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Original Research Article

Effect of topical anesthetics on pain during needle insertion of maxillary infiltration anesthesia: a systematic review and meta-analysis study

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Abstract: Topical anesthetics are frequently used to reduce the pain of the needle insertion administration of topical anesthesia. The aim of this study is to evaluate the effect of topical anesthetics on pain during needle insertion of maxillary infiltration anesthesia. The studies searched in seven databases (PubMed/Medline, ISI Web of Science, Science direct, Cochran library, IranMedex, Google scholar and Scopus) before the summer of 2016 for English-language publications. The criteria were identified for selecting of studies in meta-analysis. The quality of studies was checked based on the Jadad score. The random-effects model was used to estimate weighted mean differences with 95% CI. Out of 14 studies in the systematic review, three studies just have high quality and eight articles reported the mean value and standard deviation of the pain and therefore, these eight articles were included in the meta-analysis. The subgroup analyses were done by type of group (benzocaine or lidocaine), time-effect (2, 3, 4, 5, and 20 min), the kind of using material (patch or non-patch) and injection area (anterior labial and posterior buccal). The pain was significantly lower in benzocaine group, lidocaine group, benzocaine group in anterior labial injection, benzocaine/patch group and the 5 min group compared with their front groups. Begg's and Egger's tests did reveal a significant evidence of publication bias among the included studies. The topical anesthetics reduced the pain compared with placebo in the maxilla. Lidocaine compounds probably are more effective than benzocaine 20% as topical anesthetics. The period of 5 minutes can be sufficient for reducing the pain after application of topical anesthetic. Also, benzocaine/patch can be more useful compared with benzocaine/non-patch in reducing of the pain of needle insertion.
Keywords: Topical anesthesia, maxilla, needle insertion, benzocaine, lidocaline.

INTRODUCTION

Pain and dentistry are often synonymous in the minds of patients [1]. The studies performed on pain reduction during injection in the maxilla [2-4]. The topical anesthetics are widely used in dentistry and commercially available that these agents are frequently used to reduce the pain of the needle insertion administration of topical anesthesia [5-7]. Some of them worked well and the others were ineffective [5]. There are two kinds of pain during local anesthesia. The first is at needle insertion and the second is during agent injection that topical anesthetics are generally used for free of pain during needle insertion [8,9]. Previous studies regarding the use of topical anesthesia for decreasing pain perception during anesthetic injections have shown different results [8,10,11] that these disagreements may be because individual difference, variations in application procedures with topical anesthesia and various concentrations of topical anesthetics [5]. Different investigations have used 30 sec [12] to 20 min [5] for application of topical anesthesia after needle insertion. Topical anesthetics must be used carefully due to the type of administration, concentration, and active ingredients used, because these drugs can cause side effects [13]. Therefore, the aim of this meta-analysis study is to evaluate the effect of topical anesthetics on pain during needle insertion of maxillary infiltration anesthesia.

METHODS

Search strategies and study criteria

We searched the studies in 7 databases (PubMed/Medline, ISI Web of Science, Science direct, Cochran library, IranMedex, Google scholar and Scopus) before summer of 2016 for English-language publications using the keywords "lidocaine", "pain",

"topical anesthesia", "penetration", "patch", "infiltration", "EMLA" and "benzocaine". None of studies were excluded for weakness of design or data quality. The articles were included in the meta- analysis only if they have the following criteria: (a) clinical trials and case-control, (b) studies that reported the people over age>18 years old, (c) the studies that reported mean or median values and standard deviations (SD) or standard errors (SE) of the pain with number of individuals in both group (case and control groups); (d) the studies reporting banzocaine or lidocaine and its components (lidocaine/Epinephrine or equal mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA)); and (e) the studies with visual analogue scale (VAS) scale for the pain. Furthermore, exclusion criteria were as follows: (a) the studies reporting only the mean or median values of the pain, (b) the studies that reported only the difference of pain between two groups, no reporting mean or median values for each group, (c) review articles; and (d) the studies reporting the comparison of between two intervention groups, not with healthy control group.

Data collection and extraction

Two authors checked and reviewed all the eligible articles and wrote following information for each study: the first author's last name, the year of publication, study group, the kind of material used, injection area, needle gauge, pain scale, conclusion, the number of cases and controls; and the mean and SD values for each group.

Quality of study

One author checked the quality of studies based on the Jadad score. It was decided that studies should be scored as high quality if they received a Jadad score of four or five (of a possible five points) and low quality if the score was equal to or less than three [14].

Pain score

To evaluate pain perception, a VAS was used that had a line of 100 mm, with 0 being no pain marked on the left and 100 being severe pain marked on the right. These represented the extremes of a straight line on which the patient marked a point corresponding to his/her pain [15].

