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Analgesic efficacy of local anesthesia during thyroid fine-needle aspiration biopsy: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Aim: The objective of this study is to evaluate the analgesic efficacy of local anesthetic (LA) agents on pain severity among patients undergoing thyroid fine needle aspiration biopsy (FNAB).

Design: A systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: Digital databases, including PubMed, Scopus, Cochrane, Web of Science, and Google Scholar, were systematically screened from inception till December 2022. The Cochrane risk of bias tool (ROB 2) was used to evaluate the quality of each RCT. The primary outcome (pain severity) was gathered as a mean difference (MD) with a 95% confidence interval (CI), under the random-effect model.

Results: Overall, 444 patients were enrolled in five RCTs. Regarding pain severity via the visual analogue scale (VAS) assessment tool, the overall effect size showed no substantial difference between LA and control groups ($n = 4$ RCTs,MD = −8.45, 95% CI [−27.41, 10.52], $p = 0.38$). Regarding pain severity via the numerical rating scale (NRS) assessment tool, the overall effect size showed no substantial difference between LA and control groups ($n = 3$ RCTs,MD = −0.85, 95% CI [−3.14, 1.45], $p = 0.47$).

Conclusion: We have found that the pain levels between the LA and control-receiving groups were comparable. Hence, we concluded that LA before FNAB provides no benefit, especially for one needle puncture and sampling.

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KEYWORDS
FNAB; thyroid nodules; local anesthesia; lidocaine; EMLA

1. Introduction

Fine needle aspiration biopsy (FNAB) is a remarkably effective cytological procedure to differentiate between benign and malignant pathologies. It is a quick and simple method that can be used in the outpatient setting. As a result, it is regarded as one the most popular, trustworthy, and affordable diagnostic techniques available. In a similar manner, the thyroid FNAB is regarded as the gold standard for diagnosing and assessing thyroid nodules as a straightforward, effective, accurate, and minimally invasive procedure [1]).

The administration of any local anesthesia (LA) before the FNAB is generally not advised since the procedure is usually linked with minimal discomfort and mild transient pain that most patients relatively tolerate well [2]. Nonetheless, many patients (particularly individuals with pain phobia) consider FNAB a traumatic and distressing procedure, and thus, frequently asking for a painless and non-invasive anesthetic [2]. As a result, prospective, randomized placebo-controlled trials (RCTs) have demonstrated the effectiveness of the needle-free injection of lidocaine (NFIL) and eutectic mixture of local anesthetic (EMLA) cream in minimizing the discomfort associated with FNAB of thyroid nodules [2–4].

It has been demonstrated that EMLA cream, which contains a mixture of lidocaine 2.5% and prilocaine 2.5%, effectively provides a local anesthetic effect for the thyroid FNAB [2–4]. In a research done by Gursoy et al., the administration of EMLA cream greatly decreased patients' reported pain severity; however, the majority of patients did not experience a full analgesic effect during FNAB. In order to give an efficient topical anesthetic effect, EMLA must be administered at least one hour before FNAB, which may affect its feasibility in busy clinics [2].

The pneumatically driven painless injection method used to provide local anesthetics is known as the needle-free approach. It may administer drugs either subcutaneously or intradermally. The needle-free approach makes it possible to administer a local

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anesthetic providing a quick onset of analgesia, without being traumatic, or infecting the patient in any way, all while causing lower pain than a needlestick injury. This technique has been used effectively for the delivery of insulin and growth hormones as well as among patients undergoing cannulation, intravenous catheter introduction, cutaneous biopsy technique, and immunization [3,5–7]. Despite the fact that a very tiny amount of anesthetic material (0.3 mL) is sealed inside, a major concern related to this method is tissue swelling at the biopsy site after injection. Which in turn can obstruct further imaging and the targeting of an undetected thyroid nodule, leading to inadequate tissue sampling [8].

