

Protocol Article

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Spinal versus conventional fine needle for ultrasound-guided thyroid nodule biopsy: a protocol for a randomised clinical trial

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ABSTRACT

INTRODUCTION. Thyroid nodules are very common and constitute an increasing clinical challenge since improved imaging capabilities and utilisation have led to a higher number of incidental findings. Ultrasound-guided fine-needle aspiration biopsy (FNAB) is the standard diagnostic tool in the work-up of thyroid nodules suspected of malignancy. Non-diagnostic results remain common and require repeated FNAB, leading to increased costs and delayed treatment of thyroid diseases, including treatment of thyroid cancer. If cytological diagnoses cannot be achieved, surgery may be warranted, which may potentially lead to overtreatment. Optimisation of the FNAB procedure is therefore essential. Spinal needles with a stylet have been found to lead to fewer non-diagnostic results, but studies on the subject are few.

METHODS. This is a multicentre, two-arm, randomised clinical trial. Adults with thyroid nodules suspected of malignancy will be included consecutively. A total of 350 patients will be assigned randomly 1:1 to have a FNAB with either a spinal (25G) or a conventional (25G) needle. The primary outcome is the rate of diagnostic cytological samples according to the Bethesda system. Secondary outcomes are patient-experienced pain, complication rate and sensitivity and specificity.

CONCLUSIONS. This trial will explore whether FNAB from thyroid nodules employing spinal needles compared with conventional fine needles improves diagnostic results, thereby providing evidence-based recommendations for a future choice of the FNAB needle. Secondary outcomes are patient-experienced pain, complication rate and sensitivity and specificity.

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Thyroid nodules are common, especially in women, and the prevalence increases with age [1]. Thyroid malignancy is a concern, whereas the vast majority of the nodules are benign [2]. Improved imaging technology has led to more incidental findings, so-called incidentalomas, which should raise awareness of the need for improving diagnostic management to compensate for the increased demand and to avoid overtreatment [3].

Ultrasound-guided fine-needle aspiration biopsy (FNAB) is the cornerstone in the evaluation of thyroid nodules. It is conducted to confirm suspicion of malignancy and its phenotype and for ruling it out, thereby allowing for observation or ultrasound-guided ablation therapies [4]. The FNAB procedure is considered safe [5] and of good diagnostic accuracy [6]. Nevertheless, 10-20% of FNABs from thyroid nodules are non-diagnostic [7], and adequacy is a fine balance between obtaining sufficient cell material while causing as little blood contamination as possible.

In case of non-diagnostic results, the recommendation is to offer repeat FNAB or surgery, especially if cytology remains non-diagnostic [8]. Repeat FNAB often implies added discomfort and anxiety, greater cost and delayed treatment, including treatment for any thyroid malignancy [9]. FNAB is typically performed with a thin needle and using the capillary technique [10-12]. In

addition, spinal needles with a stylet are theoretically less prone to contaminate blood, and were found to have a diagnostic rate above 95% and to be cost effective [13]. Despite these promising results, spinal needles are rarely used in today's clinical practice, which is justified by a lack of research on their use. Only two research groups have tested spinal needles in a randomised fashion and their studies were conducted in a very strict setting with a single clinician performing the procedures and a single pathologist evaluating the samples [13, 14].

The aim of the "SPInal needles versus conventional fine needles for ultrasound-guided fine Needle Aspiration Biopsy" (SPINAB) trial is to compare spinal and conventional needles in FNAB from thyroid nodules and thereby assess the diagnostic performance in a clinically representative "real-life setting" across multiple centres, clinicians and pathologists. Our hypothesis is that a spinal needle will lead to fewer non-diagnostic results than a conventional fine needle without decreasing accuracy, increasing patient-experienced pain or causing more adverse events. The 25G needle was chosen for the purpose of this trial since this needle is routinely used and was recommended in a recent systematic review [12].

