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REVIEW ARTICLE

A COMPARATIVE STUDY BETWEEN 0.5% CENTBUCRIDINE HCL AND 2% LIGNOCAINE HCL WITH ADRENALINE (1:200,000): SYSTEMATIC REVIEW AND META-ANALYSIS.

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Key words:-
Dental extractions; local anesthesia; local anesthetics; centbucridine; lidocaine; lignocaine.

Abstract

Purpose: The aim of the present study was to identify significant differences between centbucridine and lignocaine with regard to efficacy of local anesthesia, cardiovascular stability, and side effects of the local anesthetics.

Materials and methods: We performed a systematic and electronic search of several databases using specific keywords, and a manual search through February 2017. The inclusion criteria were clinical human studies, including randomized controlled trials (RCTs), controlled clinical trials (CCTs), and retrospective studies, with the aim of comparing the two drugs in dental/oral surgical practice. Meta-analysis was used to select a fixed or random effects model according to the heterogeneity of the studies. Heterogeneity was assessed using Cochran's Q - test and I^2. The standard difference in means (SDM) was used as the effect measure for all variables. The results were graphically presented using Forest plot. Funnel plot was used to assess publication bias. The significance level was set at p-value ≤ 0.05

Results: Three studies met our inclusion criteria. No statistically significant difference was found between the 2 groups regarding onset of anesthesia ($P = 0.870$), duration of anesthesia ($p=0.327$), depth of anesthesia ($P=0.794$), and pulse rate after 10 minutes ($p=0.087$). A statistically significant difference was found between the two drugs regarding pulse rate after 30 minutes ($p = 0.017$).

Conclusion: The results of the meta-analysis have shown that Centbucridine significantly reduced pulse rate 30 minutes after dental extractions compared with the lignocaine.

Introduction:-

The development of local anesthetics (LAs) has marked the beginning of new era in the field of dentistry. The use of local anesthetics in dentistry and other surgical procedures for adequate pain control with minimum systemic side effects is one of the major concerns all over the world. Control of pain has been one of the medical portents of twentieth century (Malamed, 2004; Gupta et al.,1989) .

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Lignocaine is the 'Gold Standard' local anesthetic agent against which all new local anesthetics are compared. Although its properties resemble an ideal LA agent, it is not completely free from cardiovascular toxicity and has an inherent vasodilating property (Malamed, 2004; Gupta et al., 1982; Patnaik et al., 1982). As a result of the vasodilating characteristic, it has to be combined with a vasoconstrictor, such as adrenaline, to decrease its rate of absorption at the injection site and hence prolong the duration and depth of anesthesia for routine minor dental or oral surgical procedures. The use of adrenaline as a vasoconstrictor is sometimes contraindicated for medically compromised patients. To overcome these disadvantages, other local anesthetics have been developed over the past few years (Dugal et al., 2009; Mansuri et al., 2011 ; Goyal et al ., 2013).

Search for a more effective local anesthetic led to the development of centbucridine (Mansuri et al., 2011) which was mainly developed in India (Muthu et al., 2007). Centbucridine, chemically known as 4-N-butylamino-1,2,3,4-tetrahydroacridine hydrochloride, is a new quinoline derivative with LA action. It was synthesized at the central drug research institute, Lucknow, India, by Patnaik , and has the advantage of having an inherent vasoconstrictor property (Patnaik & Dhawan , 1982). It has an inherent vasoconstrictor effect so it does not need adrenaline to be added. Its efficacy and safely has been proven with its use in subdural anaesthesia and ocular anaesthesia but it has not been widely used for dental anaesthesia (Muthu et al., 2007).

Many studies have been performed on centbucridine in the medical field including ophthalmic surgery (Gupta et al., 1985; Ghose et al., 2004), subarachnoid (Dasgupta et al., 1984), and spinal blocks (Samsi et al., 1983). Most of the clinical work on centbucridine has been published in Indian medical journals. Centbucridine does not affect the central nervous or central vascular system except when administered at very large doses (Gupta et al., 1982; Goyal et al ., 2013). However, in dentistry, only a few studies have been published (Gupta et al., 1989; Vaccharajani et al., 1983; Dugal et al., 2009) and most of them were carried out in the early 1980s. All of the published literature has shown centbucridine to be a potent and reversible LA. One study reported it to be four to five times more potent than lignocaine (Dasgupta et al., 1984). The aim of this study is to focus on the question: "Is there a significant difference in the clinical outcomes between the two drugs in dental/oral surgical practice?

