some cases with formation of haematoma in the subsequent period [3,4]. Bleeding results from venous extravasation of blood into or out of the nodule. In most cases is easily managed through compression and local cryotherapy. This haemorrhagic complication is more frequent in highly vascularized thyroid glands or in patients with haemorrhagic risk factors, such as conditions that affect coagulation cascade (hypothyroidism, hepatic cirrhosis, chronic renal disease, among others) or under anticoagulation/antiplatelet therapies [4]. Thyroid dysfunction modifies the physiological balance between coagulation and fibrinolysis. Thyroid hormone deficiency induces a tendency towards hypo-coagulation by reducing coagulation factors such as von Willebrand factor and VIII, IX and XI factors. Thus, patients with uncontrolled hypothyroidism who perform thyroid FNA have a higher risk of haemorrhagic complications [5-7]. In addition to previously mentioned factors, haemorrhagic complications could be inherent to the technique itself, such as use of larger diameter needles, an abrupt reduction of intra-nodular pressure during aspiration of nodules with a cystic component or even lack operator experience [4].

In recent years, not only has been an increase in the number of US-FNA performed, but also, a greater complexity of the patients with respect to associated comorbidities and therapeutics. There is currently an increase in number of patients referred to thyroid US-FNA who are under anticoagulants/antiplatelet therapy. These drugs are mostly used to prevent thromboembolic events. The anticoagulants currently available on the portuguese market include: coumarins such as vitamin K antagonists and the direct oral anticoagulant (DOAC) which include direct inhibitors of thrombin and factor Xa. Antiplatelet medication includes Irreversible inhibitors of cyclooxygenase (COX1), Adenosine Di Phosphatase (ADP) receptor inhibitors and Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors. Table 1 summarizes these different pharmacological classes available in Portugal. Since bleeding is a possible complication of thyroid US-FNA, performing this procedure in patients under anticoagulants/antiplatelet therapy is a challenge for both the prescribing professional and the practitioner. The danger of suspending treatment and thus

increasing the risk of thrombotic events [8] and on the other hand, the risk of haemorrhagic complications due to the trauma caused by the procedure in hypo-coagulated patients, creates a dilemma for clinicians [9,10].

There is no consensus in national and international recommendations regarding the need to suspend anticoagulant/antiplatelet therapy prior to thyroid US-FNA (Table 2). There are few recommendations regarding thyroid cytology specifically, being more frequent protocols of action directed to invasive and surgical procedures. However, taking into account the characteristics of the thyroid FNA, we can include this procedure in the minor haemorrhagic risk procedure group. The purpose of these types of guidelines is to balance between the risk of thromboembolic events (in case of treatment interruption) and the haemorrhagic risk during the procedure (in case of keeping therapy). Regarding Cardiovascular and Interventional Radiological Society of Europe (CIRSE) guidelines, if INR ≤ 2 vitamin K inhibitors or Acetyl Salicylic Acid (ASA) monotherapy should be maintained [11]. However, clopidogrel monotherapy should be stopped before performing FNA. Nowadays the use of DOAC has been overlapping vitamin K antagonists, allowing a more simplified approach. Based on the protocol developed by Portuguese Anaesthesia Society, thyroid US-FNA could be included in the group of invasive procedures that do not require suspension of anticoagulant therapy [12]. It recommends INR value < 3 in the case of vitamin K inhibitors therapy and in the case of DOAC, to stop taking the day of the procedure and resume administration six to eight hours after the procedure with half of the usual dose. Regarding antiplatelet therapy this same consensus recommends suspension 3-5 days earlier if doing monotherapy in primary prevention, or maintenance the treatment if monotherapy in secondary prevention or in case of double anti-aggregation (and if both low haemorrhagic and thrombotic risk). Recently European Society of Cardiology in the latest DOAC management guidelines and double antiplatelet therapy update, reinforces the maintenance of these drugs when performing minor bleeding risk procedures, such as US-FNA [13,14]. Specifically to thyroid US-FNA, Korean Society of Thyroid Radiology present more preventive recommendations advising to discontinue vitamin K antagonists 5 days prior the procedure and performing US-FNA only if INR < 1.7 [3]. However, if thrombotic risk so requires, anticoagulation should be replaced by subcutaneous low molecular weight heparin within 2 days prior the procedure. In patients receiving antiplatelet therapy (ASA or clopidogrel), this therapy should be discontinued within 3-5 days prior, until 3 days after US-FNA, unless contraindication for discontinuation required by attending physician. There are few studies evaluating the safety of thyroid FNA in anticoagulated/antiplatelet patients in the literature [9,10,15]. Studies with FNA in breast and prostate tissue demonstrate that these drugs can be safely maintained [16-18].