It is still unclear if administering local anesthetic is necessary or effective, despite the fact that there have been several publications discussing FNAB of thyroid nodules. For instance, FNAB of thyroid nodules has been done without LA by Yokozawa et al. [9] and Danese et al. [10], but it has also been done with LA by Rausch et al. [11] and O'Malley et al. [12]. Therefore, the objective of this study was to evaluate the pain levels by visual analogue scale (VAS) and numerical rating scale (NRS) for patients undergoing thyroid FNAB with or without the administration of LA.

2. Methods

2.1. Research protocol

We adopted Cochrane Handbook guidelines for Systematic Reviews [13], besides the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. Ethical approval was exempted because this type of research is based on published articles. The research protocol was not recorded in the International Prospective Register of Systematic Reviews (PROSPERO).

2.2. Literature search strategy

Digital databases, including PubMed, Scopus, Cochrane, Web of Science, and Google Scholar, were systematically screened from inception till December 2022. Our search strategy comprised: ((“fine-needle aspiration” OR “fine needle aspiration” OR FNA OR FNAB OR “fine needle aspiration biopsy” OR FNAC OR “fine needle aspiration cytology”) AND (“local anesthesia” OR lidocaine OR prilocaine OR EMAL OR “lidocaine-prilocaine” OR lignocaine OR xylocaine). To make sure that no research was missed and to ensure high-quality screening, all of the listed studies' references were checked. Furthermore, Clinicaltrials.gov and World health organization (WHO) clinical trials registry were considered during our search. Table 1. depicts the exact literature search strategy used in every database.

2.3. Eligibility criteria and study selection

We included: (*a*) Patients: patients undergoing for thyroid FNAB, (*b*) Intervention: local anesthesia (LA), (*c*) Comparison: placebo, no treatment, or other LA agents, (*d*) Outcome: pain severity, (*e*) Study design: randomized controlled trials (RCTs). The exclusion criteria comprised: studies other than RCTs, such as case reports, observational studies, review articles, and letters.

2.4. Screening and study selection

Using Endnote software, we gathered the various records from the various databases and eliminated duplicates. To determine their applicability, the retrieved references were examined. Title and abstract screening were done first, after which a full-text screening was performed to determine final eligibility. Each stage was completed by at least two different authors, and the results were compared and discussed.

2.5. Quality assessment of the included studies

The Cochrane risk of bias tool (ROB-2) was used to evaluate the quality of each trial [15]. Each assessed domain was given a score for bias risk, which ranged from low to some concerns to high. Two co-authors evaluated the quality of included studies, and for

Table 1. The exact literature search strategy used in every database.

(1) **PubMed**
All Fields: (“fine-needle aspiration” OR “fine needle aspiration” OR FNA OR FNAB OR “fine needle aspiration biopsy” OR FNAC OR “fine needle aspiration cytology”) AND (“local anesthesia” OR lidocaine OR prilocaine OR EMAL OR “lidocaine-prilocaine” OR lignocaine OR xylocaine).

(2) **Scopus**
Article title, Abstract, Keywords: (“fine-needle aspiration” OR “fine needle aspiration” OR FNA OR FNAB OR “fine needle aspiration biopsy” OR FNAC OR “fine needle aspiration cytology”) AND (“local anesthesia” OR lidocaine OR prilocaine OR EMAL OR “lidocaine-prilocaine” OR lignocaine OR xylocaine).

(3) **Web of Science**
All Fields: (“fine-needle aspiration” OR “fine needle aspiration” OR FNA OR FNAB OR “fine needle aspiration biopsy” OR FNAC OR “fine needle aspiration cytology”) AND (“local anesthesia” OR lidocaine OR prilocaine OR EMAL OR “lidocaine-prilocaine” OR lignocaine OR xylocaine).

(4) **Cochrane CENTRAL**
Title Abstract Keyword: (“fine-needle aspiration” OR “fine needle aspiration” OR FNA OR FNAB OR “fine needle aspiration biopsy” OR FNAC OR “fine needle aspiration cytology”) AND (“local anesthesia” OR lidocaine OR prilocaine OR EMAL OR “lidocaine-prilocaine” OR lignocaine OR xylocaine).