Patients and Methods:-

Data sources and key words:-

An electronic search was performed without language and date restrictions in February 2017 in the following databases: Pub Med, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (Central) and manual search

The key words and their combinations used in this search included
In PubMed: ((((((((((((tooth extraction [MeSH Terms]) OR oral surgery [MeSH Terms]) OR oral surgical procedure [MeSH Terms]) OR tooth extraction [Title/ Abstract]) OR dental extractions [Title/Abstract]) OR dental extraction [Title/ Abstract]) OR tooth extractions [Title/Abstract]) OR minor oral surgery [Title /Abstract]) OR oral surgery [Title/Abstract]) OR dental surgery [Title/Abstract])) AND (((((((local anesthesia [MeSH Terms]) OR local anesthetics [MeSH Terms]) OR centbucridine [Title/Abstract]) OR centbucridine HCl [Title/Abstract]) OR local anaesthesia [Title/Abstract]) OR local anesthesia [Title/Abstract]) OR local anesthetics [Title/ Abstract])) AND (((lidocaine [MeSH Terms]) OR lidocaine [Title/Abstract]) OR lignocaine [Title/Abstract]).

In Cochrane Database: (Tooth extraction [MeSH Terms]) OR (surgery, oral) [MeSH Terms]) OR (oral surgical procedure [MeSH Terms]) OR "tooth extraction" (Title, Abstract, keywords) OR dental extraction (Title, Abstract, keywords) OR tooth extractions (Title, Abstract, keywords) OR minor oral surgery (Title, Abstract, keywords) OR oral surgery (Title, Abstract, keywords) OR dental surgery (Title, Abstract, keywords) AND Anesthesia, local [MeSH Terms] OR anesthetics , local [MeSH Terms] OR "centbucridine" (Title, Abstract, keywords) OR local anaesthesia(Title, Abstract, keywords) OR local anesthesia(Title, Abstract, keywords) OR local anesthetics (Title, Abstract, keywords) AND lidocaine [MeSH Terms] OR lidocaine (Title, Abstract, keywords) OR lignocaine (Title, Abstract, keywords).

A manual search of oral and maxillofacial surgery related journals including British Journal of Oral and Maxillofacial Surgery, the International Journal of Oral and Maxillofacial Surgery, Journal of Maxillofacial and Oral Surgery, Journal of Craniofacial Surgery, Journal of Oral and Maxillofacial Surgery, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Journal of CranioMaxillofacial Surgery was performed. Relevant reviews on the subject and the reference lists of the studies identified were scanned for possible additional studies.

Inclusion and exclusion criteria:-
Inclusion criteria were studies in humans including randomized controlled trials (RCTs), controlled clinical trials (CCTs), prospective studies (RS), and retrospective studies (RS). The aim of the studies had to be a comparison between centbucridine and lignocaine in physically fit (ASA Class I) adult patients of either sex scheduled for extraction of teeth using nerve blocks, with the outcome variables being efficacy of local anesthesia, , cardiovascular stability and side effects of the anesthetics.

Exclusion criteria were: highly anxious patients, patients with a history of allergies to local anesthetic agents and known cardiovascular problems, cases with acute infection in the orofacial area, technical reports, case reports, in vitro studies, animal studies, and review papers.

Selection of relevant studies:-
The following data were extracted from the studies included in the final analysis: authors, year of publication, study design, number of participants, patient age range and/ or mean age, sex, site of extraction , types of local anesthesia, intradermal sensitivity test, informed written consent, efficacy of local anesthesia including onset of anesthesia, duration of anesthesia, the depth of anesthesia, cardiovascular stability (blood pressure and pulse rate), side effects to the anesthetic (if any).

Assessment of quality:-
A methodological quality analysis was performed by merging the proposed criteria of the Strobe statement (Von Elm et al., 2007), Moose statement (Stroup et al., 2000), and Prisma statement(Moher et al., 2009), to verify the force of scientific evidence in making clinical decisions. The classification of the risk of potential bias for every article was based on the following criteria: random selection in the participants, definition of inclusion and exclusion criteria, report of losses to follow up (attrition bias), validity of assessments, and statistical analysis. A study that comprised all the criteria mentioned above was categorized as having a low risk of bias, a study that did not comprise one of these criteria was categorized as having a moderate risk of bias. If two or more criteria were missed, the study was classified to have a high risk of bias.

Meta-Analysis:-
Meta-analysis of the present study was performed using Comprehensive Meta-analysis version 2.2.048 software (Biostat, Inc , Englewood, NJ, USA). The first step in meta-analysis is to select the model to be used whether fixed or random effects model according to heterogeneity of the studies. A variety of heterogeneity measures were provided to decide on the fixed or random effects approach. Cochran's Q provides a P-value for the test of homogeneity. I^2 was deemed to be more reliable in assessing inconsistency between studies, with values of 25%, 50% and 75% corresponding to low, moderate and high heterogeneity respectively (Higgins et al ., 2003).

Whenever heterogeneity was identified with Cochran's Q - test and/or I^2, a random effects model was preferred over the fixed effects. Heterogeneity was identified by rejecting the homogeneity hypothesis. Meta-analysis done for prevalence of post-operative sensitivity used the Odds Ratio (OR) as the effect measures while meta-analysis for pain scores (VAS) used the standard difference in means (SDM) as the effect measure.