Statistical analysis

All data were analyzed using the REVIEW MANAGER 5.3 (RevMan 5.3) software provided by the Cochrane Collaboration, but the funnel plot was plotted by COMPREHENSIVE META ANALYSIS 2.0 (CMA 2.0). The random-effects model was used to estimate weighted mean differences (MDs) with 95% CI. Furthermore, subgroup analyses were done by type of group (benzocaine or lidocaine), time-effect (2, 3, 4, 5, and 20 min), the kind of using material (patch or none-patch) and injection area (anterior labial and posterior buccal). Heterogeneity across studies was evaluated by the Q and I^2 statistic and for the Q statistic, considering significant statistical heterogeneity as $p<0.1$. An I^2 value of 0% denotes no observed heterogeneity, whereas, 25% is "low", 50% is "moderate" and 75% is "high" heterogeneity [16]. We estimated the mean and SD from median, range, and the size of a sample in a few studies [17]. If the data were presented using the standard error (SE), then the formula of "$SE = \frac{SD}{\sqrt{N}}$" to calculate and if the data were presented using several SDs, the mean SD calculated by the formula of

$$\text{“}SD_{mean} = \sqrt{SD^2_{mean}} = \sqrt{\frac{SD^2_A}{N_A} + \frac{SD^2_B}{N_B} + \ldots}\text{”}$$ (N= sample size).

RESULTS

The systematic review

Out of 208 searched articles, forty-six articles were relevant by the judgment of reviewers. Fourteen articles of clinical trials were included in the systematic review [3-8,10,12,13,18-22] that only two articles [4,8] were nonrandomized clinical trials. The results of these studies are in Table 1. Figure 1 shows the process of selecting studies for inclusion in the meta-analysis.

Table-1: The articles identified in the systematic review and in the meta-analysis (n=14 clinical trials)

Study, year	Number	Study group	The kind of material used/time-effect	Prick area/Injection area	eedle gauge	Pain scale (VAS)	Conclusion
Fukayama, 2002*	20	Benzocaine 20%	None-patch/ 20min	Anterior labial	30	12	Significant between case groups and placebo
	20	Placebo	None-patch/ 20min	Anterior labial	30	27	
	20	Lidocaine 60%	None-patch/ 20min	Anterior labial	30	0.5	
	20	Placebo	None-patch/ 20min	Anterior labial	30	34.8	
Parirokh, 2012*	25	Benzocaine 20%	None-patch/-	Anterior labial	-	15	No significant
	25	Placebo	None-patch	Anterior labial	-	16	
Hersh, 1996	33	Lidocaine 10%	Patch/2 min	Posterior buccal	25	39.3	* Significant between lidocaine and placebo for every time ** No significant between lidocaine 20% and lidocaine 10% for every time *** Significant for lidocaine 20% between 2, 5 and 15 min (lowest pain) **** Significant for lidocaine 10% between 2 and 5 min
	35	Lidocaine 20%	Patch/2 min	Posterior buccal	25	41.8	
	32	Placebo	Patch/2 min	Posterior buccal	25	51	
	33	Lidocaine 10%	Patch/5 min	Posterior buccal	25	34.3	
	35	Lidocaine 20%	Patch/5 min	Posterior buccal	25	33.8	
	32	Placebo	Patch/5 min	Posterior buccal	25	53	
	33	Lidocaine 10%	Patch/15 min	Posterior buccal	25	35.3	
	35	Lidocaine 20%	Patch/15 min	Posterior buccal	25	28.8	
	32	Placebo	Patch/15 min	Posterior buccal	25	51	
Nakamura, 2013*	20	Lidocaine 2%	Patch/2 min	Anterior labial	30	6.5	* No significant between Lido and Lido/Epi treatments ** Significant between Lido/Epi followed with 30G needle (lower pain) insertion versus 30G *** No significant between Lido and Lido/Epi treatments (lower pain) versus placebo **** Significant for Benzo/Patch treatment (lower pain) versus placebo ***** Significant
	20	Lidocaine 2% and Epinephrine 0.75µg	Patch/2 min	Anterior labial	30	6	
	20	Benzocaine 20%	Patch/2 min	Anterior labial	30	9	
	20	Benzocaine 20%	None-patch/2 min	Anterior labial	30	13	
	20	Placebo	Patch/2 min	Anterior labial	30	21	
	20	Lidocaine 2%	Patch/5 min	Anterior labial	30	3.1	
	20	Lidocaine 2% and Epinephrine 0.75µg	Patch/5 min	Anterior labial	30	3.75	
	20	Benzocaine 20%	Patch/5 min	Anterior labial	30	8.5	
	20	Benzocaine 20%	None-patch/5 min	Anterior labial	30	13.75	
	20	Placebo	Patch/2 min	Anterior labial	30	20.37	
	20	Lidocaine 2%	Patch/2 min	Anterior labial	33	2.25	
	20	Lidocaine 2% and Epinephrine 0.75µg	Patch/2 min	Anterior labial	33	2.25	
	20	Benzocaine 20%	Patch/2 min	Anterior labial	33	7.5	
	20	Benzocaine 20%	None-patch/2 min	Anterior labial	33	10.62	
	20	Placebo	Patch/2 min	Anterior labial	33	18.37	
	20	Lidocaine 2%	Patch/5 min	Anterior labial	33	1.75	

