



CASEIN PHOSHOPEPTIDE AMORPHOUS CALCIUM PHOSPHATE, A POTENT DESENSITIZING AGENT, TO REDUCE POSTOPERATIVE SENSITIVITY AFTER VITAL TOOTH BLEACHING – A SYSTEMATIC REVIEW AND META-ANALYSIS

Dental Science

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ABSTRACT

Objective: Does Casein phospho peptide - Amorphous calcium phosphate has any effect on reducing post-operative sensitivity after tooth bleaching?

Materials and Methods: Search strategy includes Pubmed Central, COCHRANE, EBSCO, and Medline from January 1998 to May 2018. Randomized control trials and Clinical trials were included based on the data extraction, including quality analysis and publication bias. The data collection form was customized.

Data collection and analysis: Two review authors independently extracted the data from included trial studies and assessed the risk of bias [based on Cochrane risk of bias tool].

Conclusion: This systematic review of the available evidence reveals that CPP ACP and potassium fluoride demonstrated good consistent endurance in clinical studies with indistinguishable performance. In the five trials included, two studies are judged as low risk and three as medium risk of bias. There was no significant difference between the CPP ACP and potassium fluoride at different periods.

Discussion: A total of 5 clinical trials included had one group of patients who received CPP ACP application as a desensitizing agent during bleaching met all inclusion criteria involving patients with discolored teeth who required vital bleaching were reviewed. Meta-analysis was performed for three included studies out of five based on homogeneity. All the studies evaluated the primary outcome measures the postoperative pain using the visual analog scale, and the secondary outcome measures the improvement in the teeth shade after bleaching.

Clinical Significance: The various commercial compounds, such as bleaching agents, vary widely in their clinical efficacy. It shows the need for systematic review and meta-analysis of clinical trials to confirm the desensitizing substances' effectiveness when associated with bleaching.

KEYWORDS

Discolored teeth, vital bleaching, in-office bleaching, casein phosphopeptide amorphous phosphopeptide, sodium fluoride, potassium nitrate, post bleaching sensitivity

Background

The appearance of teeth is crucial to all age groups, and it is often associated with a perception of health and fitness. Tooth discoloration is a significant concern, and it may be intrinsic or extrinsic. Various methods are employed to treat the discolored teeth, such as bleaching, microabrasion, macro abrasion, and using composites, ceramics, or veneers as restorative materials. Tooth bleaching is considered the most conservative and aesthetic treatment option, and it is noninvasive. It is one of the most popular cosmetic dental procedures opted for by patients who desire a pleasing smile. Many dentists prefer highly concentrated bleaching agents in clinical practice because it affords the professional greater control, ensures more excellent patient safety, and requires fewer applications.

Description of the intervention:

Bleaching agents show an oxidizing action that leads to free radicals release, reactive oxygen species, and hydrogen peroxide ions. These free radicals as reactive molecules attack chromophores, causing their degradation and resulting in a bleaching effect.

Contemporary bleaching or whitening systems are based primarily on hydrogen peroxide or one of its precursors, notably carbamide peroxide. These are in combination with an activating agent such as light and heat.

The primary and common adverse effect resulting from bleaching is dentinal sensitivity, characterized by acute short-term or transient pain. Peroxides forms bubbles that move the intratubular fluid and activate interdental nerves causing postoperative sensitivity. Therefore, this hypothesis suggests that sensitivity after bleaching results from peroxide penetration into the internal tooth structures, causing direct activation of neuronal receptors.

Although saliva has a known remineralization action, it alone may not maintain adequate levels of available calcium and phosphates in the oral cavity to prevent the incidence of postoperative sensitivity. So there is a need to achieve a positive balance between demineralization and remineralization. Hence fluorides and or remineralizing solutions have been proposed. Bioactive agents containing calcium and phosphate ions have thus been used to treat dentinal sensitivity. These ions releases into saliva occlude the open dentinal tubules and form

biofilms, reducing nerve endings excitability without affecting the tooth bleaching process.

Several methods are available to minimize tooth sensitivity. Reduced time of wearing the tray and application frequency, using a desensitizing agent, and incorporating them into bleaching agents are well known.