(5) **Google Scholar**
All Fields: (“fine-needle aspiration” OR “fine needle aspiration” OR FNA OR FNAB OR “fine needle aspiration biopsy” OR FNAC OR “fine needle aspiration cytology”) AND (“local anesthesia” OR lidocaine OR prilocaine OR EMAL OR “lidocaine-prilocaine” OR lignocaine OR xylocaine).

discrepancies, we adopted consultation with the principal investigator.

2.6. Data extraction and outcome

Two coauthors independently collected data using a predesigned extraction sheet, and discrepancies were settled by consultation with the principal investigator. Extracting summary of included studies included country, study design, total sample size, intervention group, control group, and type of administration. Baseline features of the participants included sample size, age, sex, nodule size (mm), and thyroid volume (ml). Our main outcome included pain severity by using the 100-mm VAS and 11-point NRS [16].

2.7. Statistical analysis

The studies were carried out using the Inverse-Variance method, and continuous data was gathered as a mean difference (MD) with 95% confidence interval (CI), under the random-effect model. Statistical heterogeneity among the studies was assessed by visual inspection of the forest plot, besides using I-squared (I^{2}) and chi-squared test statistics [17]. For all endpoints, statistical significance was determined as $p < 0.05$. RevMan software (version 5.4 for Windows) was adopted for statistical analysis. All analyses were done using the random-effect model. Subgroup meta-analysis were performed according to the type of the LA agents.

3. Results

3.1. Summary of literature search

From the literature search, we obtained 819 studies, out of which 587 were duplicates. Of the remaining 232 citations, 219 studies were omitted during title/abstract screening, and the reaming 13 studies qualified to full-text screening. Finally, five RCTs were included in our pooled analysis [2,8,18–20]. Figure 1. summarizes the PRISMA flowchart.