	20	Lidocaine 2% and Epinephrine 0.75µg	Patch/5 min	Anterior labial	33	1.37	for Benzo/Cotton treatment (lower pain) versus placebo ******No significant between Benzo/Cotton and Benzo/Patch treatments
	20	Benzocaine 20%	Patch/5 min	Anterior labial	33	5	
	20	Benzocaine 20%	None-patch/5 min	Anterior labial	33	7.75	
	20	Placebo	Patch/2 min	Anterior labial	33	18.75	
Nusstein, 2003	128	Benzocaine 20%	None-patch/ 1 min	Anterior labial	27	28	* Significant for anterior buccal ** No significant for posterior buccal
	294	Placebo	None-patch/ 1 min	Anterior labial	27	38	
	122	Benzocaine 20%	None-patch/ 1 min	Posterior buccal	27	46	
	157	Placebo	None-patch/ 1 min	Posterior buccal	27	50	
Rosa, 1999*	20	Lidocaine 5%	None-patch/ -	Posterior palatal	27	16.9	* Significant for every drug with placebo ** No significant bestrewn two drugs
	20	Placebo	None-patch/ -	Posterior palatal	27	33.65	
	20	Benzocaine 20%	None-patch/ -	Posterior palatal	27	19.6	
	20	Placebo	None-patch/-	Posterior palatal	27	25.35	
Rosivack, 1990	60	Lidocaine 5%	None-patch/ 3 min	Anterior labial	27	4.9	* No significant for two drugs ** Significant between every drug with placebo
	60	Benzocaine 20%	None-patch/ 3 min	Anterior labial	27	7.1	
	60	Placebo	None-patch/ 3 min	Anterior labial	27	12	
Carr, 2001	20	Benzocaine 20%	None-patch/ 0.5 min	Posterior buccal	27	Difference: 5.7	Significant
	20	Lidocaine 5%	None-patch/ 15 min	Posterior buccal	27	Difference: 48.2	
de Freiras, 2015*	38	Benzocaine 20%	None-patch/ 2 min	Posterior buccal	27	1.78	No significant
	38	Placebo	None-patch/ 2 min	Posterior buccal	27	1.81	
Svensson, 1992*	20	EMLA	None-patch/ 5 min	Posterior palatal	27	14.5	Significant
	20	Placebo	None-patch/ 5 min	Posterior palatal	27	26.5	
	10	EMLA	None-patch/ 5 min	Anterior palatal	27	35	
	10	Placebo	None-patch/ 5 min	Anterior palatal	27	39	
Alqareer, 2006*	36	Benzocaine 20%	None-patch/ 4 min	Anterior labial	25	13.31	Significant
	36	Placebo	None-patch/ 4 min	Anterior labial	25	24.5	
Meechan, 1999	10	Lidocaine 5% compared with EMLA	None-patch/ 5 min	Posterior buccal	30	10 units was less in ELMA	No significant
Martin, 1994*	64	Benzocaine 20%	None-patch/ 3 min	Posterior buccal	25	11.2	No significant
	64	Placebo	None-patch/ 3 min	Posterior buccal	25	7.3	
Singh, 2015	80	Benzocaine 20%	None-patch/ -	Anterior palatal	26	37.2	Significant
	80	EMLA	None-patch/ -	Anterior palatal	26	17.1	

Abbreviation: EMLA: equal mixture of 2.5% lidocaine and 2.5% prilocaine.

(*) Studies included in the meta-analysis (N=8).