Desensitizing agents have been tried in this attempt to counteract bleaching related sensitivity. A combination of potassium nitrate and fluoride has been introduced to reduce sensitivity. Sodium fluoride works on the principle of tubule occlusion, and the fluoride component is thought to reduce the solubility of dentin, thus reduces postoperative sensitivity. The effect of fluoride on reducing tooth sensitivity, however, remains controversial.

Tooth mousse is a sugar-free water-based cream containing 10% CPP ACP and a polishing cleaning and dentinal tubule sealing effect. It can exert a rapid desensitizing effect on protein binding, followed by the deposition of calcium and phosphate compounds within exposed dentinal tubules. Adding CPP ACP to home bleaching agents resulted in a significant reduction of sensitivity during in-office bleaching.

Importance of this review

It is a known fact that remineralizing bioactive agents effectively treat hypersensitivity. They can affect bleaching quality by altering the enamel permeability. Depression of ionic crystals may present, leading to the penetration of reactive oxygen species and free radicals on the tooth surface. The various commercial compounds vary widely in their clinical efficacy. It shows the need for systematic review and meta-analysis of clinical trials to confirm the desensitizing substances' effectiveness when associated with bleaching. Literature review revealed no systematic review and meta-analysis related to tooth sensitivity after an in-office tooth bleaching.

OBJECTIVES:

The criteria for considering clinical trials for this review:

METHODS:

Types of studies: randomized clinical trials, controlled clinical trials; clinical studies will be included in the study recruited patients with

discolored teeth required vital bleaching. Trials included should have had one group of patients who received CPP ACP application as a desensitizing agent during bleaching.

Type of participants:

Inclusion criteria- Adult patients with tooth discoloration requiring vital bleaching.

Exclusion criteria: patients who have

- restorations in anterior teeth,
- using analgesics or anti-inflammatory drugs
- spontaneous tooth sensitivity
- non-carious lesions
- tetracycline stains,
- teeth with developmental defects anomalies and
- pathological conditions like dental caries need for endodontics or orthodontics.

Intervention- vital bleaching with the application of CPPACP

Comparison- vital bleaching without application of CPPACP

Primary outcome- assessment of tooth sensitivity after bleaching

Secondary outcome- degree of color change

Search methods for identification

Searched Databases

- PubMed (from January 1998 to May 2018)
- PubMed Advanced Search
- COCHRANE
- EBSCO
- MEDLINE

Hand Searching

The following journals were hand-searched

- Journal of conservative dentistry
- Operative Dentistry
- Journal of adhesive dentistry
- Quintessence international
- Dental Materials
- Journal of Clinical and Experimental Dentistry
- Journal of Dental Research

The review registered in PROSPERO 2018 CRD42018092681

Quality Assessment :

The authors assessed the quality of the included articles independently according to the GRADE methods using GRADE PRO 2008. We evaluated and assessed the quality of the body of evidence as higher, as shown in the grade table. Quality of evidence grade table] by considering the overall risk of bias, the directness of evidence, consistency of results, precision of the estimates, and publication risk bias.

The measure of Effect Size:

The success in the included six trials measured on an ordinal scale is a binary outcome. The odds ratio was calculated in the form of a measure of effect size compared to CPP ACP and NaF. The design of all six studies are presented in Table 1, and the study characteristics are given in table 2.

Data collection and analysis

RESULTS

A single operator carried out / a calibrated examiner blinded the study groups recorded tooth sensitivity perceived by the patient at two-time intervals. The extracted data are mentioned in the table. The obtained data includes the name of the first author, year of the publication, patients information, study design, follow-up time, and dropouts given in table 3.

In the five included studies, the reduction in postoperative sensitivity compared between CPP ACP & NAF in three studies. One study compared novamin & CPP ACP one study compared KNO₃, NaMFP & CPP-ACP with different follow-up periods starting from baseline, day 7, 14, 21, and 30. The outcome [pain] was measured by calibrated examiners at several time intervals after vital tooth bleaching using a visual analog and scaffe's scale.

In the visual analog scale, tooth sensitivity measurement was scored on a printed form consisting continuous scale of 0 through 10 points for each day.

The vitapan shade guide in four studies and spectrophotometer in one study evaluated tooth shade.

Assessment of risk of bias of the included studies:

Two authors independently assessed the risk of bias in the included five clinical trials using the Cochrane collaboration tool for risk assessment of the review manager. The following domains are evaluated and classified as low, moderate, high, or unclear risk of bias.