The research question posed is: In adult patients with thyroid nodules suspected of malignancy, is the spinal needle using a stylet superior to the conventional fine needle in achieving a higher diagnostic rate of FNABs without decreasing accuracy, increasing patient-experienced pain or leading to more adverse events?

METHODS

This SPINAB trial is a multicentre, two-arm, single-blinded and randomised controlled trial. The protocol is registered with clinicaltrials.gov (Trial identifier NCT04879355) and adheres to the SPIRIT guidelines. Results will be reported according to the CONSORT guidelines. Positive and negative findings will be published in a peer-reviewed journal. Centres including patients are:

The Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital, Køge, Denmark.

The Department of Endocrinology and Metabolism, Herlev University Hospital, Herlev, Denmark.

The Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen, Denmark.

Eligibility criteria

Patients ≥ 18 years of age are eligible.

Patients referred for evaluation of a cold nodule on thyroid scintigraphy and with one of the following criteria:

European Thyroid Imaging and Reporting Data System (EU-TIRADS) score 3 and 20 mm in longest diameter or

EU-TIRADS score 4 and 15 mm in longest diameter or

EU-TIRADS score 5 and 10 mm in longest diameter.

Clinical suspicion of thyroid cancer:

PET-positive thyroid tumour.

Thyroid tumour and palsy of the recurrent laryngeal nerve.

Rapidly growing thyroid tumour.

Hard and/or immobile thyroid tumour.

Tumour in the thyroid with suspicious lymph nodes.

Exclusion criteria

Previous participation in the trial.

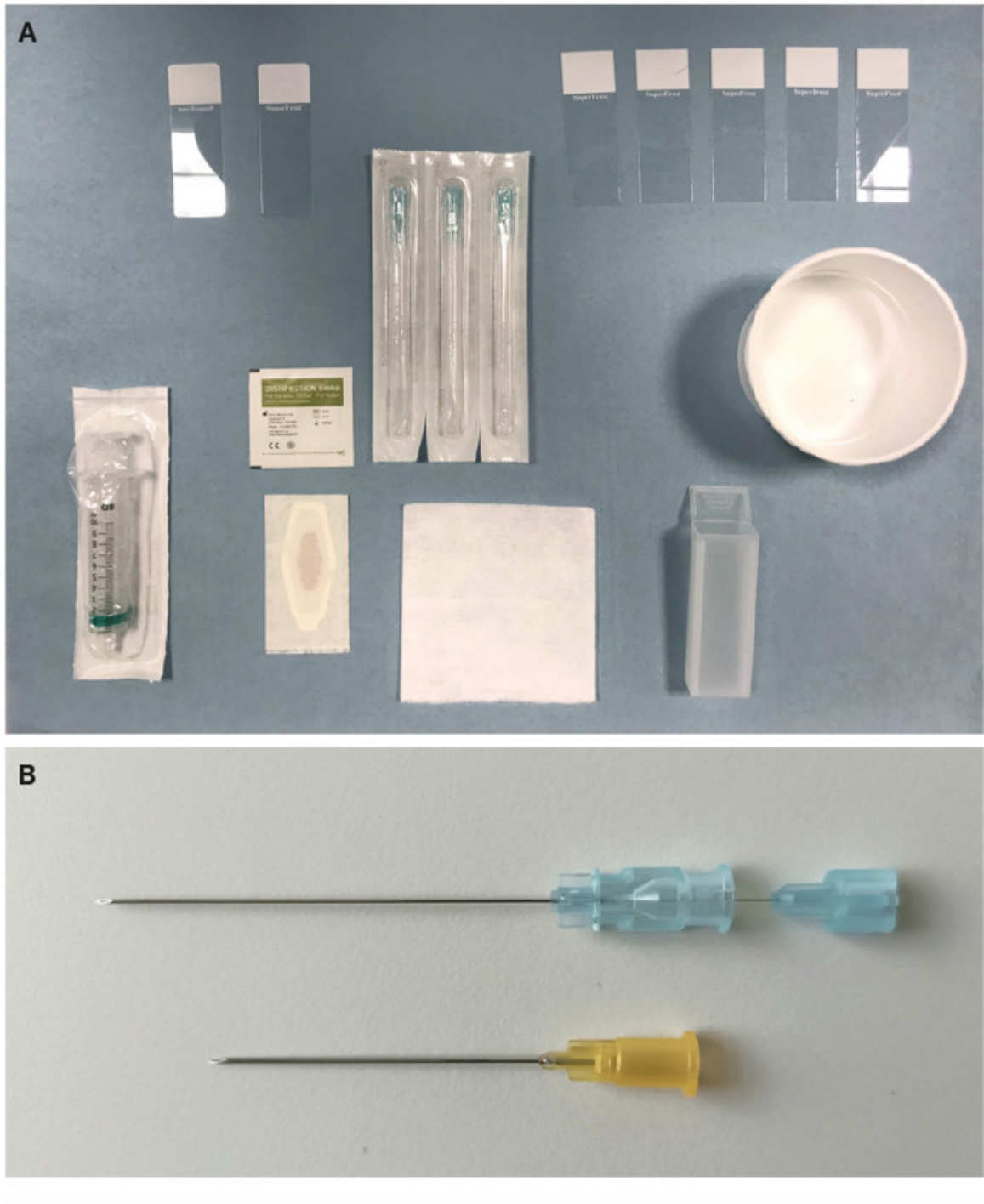
Language or other barriers not allowing for adequate information.