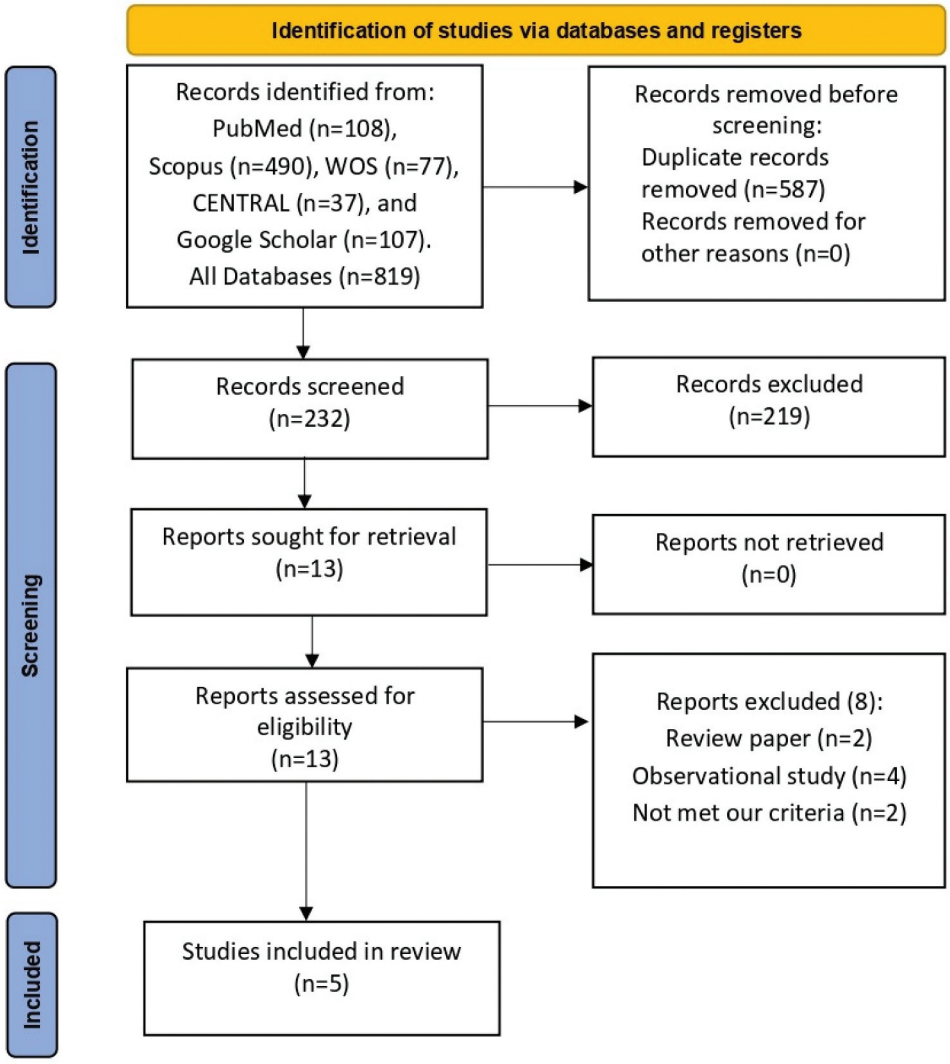

Figure 1. PRISMA flow diagram for screening process and study selection.

3.2. Summary of the characteristics of the included studies and participants

Five RCTs [2,8,18–20] met our inclusion and exclusion criteria with a total of 444 patients were involved. Four RCTs [2,18–20] compared LA with a control group, and only one RCT [8] compared two LAs together. Only two types of LA agents were used among the included RCTs, either lidocaine (injection) or EMLA (lidocaine-prilocaine cream). The majority of included patients were adults (>50-year-old), and Demirci et al. [18] included only female patients. Table 2. and Table 3. depicts summary and baseline characteristics of the included trials.

3.3. Quality assessment

Figure 2. depicts risk of bias summary of the included trials. Overall, three RCTs [2,8,20] were evaluated as low risk of bias, and two RCTs [18,19] were evaluated as having some concerns of bias. Demirci et al. provide no information regarding randomization and allocation concealment process. Also, Kim et al [19] did not use a placebo solution for the control group but there was little potential for a substantial impact on the estimated effect of intervention.

3.4. Meta-analysis of pain severity

Regarding pain severity via VAS assessment tool, overall effect size showed no substantial difference between LA and control groups ($n = 4$ RCTs,MD = −8.45, 95% CI [−27.41, 10.52], $p = 0.38$). According to subgroup analyses, in EMLA subgroup; there was no substantial difference between LA and control groups ($n = 2$ RCTS,MD = −9.24, 95% CI [−21.04, 2.57], $p = 0.13$). Similarly, in the Lidocaine subgroup, there was no substantial difference between LA and control groups ($n = 2$ RCTs,MD = −8.09, 95% CI [−44.43, 28.17], $p = 0.66$). All pooled analyses were heterogeneous (Chi-square $p < 0.01$, I-square>50%). (Figure 3).

Regarding pain severity via NRS assessment tool, overall effect size showed no substantial difference between LA and control groups ($n = 3$ RCTs,MD = −0.85, 95% CI [−3.14, 1.45], $p = 0.47$). According to subgroup analyses, in EMLA subgroup; there was a substantial difference that favor LA group over control group ($n = 1$ RCT,MD = −1.10, 95% CI [−2.05, −0.15], $p = 0.02$). However, in the Lidocaine subgroup, there was no substantial difference between LA and control groups ($n = 2$ RCTs,MD = −0.73, 95% CI [−4.16, 2.70], $p = 0.68$). All pooled analyses were heterogeneous (Chi-square $p < 0.01$, I-square>50%). (Figure 4). All RCTs [2,8,18–20] reported that there were no serious adverse events or systemic complications.