It is important to highlight possible consequence of bleeding in the acquisition of cellular material suitable for pathological anatomy analysis. According to Bethesda classification for thyroid US-FNA, a non-diagnostic result is defined as a sample with insufficient number of thyroid cells associated with a cystic or haematic fluid component [1]. In these cases, it is recommended to repeat the cytological procedure. There are insufficient studies establishing relationship between FNA in hypo-coagulated patients and non-diagnostic samples, although published studies do not demonstrate causal link between the two variables [15].

With this study, it is our purpose to verify if performing thyroid nodules US-FNA in patients under anticoagulant/antiplatelet medication, increases risk of haemorrhagic complications or on-diagnostic results.

Materials and methods

This is a retrospective study of patients undergoing thyroid US-FNA in Radiology department of Portuguese Armed Forces Hospital-Lisbon (HFAR-PL) between January 1st of 2017 and June 30th of 2018. All FNA were guided by ultrasound and performed systematically by the same radiologist, with the same device (ACUSO-S2000) and analyzed by the same pathologist. A total of 223 clinical processes were analyzed and telephone contact was made with all patients to confirm information from the clinical process. Variables assessed were age, sex, anticoagulant or antiplatelet therapy, presence of complication (pain, hematoma or other) and US-FNA result. Exclusion criteria were: FNA performed outside radiology department of HFAR-PL or by other professional and absence of available cytological results in clinical process. The final sample includes a total of 278 US-FNA. None of patients stopped anticoagulation/antiplatelet medication before the procedure. Patients were divided into two groups classified as: Hypo-coagulated group if under anticoagulant/antiplatelet therapy (including: warfarin, clopidogrel, Acetyl Salicylic Acid (ASA), ticlopidine, triflusal and Direct Oral Anti Coagulants (DOAC): Rivaroxaban, dabigatran and edoxaban); or Control group included patients without this kind of medication. In addition to consulting the clinical process, anticoagulant/antiplatelet medication as well as the report of complications after procedure were confirmed with each patient. Statistical analysis was performed using SPSS with significance index $p < 0,05$. All values of p value were calculated by chi-square test.

Results

We analyzed 278 thyroid US-FNA from 223 patients. 55.6% of thyroid US-FNA were performed in female patients and

44.4% of males, aged between 22 and 89 years (mean age of 66.8 years). Patient’s characteristics are shown in Table 3. Control group comprised 73.4% (n=204) of total US-FNA performed and hypo-coagulated group included 26.6% (n=74). In the Hypo-coagulated group: 67.5% of US-FNA were performed in patients receiving antiplatelet therapy (20% under ASA, 1.35% with dual ASA and clopidogrel aggregation, 41.9% with clopidogrel, 2.7% with triflusal and 1,35% with ticlopidine), 25.6% in patients taking DOAC (14.9% under rivaroxaban, 9.5% under dabigatran and 1.35% under edoxaban), and 6.7% in patients under vitamin K antagonist (warfarin). Complications (haemorrhagic or not) were reported in 2.5% (n=7) US-FNA performed: 1.96% for the control group and 4.1% for the hypo-coagulated group ($p \text{ value} = 0.32$). Control group did not present any registry of haemorrhagic complications. In the hypo-coagulated group, haemorrhagic complications were reported in only one US-FNA procedure (1.35%). It was reported as a small hematoma formation without need for medical evaluation or treatment. This was a patient receiving rivaroxaban. Haemorrhage was not statistically significant between control and hypo-coagulated groups ($p \text{ value} = 0.11$). Analyzing specifically the group of patients under DACO (n=19) in comparison to control group (n=204) there is a difference with statistical significance ($p < 0.001$). However, this result appears to be biased in view of the size of the compared samples and should not therefore be extrapolated. Non-haemorrhagic complications, such as pain or cervical discomfort up to 48 hours after procedure, were found in 2.2% of US-FNAs: 1.96% in control group and 2.7% in hypo-coagulated group (patients on antiplatelet therapy with ASA and clopidogrel), with no statistical difference between the 2 groups ($p \text{ value} = 0.71$). Non-diagnostic samples (Bethesda System) were recorded in 2.5% of all US-FNA, 1.47%(n=3) in control group and 5.4% (n=4) in hypo-coagulated group. In the latter group, all non-diagnostic samples were from patients under DOAC, specifically rivaroxaban (50%/n=2) and dabigatran (50%/n=2). The difference between the groups was not statistically significant ($p \text{ value} = 0.07$). Results are resumed in table 4.