If a patient has multiple thyroid nodules qualifying for biopsy, the one with the highest EU-TIRADS [15] score is included. If two nodules have the same EU-TIRADS score, the largest nodule is included.

Randomisation and blinding

Eligible patients are randomised at a 1:1-ratio to one of two parallel groups, and all patients are included in the analyses on an intentiontotreat basis. Participants are enrolled via REDCap Software (Tennessee, USA). Prior to inclusion, randomisation is performed by the first author (TVA) using a random permuted blocks technique available online. The randomisation and the equipment are prepared in envelopes before initiating the trial. After inclusion of a patient, the clinician will open the sealed envelope, which contains the equipment needed to perform a FNAB with either a spinal or a conventional needle (**Figure 1**). The patients and the pathologists are blinded towards the intervention, whereas the clinicians performing the FNABs are not.

FIGURE 1 A. The experimental set-up.
B. The conventional needle (control group) below and the spinal needle (intervention) above.



Interventions

Participants are randomised to undergo FNAB with either a spinal (intervention group) or a conventional (control group) needle. Both needles are 25G, and the dimensions of the needles are 0.50 × 50 mm for the spinal and 0.5 × 40 mm for the conventional needle (Figure 1). Different needle lengths are used since these are the ones available on the market with the respective gauge. Importantly, needle length has not been shown to influence the diagnostic rate [16]. All physicians are required to be consultants with experience in ultrasound-guided FNAB or physicians in training as otolaryngologists who have undergone formal training and certification in ultrasound-guided FNAB. In addition, all physicians will receive instruction followed by supervision in US-guided FNAB on a phantom to ensure correct handling of the needle and removal of the stylet. The physicians are encouraged to follow the recently published guidelines on FNAB of thyroid nodules by our research group [17] and are thoroughly instructed to use only the capillary technique for both the standard and spinal needle. Three passes are performed in each nodule [18]. See **supplemental part 3.A** for the full description of the FNAB technique.

Outcomes

The primary trial outcome is the rate of diagnostic FNABs from thyroid nodules. Secondary outcomes are patient-experienced pain, complication rate and sensitivity and specificity. Pain is assessed using a numerical rating scale (NRS) [19] immediately after the procedure. During the procedure, we will record complications, such as infections, bleeding, haematomas requiring treatment or admission to hospital, and recurrent laryngeal nerve injury. All patients are instructed to contact the department responsible for their management if they suspect complications. Such complications will then be documented in the individual patient's medical record. At the end of the trial period, the patients' medical records will be reviewed for admissions or contacts concerning complications. Regarding sensitivity and specificity, thyroid tissue histology from patients who undergo surgery during the course of the trial will be used as a diagnostic reference to calculate the diagnostic sensitivity and specificity for the two needle types (see **supplemental part 3.D** https://ugeskriftet.dk/files/a03220165_-_supplementary_ny.pdf). For the primary outcome, subgroup analyses will be performed on nodule characteristics and the experience of the physicians performing the FNAB (see **SAP in supplemental part 4** https://ugeskriftet.dk/files/a03220165_-_supplementary_ny.pdf).