Sequence generation

Allocation

Blinding of participants and personnel

Incomplete outcome data

Selective outcome reporting

Allocation

All the investigators in five included studies randomized participants to intervention and comparison groups with a block of 4 to 6. The sequence generation was judged as being at low risk of bias. Among the five Laries, Dias alexandrine et al. and GA Maghairn et al. concealed the allocation sequence.

Blinding

Blinding of participants, the investigators, and outcome assessors were reported and explained in all the five studies, which placed this review at low risk of performance bias.

Outcome data

The number and description of dropouts were made clear in the trials by Jyothi kasha et al. and Larissa Dias alexandrine. The number of dropouts mentioned without reasoning in the trials done by Manjyoth Singh et al., Nadeem Tarique et al., and GA Marghaireh et al.

Primary outcome:

The reduction of pain and sensitivity after vital bleaching recorded using the VAS scale, and tooth shade evaluated using shade guides from day one till day 21 participants reported in the tables. In the study by Jyothi et al., 66 subjects recalled for follow-up on the seventh, eighth, and 14th day of the study. On day 14, there is a significant statistical reduction in the incidence and intensity of the sensitivity. In the study by M Singh et al. intensity of pain was observed to be significantly higher in the patients in the fluoride group than the CPP-ACP group but no statistical significance in reducing pain on day 14th in both the groups. Tooth shade, there was a significant decrease in the tab values in the studies used vitapan shade guide showed that the smallest number of shade tab change was three tabs, and the largest was eight tabs.

In the study by Larissa et al., there is a significant reduction in the post bleaching sensitivity in the CPP-ACP group after three sessions. Tooth bleaching with CPP-ACP causes less sensitivity in treated teeth than a bleaching agent alone or a bleaching agent along with novamin. In the study by Nadeem Tarique et al., CPPACP exhibited reduced sensitivity after vital bleaching.

In the study by GA Maghaireh et al., the results showed that sensitivity has dramatically reduced by the 14th day in CPP ACP group participants followed by Na F group. Participants had a significant shade improvement by an average of 68 units of shade change.

Meta-analysis

The outcome measure represents the success or failure of the binary data and the presence or absence of sensitivity through VAS scales. Out of five included trials, three were homogenous as two groups interventions, and comparisons were common in all of them. It was measured in the form of forest plot one as I² 9%. Heterogeneity was mentioned in the form of I² 9% on day 14.

The Pooled estimate, which is represented in the form of the diamond, crosses the centerline of no effect, concluding there was no significant difference between the two desensitizing agents Na F and CPP ACP in reducing the postoperative sensitivity. Risk difference is 1 [p=0.29] at 95 % confidence interval. Based on these data, there is no difference in the clinical success between the two treatment regimens. The meta-analysis of three studies showed that CPP ACP is 1.38 times more successful than the NaF at 95% CI

The analysis concludes that there was no significant difference

between the intervention CPP ACP and NaF groups using the random-effects model.

DISCUSSION

Summary of the main results

The clinical research studies reported tooth sensitivity during bleaching in a range of 18-78%. It is usually related to the small microscopic enamel defects and subsurface pores and the rapid diffusion of hydrogen peroxide to the pulp or other toxic components released with bleaching gels' degradation. All the five included studies used an objective and subjective assessment to evaluate postoperative sensitivity intensity. According to the objectives, the incidence and intensity of sensitivity were less in experimental groups after each bleaching session. According to the VA scale on day 14 at the end of the evaluation period, significantly less sensitivity was experienced to the experimental groups' subjects. Traditionally, fluoride application was used to manage sensitivity, and it acts as a tubule blocker to control the pulp's fluid flow. The fluoride's primary mechanism of action is dentinal tubules' occlusion or an increase in enamel hardness. The desensitizing agents were applied on the bleached tooth's labial surface for 10 minutes in the included clinical trials. The observations are per Haywood et al. there is no systematic review and meta-analysis cited in the literature to evaluate desensitizing agents' effect on tooth sensitizing following in-office tooth bleaching.