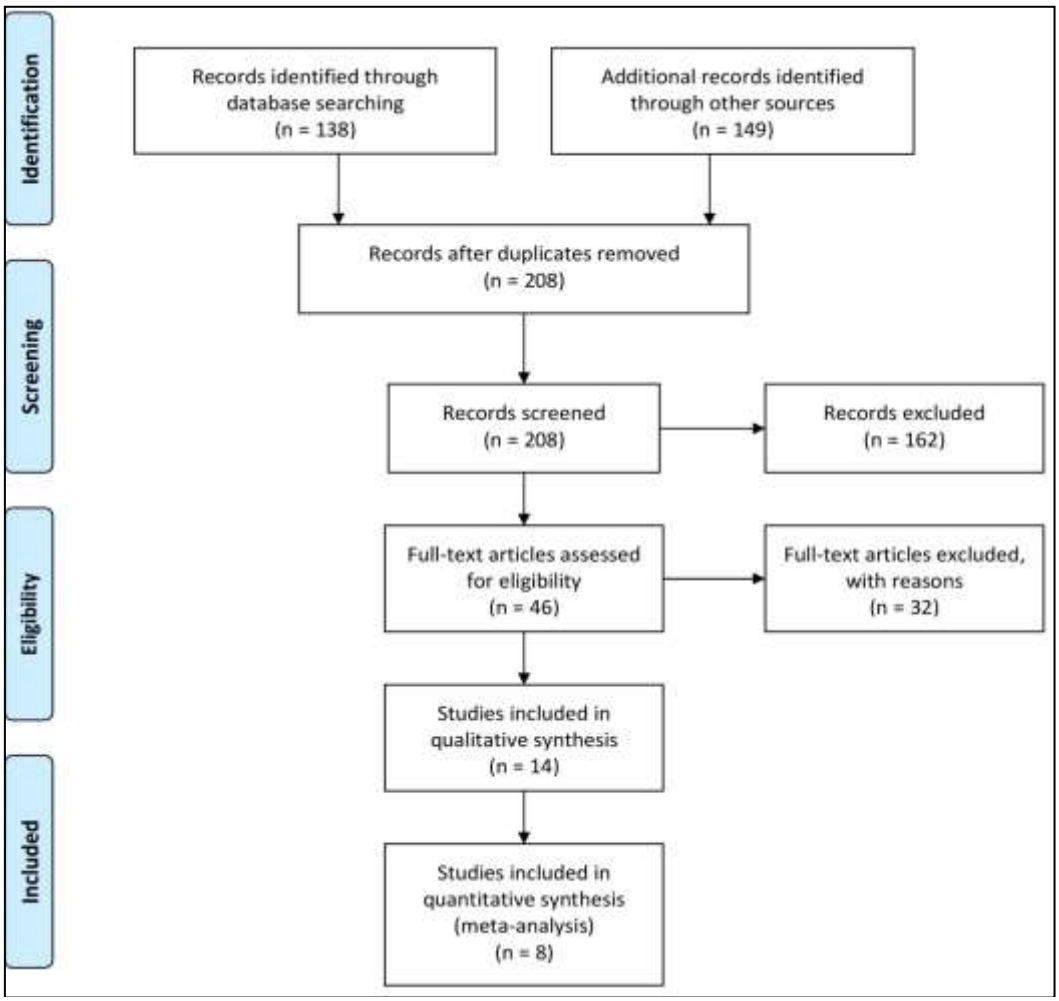

Fig-1: The PRISMA flow chart of study

Quality of studies

Table 2 shows the quality score for every study based on the Jadad scale. Out of 14 studies, three studies just have high quality [13,18,22].

Meta-analysis

Out of 14 articles selected for the systematic review, eight articles reported the mean and SD/SE of the pain. Therefore, these eight articles [3,5,7,10,18-22] were included in the meta-analysis. Furthermore, four articles by Fukayama et al. [5], by Nakamura et al. [18], by Rosa et al. [19] and by Svensson et al. [7] reported data from types of interventions and thus, they were separated in 2, 16, 3 and 2 sub-studies, respectively (**Table 1**). A total of 1226 participants without any systemic disease and sensitivity to local anesthetics were included in the analysis (613 in intervention group and 613 in the control group).

Intervention group versus placebo

The result of a random effects model for combined data from suggested studies showed a significant difference in pain between intervention and control groups [MD: -10.98, 95%CI: -14.44, -7.51; p<0.00001] (**Figure 2**). There was considerable heterogeneity among the studies (I^2=96%, p<0.00001). Thus, the pain was significantly decreased in the intervention group compared with controls.

Benzocaine 20% versus placebo

The difference of pain between benzocaine and control groups has been shown in **Figure 3**. There was a significant difference between benzocaine and control groups [MD: -7.56, 95% CI: -11.34, -3.77; p<0.0001) and a considerable heterogeneity (I^2=94%, p<0.0001). Thus, the pain was significantly lower in benzocaine group compared with controls.

Table-2: Assessing the quality of studies of randomized clinical trials based on the Jadad scale

Study	Randomization	Allocation Concealment	Blinding (observer)	Blinding (Patient)	Adequate follow-up	Score
Fukayama, 2002	*	*				2
Parirokh, 2012	*		*	*		3
Hersh, 1996	*		*		*	3
Nakamura, 2013	*	*	*	*		4
Nusstein, 2003						0
Rosa, 1999	*		*			2
Rosivack, 1990	*		*	*		3
Carr, 2001	*		*			2
de Freiras, 2015	*	*	*			3
Svensson, 1992	*		*			2
Alqareer, 2006	*		*			2
Meechan, 1999	*	*	*	*		4
Martin, 1994	*	*	*	*		4
Singh, 2015				*		1