The results were graphically presented using forest plot. In forest plot, each study is represented by a line. There is a box (or circle) in the line for each study. The mid-point of the box (or circle) represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box (or circle) represents the weight given to the study. The diamond below the studies represents the overall effect. The width of the line showed the confidence interval (95% CI) of the effect estimate of individual studies. The width of the diamond shows the confidence interval (95% CI) of the overall effect estimate. The vertical line in the middle of the Forest plot (Corresponding to the value 0) is the line of no effect. If the confidence interval overlaps this line (Overlaps 0 value), then there is no statistical significance at 0.05 significance levels. If 0 value is not included in the 95% CI, the results are statistically significant at 0.05 significance level. This is applicable for the effect estimates for the individual studies and the overall estimate.

Funnel plot was used to assess publication bias. The plot by precision is the traditional form. Large studies appear toward the top of the graph, and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph, and (since there is more random variation in the small studies) are dispersed across a range of values. This pattern tends to resemble a funnel, which is the basis for the plot's name. In the absence of publication bias the studies will be distributed symmetrically about the combined effect size. By contrast, in the presence of bias, the bottom of the plot would tend to show a higher concentration of studies on one side of the mean than the other.

Egger's test of the intercept was used to quantify the display of the funnel plot. This approach may offer a number of advantages over other approaches. Under some circumstances this may be a more powerful test. Additionally, this approach can be extended to include more than one predictor variable, which means that we can simultaneously assess the impact of several factors, including sample size, on the treatment effect. The significance level was set at p-value ≤ 0.05.

Results:-

Summary of the study selection process is shown in Fig. 1. The electronic search resulted in 575 studies; three additional articles were added from hand-searching and other sources. After the initial screening of articles, 123 articles were excluded because of duplication. Of the remaining 455 articles assessed, 380 were excluded by title and abstract because they were not related to the topic. Seventy five studies were selected for full text analysis leading to the exclusion of 72 articles because they did not meet the inclusion and exclusion criteria. Thus, a total of 3 articles were included in this systematic review and meta-analysis.

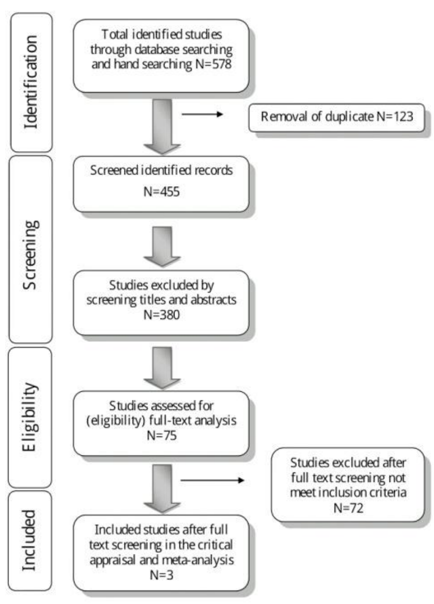

Fig.1:- Flow diagram of study selection process

Description of included studies:-

Extracted data of the included 3 studies are listed in Table 1. Three prospective studies were included in this study (Dugal et al., 2009; Mansuri et al., 2011; Goyal et al ., 2013). A total of 760 patients were enrolled in the three studies. 390 patients in interventions group (0.5% Centbucridine) and 370 patients in control group (Lignocaine HCl with Adrenaline 1:200,000). The ages ranged from 16-60 years. Intradermal sensitivity test was performed for all patients and informed written consent was obtained from all patients.

In first study the patient received 3 ml of anesthetic for nerve blocks using either 0.5% Centbucridine HCI or 2% Lignocaine HCI with adrenaline (1:200,000) (Dugal et al., 2009).In the second study patients randomly received a single anesthetic dose of either 0.5% Centbucridine HCI or 2% Lignocaine HCI with adrenaline (1:200,000) (Mansuri et al., 2011). In last study both drugs were supplied in equal amounts in identical vials labeled only with a code number (Goyal et al ., 2013).

Table 1:- Studies comparing 0.5% Centbucridine HCl and 2% Lignocaine HCl with Adrenaline (1:2,00,000).

