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Aspirin Increases the Risk of Nondiagnostic Yield of Fine-Needle Aspiration and Biopsy of Thyroid Nodules

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Thyroid nodules · Fine-need aspiration · Fine-needle aspiration and biopsy · Aspirin · Diagnostic yield

Abstract
Background: The link between the diagnostic yield of thyroid fine-needle aspiration and biopsy (FNAB) in patients taking antithrombotic or anticoagulant medications (AT/AC) remains poorly characterized. ***Objectives:*** We studied the risk of obtaining a nondiagnostic sample with ultrasound-guided thyroid FNAB in patients taking AT/AC medications. ***Methods:*** This is a retrospective cohort study using medical records of 556 patients who underwent thyroid FNAB. All cytology samples were reported using the Bethesda classification. For patients with a nondiagnostic cytology, logistic regression was used to calculate OR for patients taking AT/AC medications. Multivariate regression was used to adjust for potential confounding variables including age, cystic ultrasound features, presence of eggshell calcifications, number of passes performed, cystic aspirate on FNAB, and position of the nodule. ***Results:*** Out of 556 patients, cytology results were available for 547 patients. Of these, 46 subjects were taking aspirin and 1 was on warfarin. Among the entire cohort, 17.5% of the subjects had a nondiagnostic cytology. Among the patients on AT/AC medications, 34% had a nondiagnostic result compared to 16% for those not taking them (OR = 2.70, $p = 0.003$). The subgroup of patients taking aspirin had similarly higher odds of a nondiagnostic cytology (OR = 2.78, $p = 0.002$). These differences remained statistically significant after multivariate adjustment. ***Conclusions:*** This is the first study to demonstrate a 3-fold independently greater risk of a nondiagnostic FNAB cytology in patients taking aspirin. Our results highlight the importance of evaluating the need for continuation of aspirin in patients undergoing thyroid FNAB as this may impact the diagnostic yield of the procedure.

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Introduction

Ultrasound-guided thyroid fine needle aspiration and biopsy (FNAB) has become the test of choice for evaluation of thyroid nodules. It combines ease of access and a high sensitivity and specificity to offer reliable results to aid decision making for surgery or clinical follow-up and is indicated as per guidelines in the evaluation of thyroid nodules [1]. Since the advent of the Bethesda classification [2], the rate of receiving a nondiagnostic cytology for thyroid FNAB stands between 7 and 10% [3].

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FNAB is generally a safe procedure, with bleeding or hematoma formation as the most frequent complication [4–6]. A retrospective chart review of FNAB samples obtained from 788 neck lesions did not find a significantly increased incidence of bleeding complications in patients on antithrombotic and/or anticoagulant (AT/AC) medications compared to patients not receiving AT/AC therapy [6]. There is scarcity of data on periprocedural complications for patients undergoing FNAB while on novel oral anticoagulants, but some published commentaries have suggested a similarly low risk [7].

The rarity of bleeding complications has led to the practice of continuing AT/AC medications before thyroid FNAB. However, there is lack of clarity in the literature regarding the link, if any, between the use of AT/AC medications and the diagnostic yield of FNAB. The only study to have investigated this link observed no statistically significant increase in nondiagnostic samples with AT/AC therapy [8], but did not correct for potential confounding variables that may independently affect the yield of thyroid FNAB.

Hence, our study objective is to determine the risk of obtaining a nondiagnostic sample with ultrasound-guided thyroid FNAB in patients taking AT/AC medications and compare them to patients not on these medications – with multivariate adjustment for confounding variables.