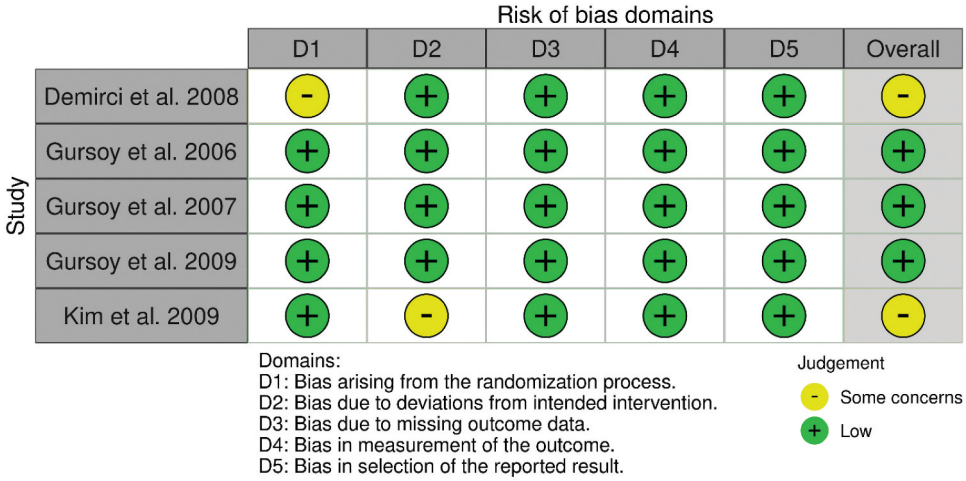

Figure 2. Risk of bias summary.

Table 2. Summary of the included trials.

Study ID	Study design	Country	Total sample size, n (intervention/control)	Trial arms		Type of administration
				Local anesthesia	Control	
Demirci et al. 2008	RCT	Turkey	n = 50 (25/25)	EMLA 5% (lidocaine-prilocaine)	Placebo	Cream
Gursoy et al. 2006	RCT	Turkey	n = 107 (55/52)	Lidocaine 0.3 ml	Placebo	Injection
Gursoy et al. 2007	RCT	Turkey	n = 99 (50/49)	EMLA 5% (lidocaine-prilocaine)	Placebo	Cream
Gursoy et al. 2009	RCT	Turkey	n = 138 (68/70)	EMLA 5% (lidocaine-prilocaine)	Lidocaine 0.3 ml	Cream and injection
Kim et al. 2009	RCT	South Korea	n = 50 (50/50)	Lidocaine 2%	Nothing	Injection

Abbreviation: LA= local anesthesia, RCT= randomized controlled trial.

Table 3. Baseline characteristics of the included trials.

Study ID	Group	Sample size	Age (years)	Sex, n[male/female]	Nodule size (mm)	Thyroid volume (ml)
Demirci et al. 2008	EMLA	n = 25	50.89 ± 12.01	[0/25]	27.33 ± 10.18	Not reported
	Control	n = 25	47.45 ± 11.61	[0/25]	23.47 ± 8.04	Not reported
Gursoy et al. 2006	Lidocaine	n = 55	50.3 ± 12.9	[45/10]	19.9 ± 7.9	22.6 ± 10.2
	Control	n = 52	46.5 ± 12.9	[45/7]	19.2 ± 6.5	22.4 ± 11.9
Gursoy et al. 2007	EMLA	n = 50	51.6 ± 11.1	[44/6]	20.7 ± 10.9	21.6 ± 9.2
	Control	n = 49	46.8 ± 13.1	[41/8]	18.5 ± 5.8	22.4 ± 11.9
Gursoy et al. 2009	EMLA	n = 68	47.5 ± 9.9	[13/55]	18.3 ± 7.6	20.8 ± 9.8
	Lidocaine	n = 70	50.1 ± 12.1	[12/58]	20.6 ± 10.6	22.1 ± 10.1
Kim et al. 2009	Lidocaine	n = 50	49.3 ± 9.8	Not reported	13.6 ± 4.10	Not reported
	Control	n = 50	49.3 ± 9.8	Not reported	13.0 ± 3.9	Not reported