Authors, Publication year	**Study design**	**P(n)**	**Patient age range (mean), years**	**Sex**	**Site of extraction**	**Type of local anesthesia**	**Groups types**	**Dose of local anesthesia**
Dugal et al ., 2009)	PS	240	Adult either sex	Either sex	Extractions (surgical/ closed method) of teeth requiring nerve block (upper anterior or lower molar teeth)	(G1) 0.5% Centbucridine (n=120) (G2) 2% Lignocaine + Adrenaline) (n = 120)	Intervention Control	3 ml of anesthetic was injected for nerve blocks
Mansuri et al., 2011	RCT	198	18 -60 (mean 37.7)	94M/ 104F	extraction of lower molars	(G1) 0.5% Centbucridine (n=100) (G2) 2% Lignocaine + Adrenaline) (n = 98)	Intervention Control	They each randomly received a single anesthetic dose of either 0.5% Centbucridine HCI or 2% Lignocaine HCI with adrenaline
Goyal et al., 2013	RCT	322	18 -60 (mean 36.7)	182M /140F	Extraction of lower molars	(G1) 0.5% Centbucridine (n=170) (G2) 2% Lignocaine + Adrenaline) (n = 152)	Intervention Control	Both drugs were supplied in equal amounts in identical vials labeled only with a code number

PS , Prospective study; RCT, randomized controlled trial; P, participants.

Assessment of quality:-

The risk of bias outcomes is summarized in Table 2. One study was considered to have high risk of bias (Dugal et al ., 2009), one was considered to have moderate risk of bias (Goyal et al., 2013) and one was considered to have low risk of bias (Mansuri et al., 2011).

Table 2:- Results of the quality assessment.

Authors and year of Publication	Random selection of participants	Definition inclusion/ exclusion criteria	Attrision bias (Loss of follow-up)	Validity of assessment	Statistical analysis	Reported potential risk of bias
Dugal et al ., 2009	No	Yes	No	Yes	yes	high
Mansuri et al., 2011	yes	yes	yes	yes	yes	low
Goyal et al., 2013	yes	No	yes	yes	yes	Moderate

Effect of intervention:-

Onset of anesthesia:-

Heterogeneity measures showed statistically significant Cochrane Q value (*p*-value <0.001). I^2 value was 91.0 % indicating high heterogeneity. So the homogeneity hypothesis was rejected and the random effects model was used.

The random effects model showed a standardized mean difference (effect size) of -0.042 with a 95% CI (-0.546 – 0.462) .The effect size was not statistically significant with *p*-value = 0.870 Fig. 2. Thus, there was no statistically significant difference between onset of anesthesia in the two groups.

The relative weight of the included studies revealed that the Goyal et al., 2013 study had the highest weight (34.3%) while Mansuri et al., 2011 study showed the lowest weight (33.0%).

Funnel plot analysis for the included studies showed no publication bias Fig. 3. This was confirmed by Egger's regression intercept which showed a non-statistically significant result (*p*-value = 0.464). As the results were not -statistically significant, we concluded that there was no publication bias.

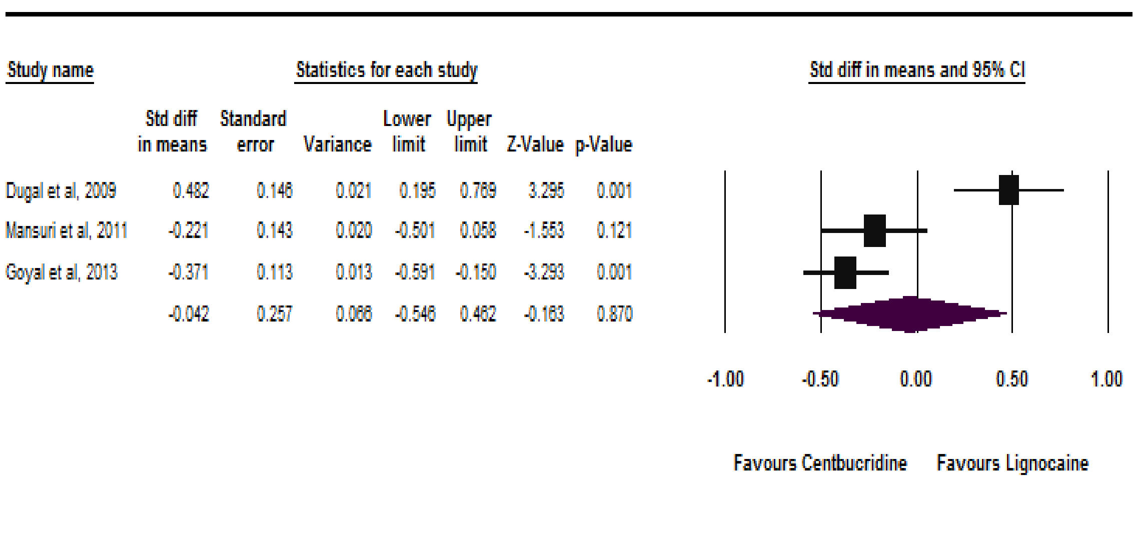

Fig. 2:- Forest plot for onset of anesthesia.