Materials and Methods

Study Population

This is a retrospective study using electronic and paper records of 556 consecutive patients who underwent ultrasound guided FNAB of thyroid nodule(s) performed between November 2009 to May 2014 in the Greater Toronto Area by a single endocrinologist (H.S.B.), who is certified to carry out these procedures. Out of these records, complete data and FNAB results were available for 547 patients, and they were used for this analysis. FNAB was performed using a 25-gauge needle and 2–4 passes per nodule using the aspiration technique described previously [9]. All cytology samples from FNAB procedures were collected in a community setting, where rapid on-site evaluation to confirm specimen adequacy was not available. Results were reported by a single cytopathologist employing the Bethesda classification using a criterion of having at least 6 groups of well visualized follicular cells with at least 10 cells per group for adequacy. All data variables, including the patients' age, gender, medical history, number of nodules, number of passes per nodule, ultrasound features including dimensions, cystic features, vascularity, and calcifications as well as type of aspirate (cellular vs. cystic, as seen by the naked eye) as described by the endocrinologist doing the FNAB (H.S.B.), were collected retrospectively from patient records and tabulated systematically. Patients were categorized as taking AT/AC medications (collectively called the AT/AC pool) and compared to those not taking them. All of the patients in the AT/AC pool were documented to have continued their medications until the day of the FNAB by self-report. Cytopathology results as per the Bethesda classification were added to the data spreadsheet. This study received no external funding. It was carried out in accordance with the principles of the Declaration of Helsinki (2004 version) and the requirements of Good Clinical Practice guidelines and was approved by the local ethics committee, with informed consent obtained for all patients.

Based on a type 1 error of 0.05 and a nondiagnostic event rate of 13.8% in the control group, our respective sample sizes would provide us with at least 80% power.

Statistical Analyses

Among patients with a nondiagnostic cytology, logistic regression was used to calculate OR for patients receiving AT/AC medications versus those not taking these therapies. Multivariate regression was used to adjust for confounding variables including patient age, cystic ultrasound features (characterized by nodules with anechoic or spongiform echogenicity together with posterior enhancement), cystic aspirate on FNAB, number of passes performed for each case, presence of egg shell calcifications, and size (<1, 1–2, and >2 cm) and position of the nodule (right cranial and middle, left cranial and middle, right caudal, left caudal, isthmus, and all others). All of the data analyses were performed using statistical software Project R version 3.1.3.

Table 1. Baseline characteristics of the entire cohort

Total patients, *n*	547
Females	450 (82.2)
Age, years	53.6±13.8
Patients on aspirin	46 (8.4)
Patients on warfarin	1 (0.2)
Total patients on aspirin and warfarin	47 (8.6)
Cystic ultrasound features	67 (12.2)
Cystic aspirate	109 (19.9)
Number of passes	2.42±0.49

Values are presented as numbers (%) or means ± SD unless otherwise stated.

Results

Out of the 556 consecutive patients who underwent FNAB, complete data variables and cytology results were available for 547 patients, who comprised our study cohort. Of these, 450 (82.2%) were female, with a mean age of 53.6 years. Forty-six patients were taking aspirin while 1 was on warfarin at the time of FNAB, adding up to a combined AT/AC pool of 47 patients. The proportion of patients with cystic ultrasound features and cystic aspirate and the mean number of passes are summarized as baseline results in Table 1.

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Table 2. Cytology based by Bethesda pattern

Diagnostic category	Total	AT group	Non-AT group
Benign	408 (74.6)	29 (61.7)	379 (75.8)
Nondiagnostic	96 (17.5)	16 (34.0)	80 (16.0)
Suspicious for malignancy or malignant	22 (4.0)	1 (2.1)	21 (4.2)
Atypia of undetermined significance or follicular lesion of undetermined significance	15 (2.7)	0 (0)	15 (3.0)
Follicular neoplasm or suspicious for follicular neoplasm	6 (1.1)	1 (2.1)	5 (1.0)

Among the entire cohort of patients, 17.5% were found to have a nondiagnostic result, while 74.6% had a benign result, 4.0% were suspicious for malignancy or malignant, 2.7% demonstrated atypia of undetermined significance or a follicular lesion of undetermined significance, and 1.1% were reported as follicular neoplasm or suspicious for follicular neoplasm (Table 2). While the nondiagnostic rate was 16.0% among the 500 patients not on AT/AC treatment, FNAB samples from 34% of the 47 patients on AT/AC medications yielded a nondiagnostic result (OR = 2.70, $p = 0.003$); 13.4% of nodules were cystic based on ultrasound criteria in the diagnostic group, while 25.3% were cystic in those with a nondiagnostic pathology. Similarly, 4.4% of nodules were <1 cm, and 47.8% each were 1–2 and >2 cm in maximum dimension in the nondiagnostic group. In comparison, in the diagnostic group, 3.7% of the nodules were <1 cm, 46.4% were 1–2 cm, and 49.9% were >2 cm in maximum diameter. The subgroup of patients taking aspirin had similarly higher odds of a nondiagnostic cytology compared to those not on AT/AC (OR = 2.78, $p = 0.002$). These differences remained statistically significant after multivariate adjustment for potential confounding variables, with an independently higher risk of a nondiagnostic sample in the AT/AC cohort (OR = 2.78, $p = 0.008$) as well as for those taking aspirin alone (OR = 2.86, $p = 0.007$).