Cytopathological examination

All slides are air dried, and May-Grünwald Giemsa stained. Four pathologists participate in the trial and one pathologist examines each sample. If the FNAB is characterised as non-diagnostic or if there is uncertainty about the diagnosis, the sample will be discussed with one of the other pathologists until a consensus on a final diagnosis is achieved. Criteria for adequacy are defined according to the Bethesda system [8] (**Supplemental part 3.C** https://ugeskriftet.dk/files/a03220165_-_supplementary_ny.pdf).

Statistics

An a priori power analysis was performed before initiating the trial. In order to define the probability of achieving a diagnosis in the control and intervention group, we used the results from Capelli et al. [13] who found the adequacy of spinal needles to be 96% versus 86% for conventional fine needles. Based on this, the sample size was determined to 175 in each group. The number of participants was calculated using a power of 0.9, a significance level of 0.05 and a dropout rate of 10%.

Continuous variables will be presented as means with a standard error of the mean and categorical variables as frequencies and percentages. A binary logistic regression will be employed to compare the categorical variables (diagnostic/non-diagnostic), and a generalised estimating equation will be used to adjust for clustering of data within each physician and hospital. The Mann-Whitney U test will be used to compare NRS scores, specificity and sensitivity. The threshold for statistical significance will be a p-value < 0.05. Data will be analysed with commercially available software (RStudio Team (2016)). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA).

Participant selection and inclusion period

All participating departments are located at university hospitals and tertiary referral centres with patients also referred from the primary and secondary sector. Participants are required to provide oral and written informed consent to participate before entering the trial. The three departments, that include patients differ regarding patient population and staff. At Herlev Hospital, three consultant physicians in endocrinology are responsible for inclusion and intervention, whereas registrars and consultants alike at the ENT departments participate. Only the ENT departments receive patients from the “Danish cancer fast track” [20]. Inclusion starts on 1 November 2021, and we expect to include five patients each week and thereby include all patients before 1 May 2023. The trial may be terminated before inclusion of all patients if the intervention is found to lead to more serious adverse events than the conventional needle.

Data-sharing statement

Once anonymised, published participant data may be shared upon request from researchers for verification of the results of this trial or for meta-analyses. Trial protocol and participant information may be made available upon request. Data will be available until five years after publication. Requests for such data sharing should be addressed to the corresponding author.

Ethics and data management

All data will be collected through medical records and analyses of the FNABs. All data will be stored in REDCap (Tennessee, USA), a clinical research database, and in accordance with the GDPR rules and the Danish data protection law. All patients will receive oral and written information about the trial before signing a declaration of consent. The trial has been approved by

the regional scientific ethics committee (record number: SJ-878) and complies with the demands issued by the Danish Data Protection Agency (record number: REG-076-2021).

Trial registration: ClinicalTrials.gov Identifier: NCT04879355. Registration date: 07032021; version: 29062022.

DISCUSSION

Several needle gauges and aspiration techniques have been examined to improve the diagnostic adequacy in fine needle aspirations from thyroid nodules [10, 11]. A recent review recommended using 24-27G needles with a non-aspirating technique [12]. This trial aims to explore whether a spinal needle offers a higher diagnostic rate than conventional fine needles, without leading to a decreased accuracy, increased patient-experienced pain or more adverse events. If so, implementation of spinal needles may improve the diagnosis of thyroid cancer and thereby reduce healthcare costs.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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