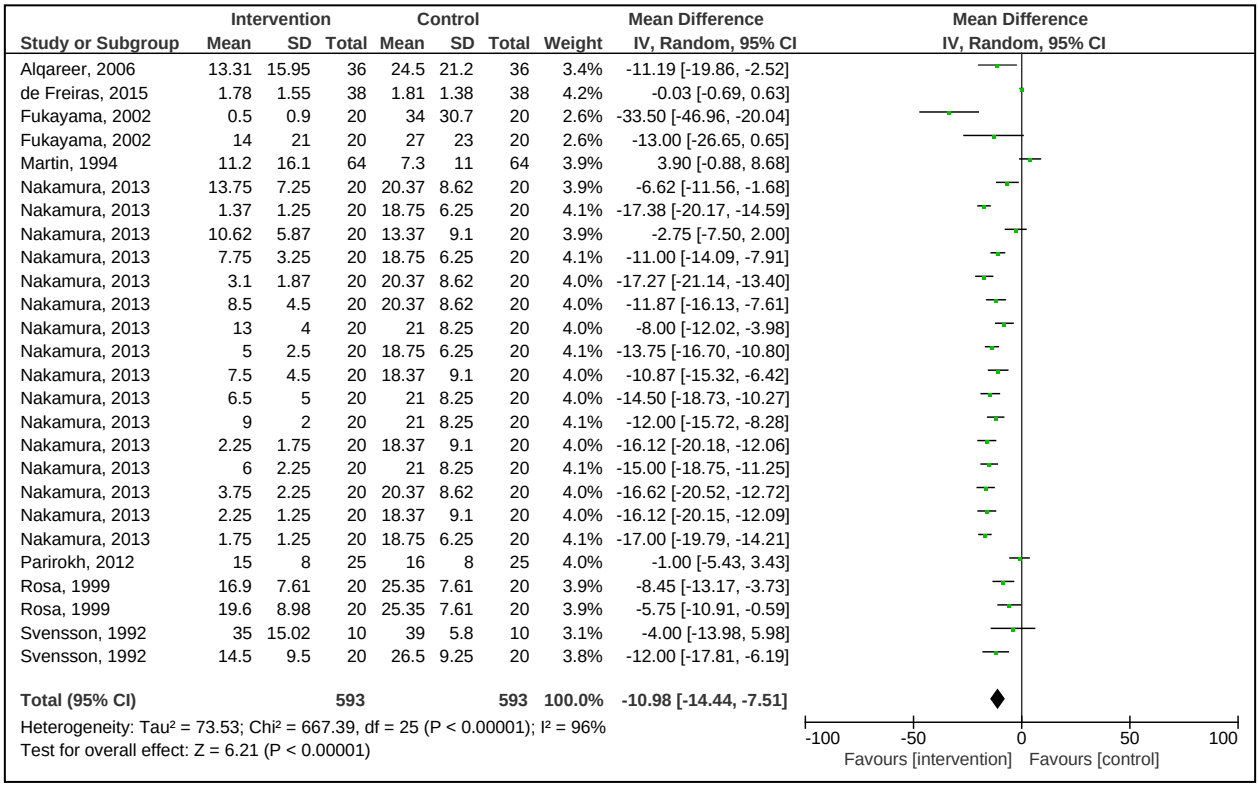

Fig-2: Meta-analysis of studies for the mean difference of pain between intervention and control groups

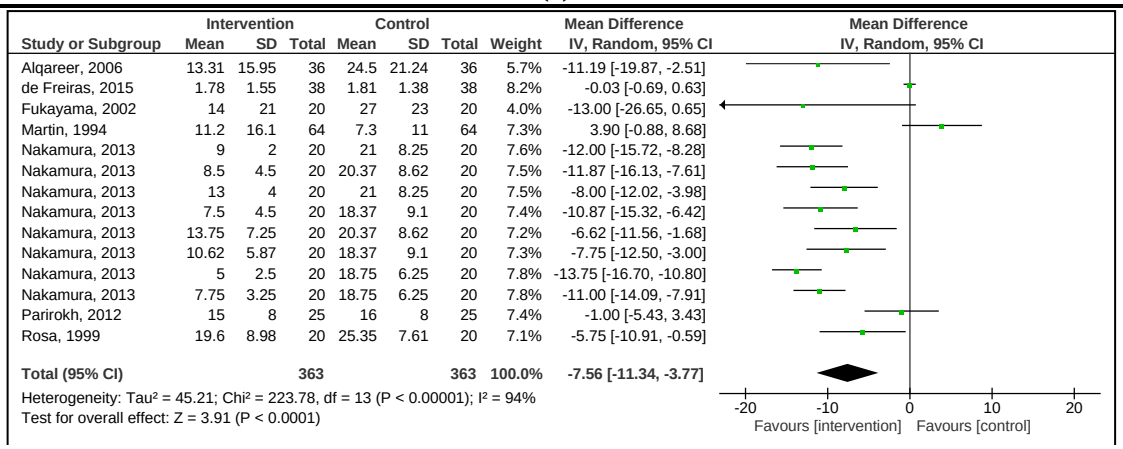

Fig-3: Meta-analysis of studies for the mean difference of pain between benzocaine and control groups

Lidocaine versus placebo

Figure 4 shows the difference of pain between lidocaine and compounds containing lidocaine groups compared with the control group that there was a significant difference between lidocaine and control groups [MD: -15.81, 95% CI: -17.58, -14.05; p<0.00001) and a significant heterogeneity (I^2=56%, p=0.01). The pain is significantly lower in the lidocaine group compared to controls. Thus, a subgroup analysis was conducted to showed difference was [MD: -34.3, 95%CI: -47.76, -20.84; p<00001], [MD: -16.44, 95%CI: -18.23, -14.65; p<00001], [MD: -16.75, 95%CI: -21.34, -12.16; p<00001], [MD: -16.47, 95%CI: -18.72, -14.72; p<00001] and [MD: -8.26, 95%CI: -16.08, -0.44; p<0.04] in subgroups of lidocaine 60%, lidocaine 2%, lidocaine 5%, lidocaine 2%/epinephrine 0.75µg and EMLA, respectively. Also, heterogeneity in subgroups of lidocaine 2%, lidocaine (2%)/epinephrine 0.75µg and EMLA was [I^2=0%, P<0.76], [I^2=0%, P<0.79] and [I^2=66%, P<0.09], respectively. Thus, the pain is significantly lower in the lidocaine group compared to controls.