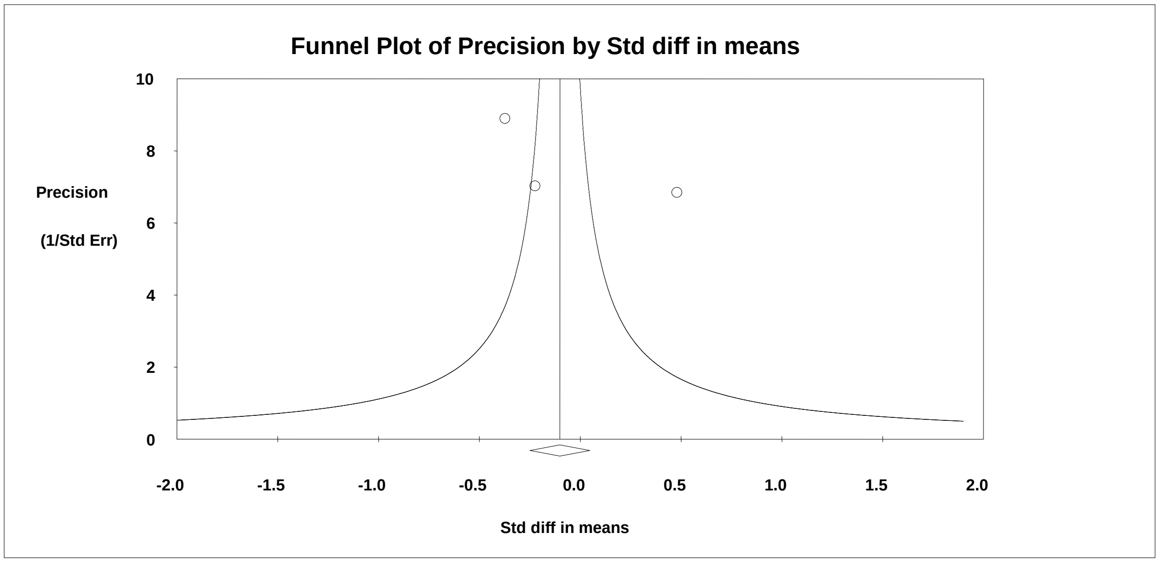

Fig . 3:- Funnel plot for onset of anesthesia.

Duration of Anesthesia:-

Heterogeneity measures showed statistically significant Cochrane Q value (*P*-value = 0.001). I^2 value was 86.6% indicating high heterogeneity. So the homogeneity hypothesis was rejected and the random effects model was used.

The random effects model showed a standardized mean difference (effect size) of 0.206 with a 95% CI (-0.206 – 0.618). The effect size was not statistically significant with *p*-value = 0.327 Fig. 4. Thus, there was no statistically significant difference between duration of anesthesia in the two groups.
The relative weight of the included studies revealed that Goyal et al ., 2013 study had the highest weight (34.7%) while Dugal et al., 2009 study showed the lowest weight (32.6%).

Funnel plot analysis for the included studies showed no publication bias Fig. 5. This was confirmed by Egger's regression intercept which showed a non-statistically significant result (*p*-value = 0.709). As the results were not statistically significant, we concluded that there is no publication bias.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Dugal et al, 2009	-0.239	0.145	0.021	-0.522	0.045	-1.647	0.100
Mansuri et al, 2011	0.475	0.144	0.021	0.192	0.757	3.295	0.001
Goyal et al, 2013	0.371	0.113	0.013	0.150	0.591	3.293	0.001
	0.206	0.210	0.044	-0.206	0.618	0.981	0.327

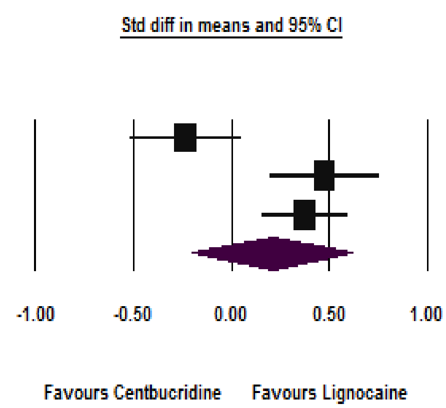

Fig. 4:- Forest plot for duration of anesthesia.