Discussion

This retrospective cohort study demonstrates, for the first time, an approximately 3-fold increase in nondiagnostic sample yield among patients maintained on aspirin while undergoing FNAB of thyroid nodules, which was independent of multiple potential confounding variables. Overall, our findings hypothesize aspirin use as an additional, novel risk factor for nondiagnostic FNAB samples.

The finding of a nondiagnostic specimen following FNAB often necessitates guideline-recommended repeat FNAB [1] in up to 80% of patients with a nondiagnostic sample [10]. Our findings identify treatment with aspirin as a novel risk factor that increases the likelihood of obtaining a nondiagnostic sample, possibly through increasing the amount of blood in the aspirate. The only other study to have examined this link [8] did not find any significant differences in the yield of nondiagnostic samples in patients on AT/AC medications (3.9%) compared to those not taking them (2.3%). Potential reasons for our antithetical findings compared to the earlier study are as follows: (1) the percentage of nondiagnostic samples (2.7%) obtained in the earlier study was lower than our rate of 17.5% – it should be noted that the latter rate is similar to those in previous reports where on site adequacy assessment was not available [3, 8]; (2) unlike the previous study, we controlled for confounding variables [11–14]; (3) all of our FNAB were performed by a single certified endocrinologist and all cytopathology reports were read by a single cytopathologist, minimizing the chance of inter-individual variability, which could have potentially impacted the results of the previous study; and (4) we used an aspiration technique rather than the capillary fill technique used in the previous study.

The results of this study have several important clinical implications. Given the proven benefits of aspirin in secondary prevention of cardiovascular diseases, and data suggesting no differences in serious complications, including hematoma formation [6], it is unlikely that our study results would necessitate a change in FNAB preparation practice in patients in whom the risk of a cardiovascular event may outweigh the benefit of obtaining a diagnostic sample [15, 16]. However, aspirin is the second most commonly prescribed medication without a known indication, after nonsteroidal anti-inflammatory drugs as per The Irish Longitudinal Study on Ageing (TILDA) [17]. Given this knowledge, and our results of a 3-fold higher risk of a nondiagnostic yield in patients on aspirin, FNAB (or a repeat FNAB procedure after a first nondiagnostic result) of thyroid nodules may offer a chance to revisit the rationale for its use in patients with a low cardiovascular risk, thereby potentially reducing drug-relat-

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ed adverse effects and increasing the likelihood of yielding a diagnostic sample.

Our retrospective cohort study has several limitations. Firstly, our findings mainly relate to aspirin rather than other AT/AC medications as all patients, except one, in our AT/AC cohort were receiving aspirin. Secondly, all of the procedures in this study were carried out by a single certified endocrinologist and read by a single cytopathologist, potentially limiting its generalizability. However, this could potentially be a strength as it limits the possibility of interobserver variability inherent in the performance and reporting of ultrasound and FNAB. Additionally, the FNA samples in our cohort were obtained with a 25-gauge needle without quantification of blood in the aspirate and it remains unknown whether the diagnostic yield with AT/AC medications varies depending on the gauge of the needle used. Finally, the observational cohort design could be considered a study limitation. Nonetheless, we believe that the following specifics of the study protocol improve the validity of our results: (1) inclusion of consecutive patients undergoing FNAB; (2) completion of all data entry including recording of the medical history, ultrasound features, and FNAB cytology before formulation of the study question, with consequent minimization of the possibility of bias; and (3) multivariate adjustment for potential confounding variables which had not been performed in earlier studies.

In conclusion, we have demonstrated, for the first time, a 3-fold greater independent risk of a nondiagnostic sample yield when ultrasound-guided thyroid FNAB is performed among patients receiving aspirin. While the demonstrated benefit of these medications when used as per indication precludes their routine cessation in all patients undergoing their first thyroid FNAB, our results suggest a thorough evaluation of the rationale for use of these medications in patients undergoing these procedures. The cessation of AT medications in lower-risk patients may not only save them from possible long-term adverse effects, but also holds the potential to improve the diagnostic yield of the FNAB procedure.

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Disclosure Statement

The authors have nothing to disclose.

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