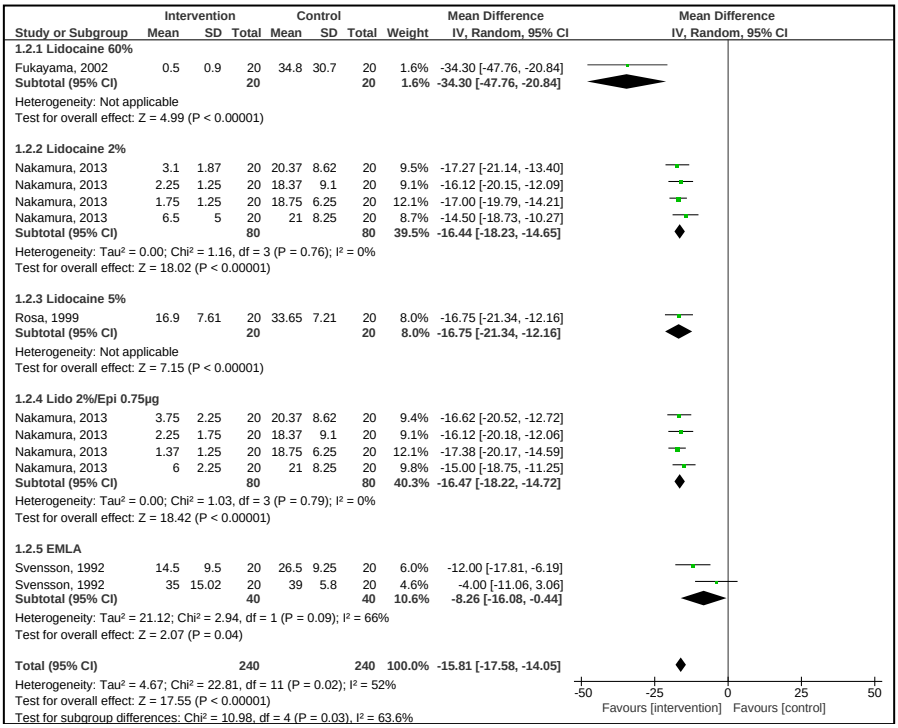

Fig-4: Meta-analysis of studies for the mean difference of pain between lidocaine and compounds containing lidocaine groups compared with control group. Abbreviations: Lido, lidocaine; Epi, epinephrine.

Benzocaine 20% versus placebo based on time-effect

The difference of pain based on time-effect for benzocaine 20% and control groups has been shown in **Figure 5**. The subgroup analysis based on time-effect was performed that 2, 3, 4, 5 and 20 min after application, the difference was [MD: -7.59, 95%CI: -

13.77, -1.42-; p=0.02 and I^2=95%], [MD: -3.9, 95%CI=-0.88, 8.68; p=0.11], [MD: -11.19, 95%CI= -19.87, -2.51; p=0.01], [MD: -11.24, 95%CI= -13. 87, -8.61; p<0.00001 and I^2=51%] and [MD: -13, 95%CI= -26.65, 0.65; p=0.06]. Also, heterogeneity between studies, in the 2 min subgroup was significantly high (I^2=95%), and moderately high in the 5 min subgroup (I^2=51%).

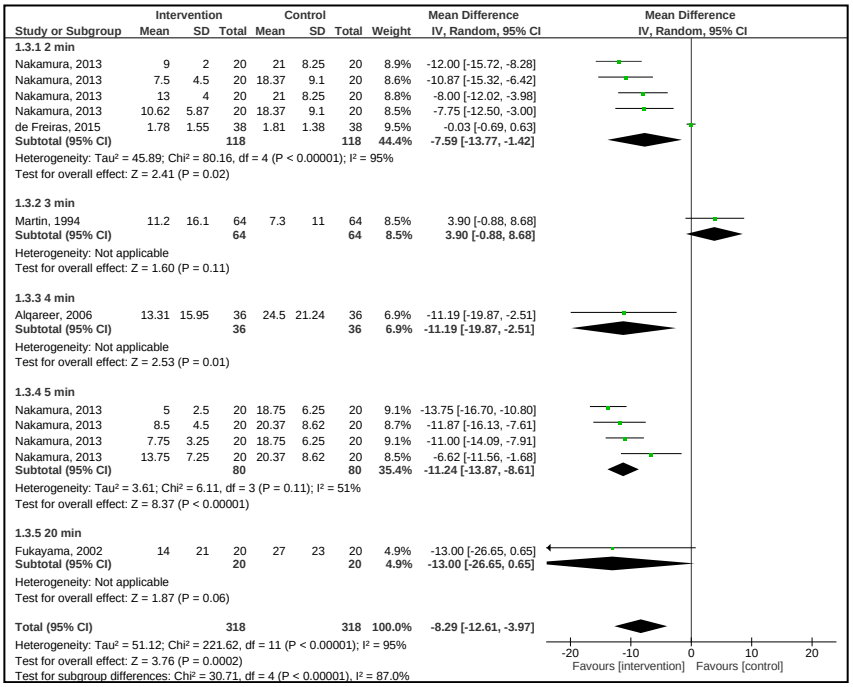

Fig-5: Meta-analysis of studies for the mean difference of pain based on time-effect for benzocaine 20% and control groups

Benzocaine 20% versus placebo based on injection area (labial or buccal)

A subgroup analysis of application areas of benzocaine 20% was done (**Figure 6**). The difference of pain was significantly lower in benzocaine group than in the control group for anterior labial injection [MD: -9.52, 95%CI: -11.91, -7.12; p<0.00001], but not in posterior buccal injection [MD: 1.19, 95%CI: -2.37, 4.76, p=0.51]. Also, heterogeneity between studies in the two subgroups was moderately high (I^2=68% and 61%, respectively).