Table 1: Anticoagulants and antiplatelet available in Portugal.

Class		Mechanism of action	Drug
Anticoagulants	Coumarins	Vitamin K inhibitors	Warfin; Acenocumarol
	Direct oral anticoagulants (DOAC)	Direct Thrombin inhibitor	Dabigatrano
		Direct factor Xa inhibitor	Rivaroxabano; Apixabano; Edoxabano
Antiplatelet	Irreversible cyclooxygenase inhibitors	Irreversible COX1 inhibitors	Acetylsalicylic acid (ASA); Triflusal
	Adenosine diphosphatase receptor inhibitors (ADP)	Irreversible receptor P2Y12 inhibitors	Ticlopidina; Clopidogrel; Prasugruel
		Reversible receptor P2Y12 inhibitors	Ticagrelor; Cangrelor
Glycoprotein IIb/IIIa inhibitors	Reversible GPIIb/IIIa inhibitors	Abciximab; Eptifibatide; Tirofiban	

Table 2: Recommendations on manipulation of anticoagulant and antiplatelet drugs prior to minor bleeding risk procedures.

	Cardiovascular and Interventional Radiological Society of Europe (CIRSE) (2012)	Portuguese Anaesthesia Society (2014)	Korean Society of Thyroid Radiology (2015)	European Society of Cardiology (Doble antiplatelet management 2017/ DOAC management - 2018)
DOAC		Maintain until 12h before; resume 6-8 hours after with half-dose;		Maintain until 12h before; resume 6-8 hours after with half-dose;

Vitamin K antagonist	Maintain if INR \leq 2	Maintain if INR < 3	Discontinue 5 days before and perform it if INR < 1.7; If high thrombotic risk, replaced by low molecular weight heparin 2 days before	
Antiplatelet	<i>Monotherapy:</i> -ASA: maintain it; -Clopidogrel: discontinue 5 days before;	<i>Monotherapy:</i> - discontinue 3-5 days before (if primary prevention); Maintain (if secondary prevention). <i>Dual antiplatelet:</i> - Maintain (if low haemorrhagic and low thrombotic risk);	<i>Monotherapy</i> -ASA or Clopidogrel: discontinue 3-5 days before and resume 3 days after procedure, unless contraindication for discontinuation required by the attending physician;	Maintain

Legend: INR: International Normalized Ratio

Table 3: Recommendations on manipulation of anticoagulant and antiplatelet drugs prior to minor bleeding risk procedures.

Variables	Total (N=223)	Hypo-coagulated group (N= 63)	Control group (N=160)
Mean Age (years)	66,8	77,5	62,3
Sex (N (%))			
Female	124 (55,6%)	23 (36,5%)	101 (63,2%)
Male	99 (44,4%)	40 (63,5%)	59 (36,8%)

Table 4: Summary of results.

n= 278 US-FNA	Hypo-coagulated Group (n=74)	Control Group (n=204)	p value
Total incidence complications (%/n)	4,1% (3)	1,96% (4)	$p= 0,32$
Haemorrhagic complications (%/n)	1,35% (1)	0% (0)	$p= 0,11$
Non-haemorrhagic complications (%/n)	2,7% (2)	1,96% (4)	$p= 0,71$
Non-diagnostic samples (%/n)	5,4% (4)	1,47% (3)	$p= 0,07$

Legend: US-FNA: Ultrasound Fine Needle Aspiration.