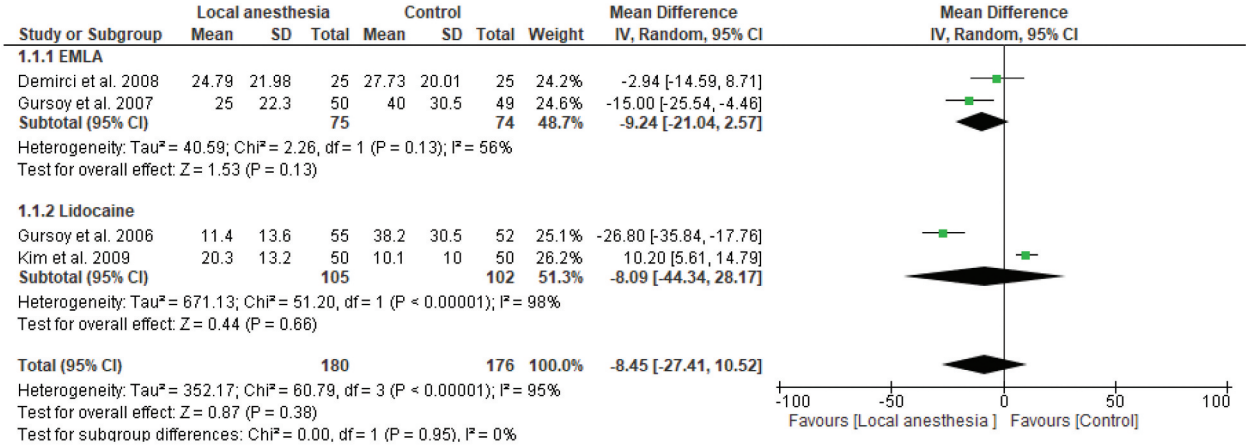

Figure 3. Meta-analysis of pain severity assessed by 100-mm visual analogue scale (VAS).

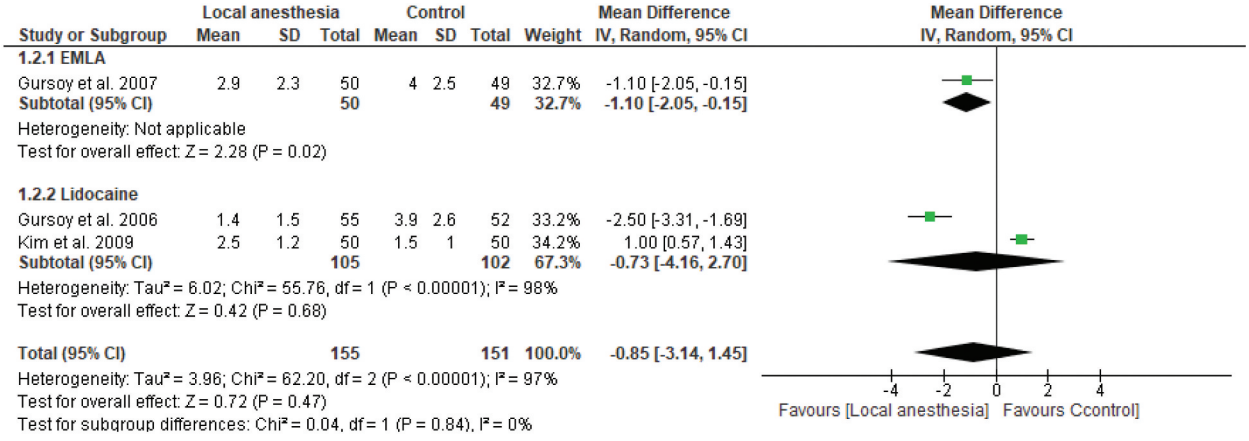

Figure 4. Meta-analysis of pain severity assessed by 11-point numerical rating scale (NRS).

4. Discussion

We investigated whether administering LA as NFIL and EMLA cream during FNAB of thyroid nodules possibly positively affected the comfort of the patient. We found that the pain levels between the LA- and placebo-receiving groups were comparable. Hence, we concluded that LA before FNAB provides no benefit, especially for one needle puncture and sampling.

FNAB is generally a well-tolerated procedure, and interruption of the procedure because of unbearable pain is uncommon. Discomfort or pain at the needle insertion point during FNAB is usually tolerated; therefore, routine use of LA is generally not suggested [2,21]. However, even if patients do not fit into a category thought to warrant anesthesia (non-anxious and pain-tolerant patients), there is still abundant evidence suggesting that the use of anesthesia may be helpful [2]. For example, the accuracy of FNAB is increased by increasing the number of biopsies. The pain level, however, may rise with the rising frequency of biopsies; therefore, LA may be advantageous in such cases. Furthermore, in such unusual circumstances

involving children, LA may be applied at the discretion of the treating doctor to reduce discomfort during this procedure [18].