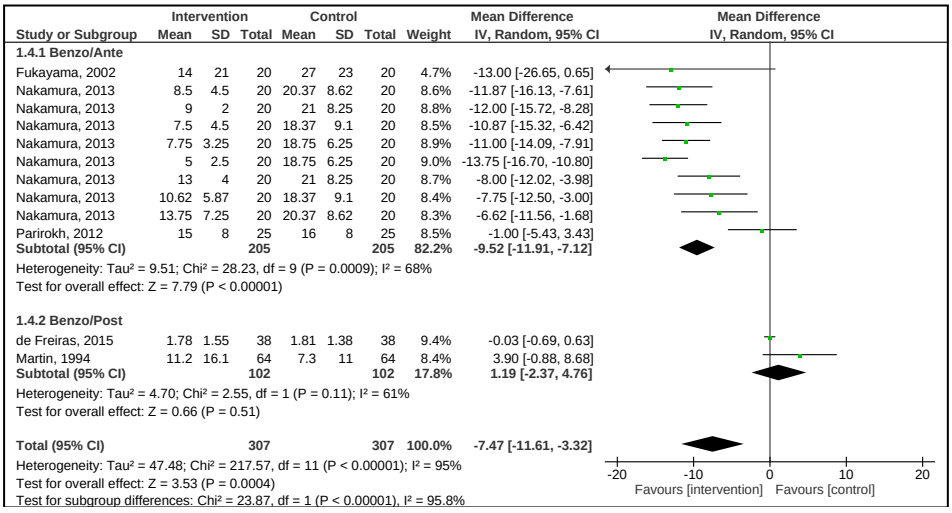

Fig-6: Meta-analysis of studies for the mean difference of pain based on application area for benzocaine 20% and control groups; Abbreviations: Ante, anterior labial; Post, posterior buccal

Benzocaine 20% versus placebo based on the kind of using material

Figure 7 shows subgroup analysis by the kind of use of material. The difference of pain was significantly lower in benzocaine/patch group than in control group [MD: -10.63, 95%CI: -12.34, -8.92; p<0.00001], but not in benzocaine/non-patch [MD: -2.33, 95%CI: -5.81, 1.14; p=0.19]. The heterogeneity between studies in the patch and non-patch subgroups was moderately high (I^2=35%) and 71%, respectively).

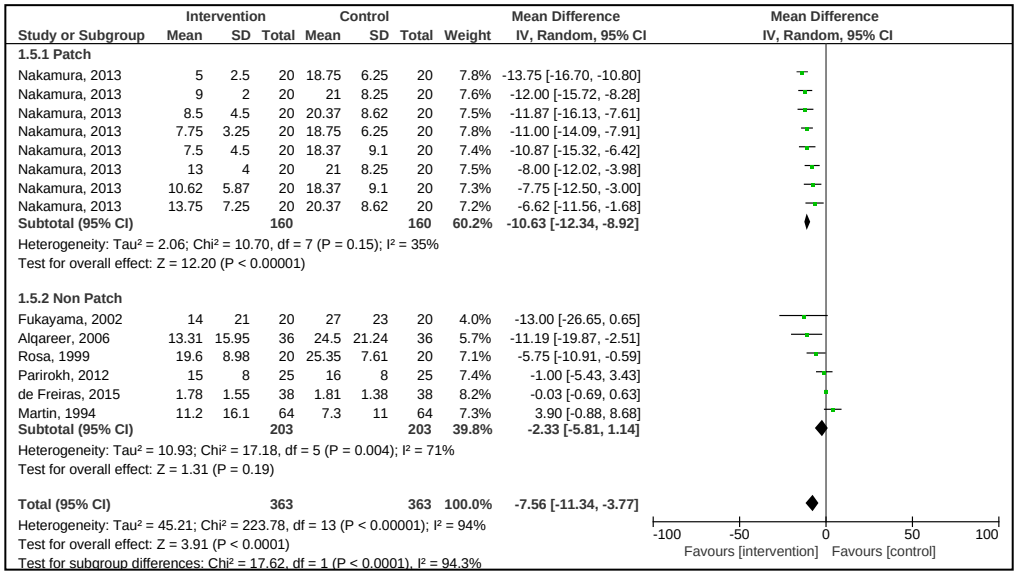

Fig-7: Meta-analysis of studies for the mean difference of pain based on the use of material for benzocaine 20% and control groups

Publication bias

Figure 8 shows the symmetric funnel plot. Moreover, Begg's and Egger's tests did reveal a significant evidence of publication bias among the included studies (Begg's test, P <0.005; Egger's test, P = 0.001).