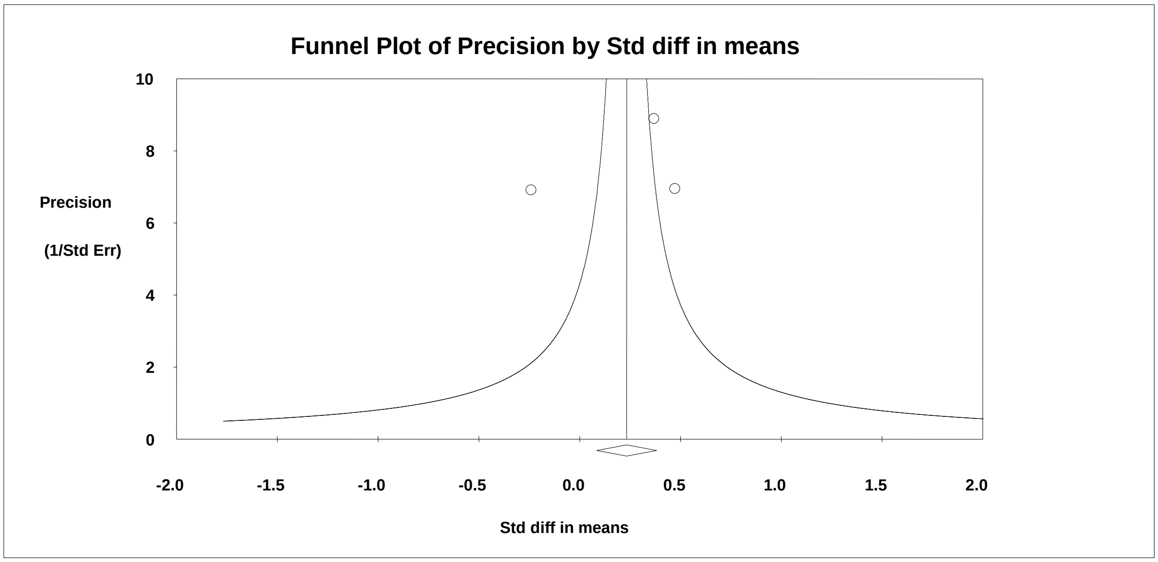

Fig. 5:- Funnel plot for duration of anesthesia.

Depth of anesthesia (VAS score):-

For the ease of calculation, the mean VAS score was computed according to the data presented in the study. However, the Dugal et al., 2009 study was not included in the meta-analysis because the standard deviation in Lignocaine group was zero (all cases had zero score on VAS).

Heterogeneity measures showed a non-statistically significant Cochrane Q value (*p*-value = 0.967). I^2 value was 0.0% indicating no heterogeneity. Thus, the homogeneity hypothesis was not rejected and the fixed effects model was used.

The fixed effects model showed a standardized mean difference (effect size) of 0.023 with a 95% CI (-0.149 – 0.195). The effect size was not statistically significant with *p*-value = 0.794 Fig. 6. Thus, there was no statistically significant difference between depth of anesthesia in the two groups.

The relative weight of the included studies revealed that the Goyal et al., 2013 study had the highest weight (61.8%) while the Mansuri et al., 2011 study showed the lowest weight (38.2%).

Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Mansuri et al, 2011	0.018	0.142	0.020	-0.260	0.297	0.128	0.898
Goyal et al, 2013	0.026	0.112	0.012	-0.193	0.245	0.231	0.817
	0.023	0.088	0.008	-0.149	0.195	0.261	0.794

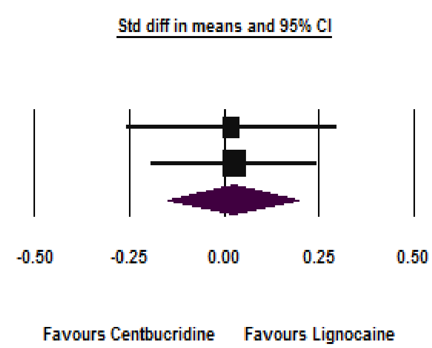

Fig. 6:- Forest plot for depth of anesthesia.

Pulse Rate:-

After 10 minutes:-

Heterogeneity measures showed non-statistically significant Cochrane Q value (*P*-value = 0.079). I^2 value was 60.6% indicating moderate heterogeneity. Thus, that the homogeneity hypothesis was not rejected and the fixed effects model was used.

The fixed effects model showed a standardized mean difference (effect size) of 0.129 with a 95% CI (-0.019 – 0.276). The effect size was not statistically significant with *p*-value = 0.087 Fig. 7.Thus there was no statistically significant difference between pulse rate after 10 minutes in the two groups.

The relative weight of the included studies revealed that the Goyal et al., 2013 study had the highest weight (45.4%) while the Dugal et al., 2009 study showed the lowest weight (26.6%).

Funnel plot analysis for the included studies showed no publication bias Fig. 8. This was confirmed by Egger's regression intercept which showed a non-statistically significant result (*p*-value = 0.473). As the results were not statistically significant, we concluded that there was no publication bias.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Dugal et al, 2009	0.406	0.146	0.021	0.121	0.692	2.787	0.005
Mansuri et al, 2011	0.069	0.142	0.020	-0.209	0.348	0.488	0.626
Goyal et al, 2013	0.003	0.112	0.012	-0.216	0.221	0.024	0.981
	0.129	0.075	0.006	-0.019	0.276	1.712	0.087

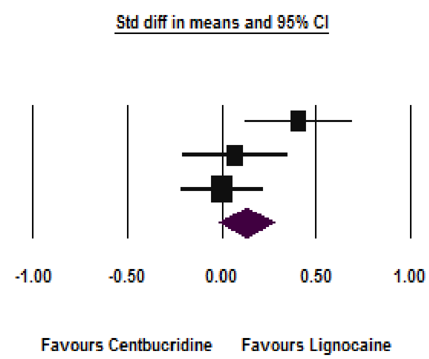

Fig.7:- Forest plot for pulse rate after 10 minutes.