Effective, quick, and portable local anesthetic induction techniques are required before cutaneous approaches like FNAB. It should not interfere with the typical departmental workflow or put the patient in further biological or physical danger [8]. Following FNAB, Cannon and Replogle assessed patient comfort, fear, and pain perceptions as well as material sufficiency at the neck regions, including thyroid using ethyl chloride or subcutaneous lidocaine administration. They found no substantial variation between the studied arms, which supports our findings [22]. Data from research comparing LA using EMLA with LA using infiltrative lidocaine administered by intradermal or subcutaneous administration differ in several ways. While infiltrative lidocaine was found to be more efficient than EMLA in three investigations, EMLA performed better in two RCTs [23].

Some medical facilities started using a 5% gel formulation of lidocaine as their primary topical anesthetic agent. When participants underwent intravenous cannula insertion, Lander et al. tested this 5% lidocaine with EMLA and discovered that EMLA was noticeably more efficient at reducing pain than lidocaine [24]. On the other hand, an RCT by Speirs et al. compared topical tetracaine with EMLA as a LA during intravenous cannulation. They discovered no statistical significance variation in the VAS-measured pain scores. As a result, the literature is conflicted over whether LA is necessary preceding FNABs [25].

Previous reports have shown that both NFIL and EMLA cream decreased the discomfort and pain related to FNAB when compared to a placebo. The primary drawback of EMLA cream is that it must be given at least an hour preceding FNAB, which may hinder its use in busy clinics. In contrast, lidocaine, provided by needle-free administration, works within one to three minutes. The quick onset and simplicity of usage reduces the amount of time needed for FNAB and allows for the frequent use of needle-free administration of lidocaine in busy facilities. The use of a needle-free delivery system was also reported to be more effective than EMLA cream, as LA with needle-free delivery of lidocaine was less time-consuming than EMLA cream. This also may contribute to the fact that the pain of needle insertion of LA may possibly be as bad as or even worse than the needle biopsies themselves, while the needle-free injection system eliminates pain related to needle insertion of LA. The targeting of the thyroid nodule for FNAB may be complicated by slight tissue swelling that develops underneath the biopsy site following the injection of lidocaine, particularly in patients with superficial nodules or nodules smaller than 10 mm. This might decrease the diagnostic yield of FNAB, which is not a problem for EMLA application [8].

4.1. Limitations

There are a number of restrictions in our study that need to be addressed. First, the study included a relatively small number of studies and is not registered in PROSPERO. Thus, we were not able to assess the publication bias. Second, there were much fewer males than females who participated. Third, there was a variation in the size of the used needles, which might have impacted a patient's pain score. Finally, the patients' delayed pain was not evaluated. That matter would be clarified by future studies looking at pain indicators (such as the patient's degree of depression or anxiety), which were not measured in our included trials.

5. Conclusion

We have found that the pain levels between the LA- and control-receiving groups were comparable. Hence, we concluded that LA before FNAB provides no benefit, especially for single needle puncture and sampling. Future research must be expanded to include more male patients in order to evaluate our results and ascertain whether our findings stay constant for both sexes. Also, the predictors of pain (including levels of anxiety or depression) and delayed patient pain must be considered in future investigations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Authorship contributions

Concept: EA, MA; Design: EA, RA, MA, KA, SH, AA; Data collection or processing: EA, RA, MA, KA, SH, AA; Analysis or interpretation: EA, KA; Literature search: EA, RA, MA, KA, SH, AA; Writing: EA, RA, MA, KA, SH, AA A; Reviewing manuscript for editorial and intellectual contents EA, RA, MA, KA, SH, AA; Approval of manuscript for submission: EA, RA, MA, KA, SH, AA.

Ethics committee approval

Not applicable as this study is based exclusively on published Literature.

Data availability statement

All data is available within the manuscript.

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