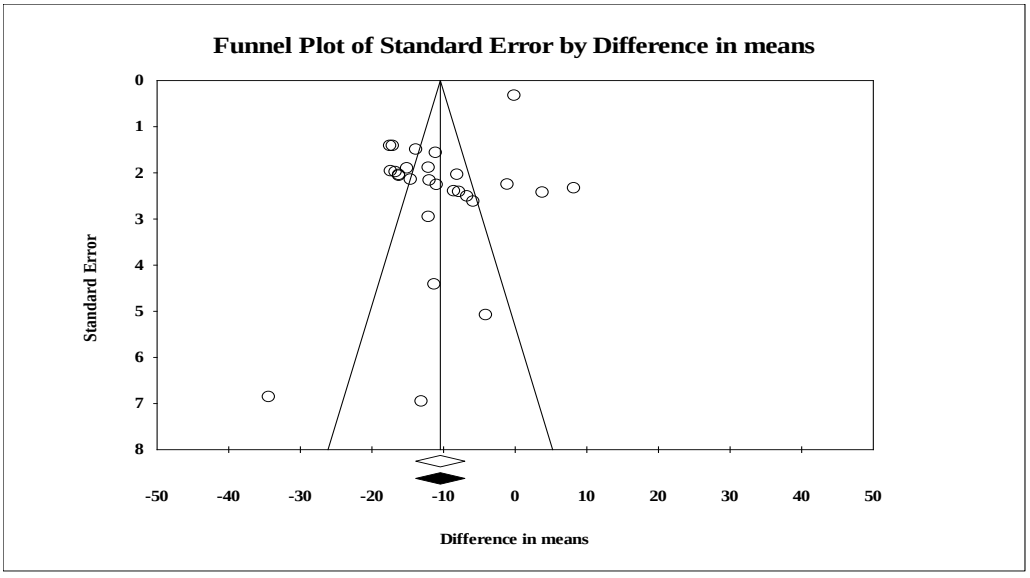

Fig-8: Funnel plot of random-effect in intervention group compared with control group for all subgroups of studies

DISCUSSION

The pain of needle insertion is a factor that causes, fewer patients are referred to the dental clinics. This subject can cause the risk of oral hygiene in these patients. Therefore, providing an effective, safe, painless and adequate anesthesia for a dentist is one of the most important skills [2] and is the first aim of dentists when carry out endodontic processes for patients [23]. Studies suggested that conventional dental topical anesthetics such as lidocaine and benzocaine do

not differ in their efficacy in anesthetizing reflected oral mucosa [24]. There were a large number of clinical trials on the use of EMLA in dentistry; however, no serious adverse effects concerning the use of EMLA on oral mucosa have been reported in the literature [25]. This meta-analysis study showed that topical anesthetics were able to significantly reduced the pain of needle insertion when compared with placebo, such as benzocaine 20% and lidocaine compounds (lidoccaine 2%, lidocaine 60%, Lidocaine 2%/Epinephrine and EMLA). Al-Melh et al. [26] concluded that topical application of EMLA before palatal anesthetic infiltration is associated with less pain than with benzocaine gel. Out of 8 substudies in study of Nakamura et al. [18] and other studies [3,5,19] confirmed the efficacy of benzocaine 20%, but no studies of de Freiras's [12] and Parirokh's studies [10]. Martin et al. [22] showed that benzocaine 20% increased the pain compared with placebo. Fukayama's [5], Nakamura's [18] in four substudies, Rosa's [19], Nakamura's studies [18] in four other substudies and Svensson's study reported that lidocaine 60%, lidocaine 2%, lidocaine 5%, lidocaine 2%/epinephrine and EMLA significantly reduced pain compared with placebo. The meta-analysis showed that lidocaine compounds were more effective than benzocaine 20% in reducing of pain compared with placebo. Also, the best time-effect after application can be different based on type of topical anesthetic, concentration and the kind of material. The meta-analysis analyzed time-effects after benzocaine 20% application (2, 3, 4, 5 and 20 min). The best time was 5 min that significantly reduced the pain that in Nakamura's study [18], this time was almost better than 2 min. Hersh et al. [6] was plotted the time-effect curves of the pain based on VAS for lidocaine 10% and 20% on the maxilla that their results showed that the curves had a decreasing trend until 15 min (minimum) and then increased. The results showed that for needle insertion only, 5% lidocaine reduced pain as determined by a significant difference in mean VAS after 2 minutes (20.1 mm), 5 minutes (15.7 mm), and 10 minutes (13.7 mm) [27] and therefore an application time greater than 2 minutes for topical anesthetics was not necessary because no difference in pain was noted during needle penetration with 2, 5, and 10 minutes of topical anesthetic application. In this meta-analysis study was resulted that the pain of anterior labial statistically is lower than posterior buccal after application of benzocaine 20% in these areas compared with placebo that Nusstein et al. [8] confirmed it. Therefore, topical anesthetics proved effective during needle penetration for anesthesia in the anterior region of the maxilla [21]. The results of this study showed that benzocaine 20%/patch significantly reduced the pain compared with placebo, but no benzocaine 20%/none-patch. Nakamura et al. [18] confirmed this result and concluded that the pain after needle insertion for benzocaine (20%)/patch was lower than benzocaine(20%)/none-patch. Kreider et al. [28] reported that a statistically significant decrease the injection pain when the patch was used compared with topical anesthetic gel.

Limitations and weaknesses

1. The use of different concentrations of lidocaine.
2. The criteria were not matched in all studies.
3. There was difference in use of needle gauge between studies.
4. The sex had not been reported in a number of studies.
5. The formulation of materials was different in the studies.
6. The quality of some studies was very low.
7. There was a bias between the studies.

CONCLUSIONS

The topical anesthetics reduced the pain compared with placebo in the maxilla. Lidocaine compounds probably are more effective than benzocaine 20% as topical anesthetics. The period of 5 minutes can be sufficient for reducing the pain after application of topical anesthetic. Also, benzocaine/patch can be more useful compared with benzocaine/non-patch in reducing of the pain of needle insertion.

Conflict of interest

None declared.

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