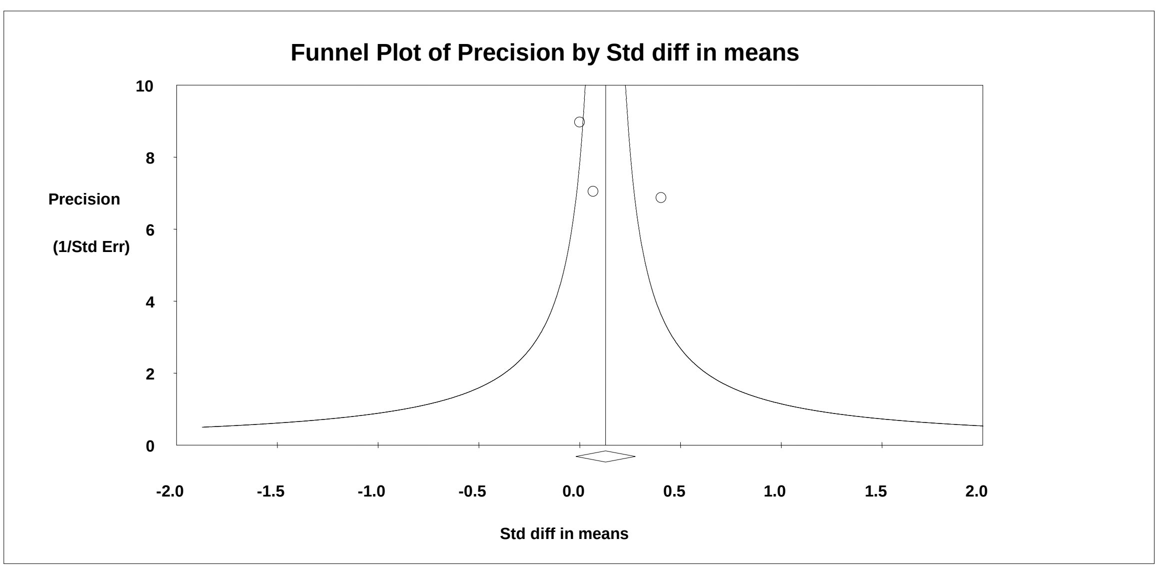

Fig. 8:- Funnel plot for pulse rate after 10 minutes.

After 20 Minutes:-

No meta-analysis could be performed because the Dugal et al ., 2009 study didn't report the pulse rate after 20 minutes and the Mansuri et al ., 2011 study reported that in Lignocaine group the pulse rate after 20 minutes was the same as pre-operative rate so no *p*-value was computed for the comparison. This left only the Goyal et al., 2013 study so no meta-analysis could be done with just one study.

After 30 Minutes:-

Heterogeneity measures showed non-statistically significant Cochrane Q value (p-value = 0.810). I^2 value was 0.0% indicating no heterogeneity. Thus, the homogeneity hypothesis was not rejected and the fixed effects model was used .

The fixed effects model showed a standardized mean difference (effect size) of 0.212 with a 95% CI (0.038 – 0.385). The effect size was statistically significant with p-value = 0.017 Fig. 9. Thus, there was a statistically significant increase in pulse rate after 30 minutes and the direction of effect is in favor of Lignocaine indicating that Lignocaine causes higher increase in pulse rate after 30 minutes compared to Centbucridine .

The relative weight of the included studies revealed that the Goyal et al., 2013 study had the highest weight (62.6%) while the Dugal et al., 2009 study showed the lowest weight (37.4%).
Publication bias could not be assessed because there were only two studies.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Dugal et al, 2009	0.239	0.145	0.021	-0.044	0.523	1.653	0.098
Goyal et al, 2013	0.195	0.112	0.013	-0.024	0.415	1.746	0.081
	0.212	0.089	0.008	0.038	0.385	2.393	0.017

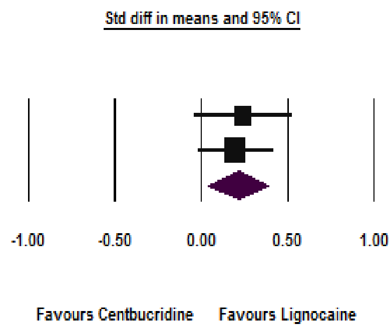

Fig. 9:- Forest plot for pulse rate after 30 minutes

After 60 minutes:-

No meta-analysis could be performed because the Dugal et al., 2009 study didn't report the pulse rate after 60 minutes and the Mansuri et al ., 2011 study reported that in both groups the pulse rate after 60 minutes was the same as pre-operative rate so no p-values were computed for the comparison. This left only the Goyal et al., 2013 study and no meta-analysis could be done with just one study.