Discussion

Comparing the two groups there were no statistically difference in number of haemorrhagic complications. The incidence of haematoma in our study was approximately 1% similar result to other previously published studies [4,9,10]. In 2011, Abu-Yousef and his colleagues [9] published a study with 593 patients under anticoagulation/antiplatelet medication undergoing thyroid FNA, whose results showed absence of statistical difference between the groups, with a total hematoma formation rate of 1%. This review questioned the real need for suspension of anticoagulant medication for thyroid FNA and the need for protocols on the topic, a suggestion that created interest and controversy, leading to several reviews about the subject. With the introduction of DOAC was also a need to update recommendations of approach in FNA procedures. Thus, Lyle M. and colleagues elaborated a review about the approach of these new drugs in patients undergoing minor invasive procedures (including thyroid FNA in this category), stating as reasonably the conservation of treatment during this kind of procedure [19]. For this conclusion they have taken into account the half-life and safety profile of these drugs. In our study, in the hypo-coagulated group about 26% of US-FNA corresponded to patients under DOAC. In this universe only one patient (1.35%) had a small haematoma formation on the day after the procedure without need of medical evaluation or treatment compared to none (0%) in control group. There was no statistically significant difference between

the groups ($p = 0.11$).

Recently, H. Khadra and his collaborators [10] have published a series of 802 patients undergoing thyroid US-FNA divided in 2 groups (control vs. hypo-coagulated). They achieved a rate of haemorrhagic complications of 0.89% in the hypo-coagulated group, with no significant difference for the control group. These results are overlapping with those found in our series (1.35% vs 0.89%). In our study haemorrhagic complications were only found in patients under DOAC anticoagulation. Analyzing this subgroup comparison with control group, the difference was statistically significant ($p < 0.001$), which could be explained by the difference in the size of both groups. Therefore, it seems improper to extrapolate these results. In our opinion this subject and in particular this therapy subgroup, need more robust studies in order to obtain more concrete results.

In the design of this study it was also our aim to evaluate if there would be an increase in non-diagnostic cytological results (according to the Bethesda classification) in hypo-coagulated group versus control group. Literature on this subject includes mainly patients treated with warfarin, clopidogrel and ASA, with reference only to one study that included patients under DOAC. They present non-diagnostic results incidence between 3.9% [15] and 6% (10). Our results were similar, with the number of non-diagnostic samples being 1.47% in the control group and 5.4% in the hypo-coagulated group (all in patients

under DOAC). None of the patients on conventional antiplatelet agents or anticoagulants presented this type of smears. This difference being no statistically significant ($p = 0.07$) confirms the non-interference of the hypo-coagulant state induced by these drugs and the quality of the acquired sample.

As limitations of our work, we point out the fact that this is a retrospective study and in presence of a substantial variety of antiplatelet/anticoagulants, it is difficult to have a representative number of patients under each drug/class, which may influence the results obtained. We conclude that thyroid ultrasound guided fine-needle aspiration is widely used and considered as a method of choice for the evaluation and diagnostic approach of thyroid nodules. The most frequently reported complications are local pain and cervical discomfort and bleeding, although rare and usually without severity. In view of our results and the published literature, haemorrhagic risk is not significantly increased in patients receiving antiplatelet or anticoagulant agents. Despite we consider it essential to carry out more robust and targeted studies in this area, in our opinion, it seems reasonable the recommendation of non-cessation of anticoagulant/antiplatelet treatment prior to thyroid US-FNA.

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References

- Gharib H, Papini E, Garber JR, Duick DS, et al. Thyroid Nodule Management, *Endocr Pract.* 2016; 22.
- Kim MJ, Kim EK, Park SI, Kim BM, Kwak JY, et al. US-guided fine needle aspiration of thyroid nodules: indications, techniques, results. *Radiographics.* 2008; 28: 1869-1887.
- Hen Lee Y, Baek JH, Jung SL, Kwak JY, Kim JH, Shin JH et al. Ultrasound-Guided fine needle aspiration of thyroid nodules: A consensus statement by the Korean Society of Thyroid Radiology. *Korean Journal of Radiology* 2015; 16: 391-401
- Polyzos SA, Anastasilakis A. Clinical complications following thyroid fine-needle biopsy: a systematic review. *Clinical Endocrinology.* 2009; 71: 157-165.
- Squizzato A, Romualdi E, Büller HR, Gerdes VE, Thyroid Dysfunction and Effects on coagulation and Fibrinolysis: a systematic review. *J Clin Endocrinol Metab,* July 2017; 92: 2415-2420.
- Yango J, Alexopoulou O, Eeckhoudt S, Hermans C, Daumerie C. Evaluation of the respective influence of thyroid hormones and TSH on blood coagulation parameters after total thyroidectomy. *European Journal of Endocrinology.* 2011; 164: 599-603.
- Elbers L, Fliers E, Cannegieter C, The Influence of thyroid function on coagulation system and its clinical consequences. *Journal of Thrombosis and Haemostasis.* 2017; 16; 1-12.
- Ferreira JS, Gil VM. Cardiovascular risk associated with interruption of antiplatelet and oral anticoagulation therapy. *Rev. Port Cardiol.* 2009; 28: 845-858.
- Abu-Yousef MM, Larson JH, Kuehn DM, Wu AS, Laroia AT. Safety of ultrasound-guided fine needle aspiration biopsy of neck lesions in patients taking antithrombotic/anticoagulant medications, *Ultrasound Q.* 2011; 27: 157-159.
- Khadra H, Kholmatov R, Monlezun D, Kandil E. Do Anticoagulation Medications Increase the Risk of Hematoma in Ultrasound Guided Fine Needle Aspiration of Thyroid Lesions? *Cytopathology.* 2018; 29: 565-568.
- Patel IJ, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS et al. Consensus Guidelines for Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-guided Interventions. *J Vasc Interv Radiol.* 2012; 23: 727-736.
- Fonseca C, Alves J, Araújo F. Manuseio Peri-Operatório dos Doentes Medicados com Anticoagulantes e Antiagregantes Plaquetários. *Rev Soc Port Anestesiol.* 2014; 23: 76-93.
- 2017 ESC focused update on dual antiplatelet Therapy in coronary artery disease developed In collaboration with EACTS, *European Heart Journal.* 2018; 39: 213-254.
- The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, *European Heart Journal.* 2018; 39: 1330-1393;
- Denham S, Ismail A, Bolus DN, Lockhart ME. Effect of Anticoagulation Medication on the Thyroid Fine –Needle Aspiration Pathologic Diagnostic Sufficiency Rate, *J Ultrasound Med.* 2016; 35: 43-48.
- Chetlan AL, Kasales C, Mack J, Schetter Zhu J. Haematoma Formation During Breast Core Needle Biopsy in Women Taking Anti-thrombotic Therapy. *American Journal of Roentgenology.* 2013; 201: 215-222.
- Somerville P, Seifert P, Destounis SV, Murphy PF, Young W. Anti-coagulation and Bleeding Risk after Core needle Biopsy, *American Journal of Roentgenology.* 2008; 191: 1194-1197.
- Raheem O, Casey RG, Galvin DJ, Manecksha RP, Varadaraj H. et al. Discontinuation of Anticoagulant or Antiplatelet Therapy for Transrectal Ultrasound-Guided Prostate Biopsies: A Single-Center Experience. *Korean journal of urology.* 2012; 53: 234-239.
- Lyle M, Dean DS. Ultrasound-Guided Fine-Needle Aspiration Biopsy of Thyroid Nodules in Patients Taking Novel Oral Anticoagulants, *Thyroid.* 2015; 25: 373-337.