No meta-analysis could be performed for blood pressure because only one study reported it.

Regarding side effects, no meta-analysis could be performed because no study reported it.

Discussion:-

Although Centbucridine is relatively new in dentistry, it has demonstrated good clinical results in the literature **(**Vacharajani et al., 1983; Muthu et al., 2007**)**. The aim of this review was to verify through a meta-analysis whether there is a significant difference in the clinical outcomes between centbucridine and lignocaine plus adrenaline. In general, the results of the present meta-analysis show statistically good results for centbucridine as a local anesthesia in dental extraction.

Regarding onset of local anesthesia, when the onset of both anesthetics is compared, there was not much difference. This is in accordance with the reports by (Gupta et al ., 1982 ; Muthu et al ., 2007).This could be due to the inherent vasoconstrictive effect of Centbucridine as compared to Lignocaine. On average, patients felt the anesthetic effect of Centbucridine a few seconds quicker than that of Lignocaine but this difference was not statistically significant and more importantly, is not clinically significant. The onset of action of Centbucridine was within the reported range of initiation of anesthesia as reported by others to be between 1 and 6 minutes (Vacharajani et al., 1983; Gupta et al ., 1989).

Regarding duration of local anesthesia, our study found the duration of anesthetic action of Centbucridine compared favorably to lignocaine with adrenaline. There was no statistically significant difference between them $p= 0.327$. This is similar to what has been reported previously **(**Gupta et al ., 1982; Muthu et al ., 2007**).** This duration is sufficient for both surgical and nonsurgical extractions. A possible reason could be the fact that since Centbucridine has a natural vasoconstrictive effect; the LA solution remained close to and around the nerve tissue for a longer period of time. The solution was prevented from being absorbed and dispersed, and this could have resulted in the sufficient duration of anesthetic time that was obtained **(** Gupta et al., 1989).

Regarding depth of local anesthesia, there was no statistically significant difference between the two groups ($p=0.794$). All patients were sufficiently anesthetized to carry out the procedures. Centbucridine showed sufficient efficacy as a local anesthetic agent. A possible reason could be the fact that since Centbucridine has a natural vasoconstrictive effect; the LA solution remains close to and around the nerve tissue for a longer period of time (Gupta et al., 1989).

Regarding pulse rate, there was no statistically significant difference between the two groups after 10 minutes (p-value = 0.087). Mild elevation of this parameter during this initial time was attributed to anxiety and fear. This has also been reported by other authors (Malamed, 2004; Gupta et al., 1989 ; Vacharajani et al., 1983).However, there was a statistically significant increase in pulse rate after 30 minutes (p-value = 0.017) and the direction of effect is in favor of Lignocaine indicating that with Lignocaine caused a higher increase in pulse rate after 30 minutes compared to Centbucridine. Lignocaine has an inherent vasodilating property, which in turn requires the addition of adrenaline. This has been shown to increase the blood pressure and heart rate in some studies (Malamed, 2004; Gupta et al., 1989); which may become more significant in cardiac cases **(** Dugal et al., 2009).

Regarding blood pressure, no meta-analysis could be done for blood pressure because only one study reported it.Three studies declared lignocaine has an inherent vasodilating property, which in turn requires the addition of adrenaline. This has been shown to increase the blood pressure and heart rate in some studies (Malamed, 2004; Gupta et al., 1989).

Regarding side effects, no meta-analysis could be done for side effects because no study reported it.One study reported side effects of Cenbucridine like headache, dizziness and nausea, which gradually resolved within 10 minutes without any medication (Dugal et al ., 2009).Other studies showed that there were no adverse, toxic, or allergic reactions to either of the LAs in their sample population and confirmed its safety (Mansuri et al ., 2011; Goyal et al., 2013). It is not surprising that there were no patients who reported adverse reactions to Centbucridine. Centbucridine has demonstrated an antihistaminic activity by blocking the H1 histamine receptors which makes it an ideal LA agent in patients with known allergy to other conventional LAs **(**Gupta et al., 1985; Gupta et al .,1989; Mansuri et al., 2011 ; Goyal et al., 2013 **).**

In conclusion, the overall results of meta-analysis showed no statistically significant difference between the 2 groups regarding onset of anesthesia ($p = 0.870$), duration of anesthesia ($p=0.327$), depth of anesthesia ($p=0.794$), and pulse rate after 10 minutes ($p=0.087$). But there was a statistically significant difference between the two drugs with regard to pulse rate after 30 minutes ($p = 0.017$)with lignocaine causing higher increases in pulse rate compared to Centbucridine. Hence Centbucridine had good CVS stability and was devoid of any cardiovascular effects. Centbucridine can be effectively used as an ideal substitute in place of lignocaine in patients undergoing minor oral surgical procedures when adrenaline is absolutely contraindicated due to systemic problems.

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