Desensitizing agents such as sodium fluoride and CPP ACP are promising in reducing the incidence and intensity of tooth sensitivity soon after an in-office vital tooth bleaching. ADAF developed CPP ACP to remineralize early enamel carious lesions. After bleaching, dental sensitivity's physiology remains unclear due to the functional and structural complexity of teeth, including nerves, odontoblastic features, and fluids' internal movements. Most of the patients experienced sensitivity after tooth bleaching as 40% hydrogen peroxide was used. All the included trials are per Tay et al. and Tang and Miller's experimental studies. In these trials, post bleaching pain was recorded using the VA scale. This scale is a horizontal line containing ten numbers from 0 to 10. Zero indicates no pain, and 10 indicate the worst pain on the scale. Patients rated along the line that best represents the intensity of their pain. Three studies showed no significant difference in pain intensity between the fluoride and the CPPACP groups.

Tooth shade evaluation performed using the vitapan classical shade guide by matching the middle third of the anterior maxillary teeth under natural light. The 16 shade tabs in the shade guide were numbered from 1 [lightest value B1] to [16 darkest value C4]. The total tab change was calculated by subtracting the tab number corresponding to the baseline shade from the tab shade number at each evaluation. Tooth shade was recorded at the baseline, before bleaching directly after bleaching, and at the 3, 7 & 14 days after bleaching.

Hydrogen peroxide at 35% concentration has a high capacity to penetrate the enamel and dentin because of its low molecular weight [34.0147g/mol] and its ability to denature the proteins, increased ionic movements, and stimulate nerve receptors. These factors together

explain the high incidence of tooth sensitivity. According to Paul et al., desensitizing agents have produced better results than pain killers and anti-inflammatory agents.

CPP ACP acts like calcium and phosphate carriers, transporting these minerals to the tooth surface promoting their super saturation. Accordingly, casein in the compound stabilizes calcium phosphate by changing the tooth surface's chemical structure and promoting remineralization. CPP ACP attaches easily to the tooth surface and promotes calcium and free phosphates, substantially increasing calcium, phosphate levels in plaque. A state of super saturation inhibits enamel demineralization and promotes remineralization. According to Khoroushi et al., CPP ACP can compensate for the loss of the enamel dentin's flexural strength during bleaching. The combination of CPP ACP, along with bleaching agents, has exhibited reduced sensitivity. Being a remineralizing agent CPP ACP interferes with the oxidizing molecules penetrating the tooth surface.

Tooth sensitivity evaluation

Incidence of tooth sensitivity: the results of the included studies agree with those of other studies in that the occurrence of sensitivity is usually high after concentrated peroxide-based whitening. All the trials recorded sensitivity occurrence until day 14 after bleaching. Most participants experienced sensitivity during the first two days in the groups with CPP ACP and F, whereas in the group with bleaching gel alone has experienced sensitivity to some days. However, there was no statistically significant difference in tooth sensitivity between CPP ACP and NaF groups.

Intensity the intensity of sensitivity was lower in participants using F gel than those in the gel without desensitizing agent group and CPP ACP group.

The stimulus of sensitivity in these studies pain was mostly spontaneous, which is comparable with reports that sensitivity does occur in healthy intact teeth without any provoking stimulus.

Duration of sensitivity reported that sensitivity associated with in-office bleaching usually peaks within one to six hours after bleaching.

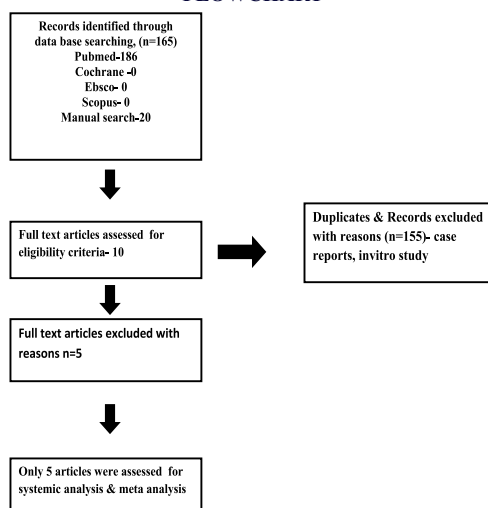
Tooth shade stability

Participants in the included trials had a significant shade improvement, an average of 6.8 units of shade change. The shade improved on day three among all groups, probably because of the temporary dehydration effect, which lasted up to 72 hours and was followed by a minor relapse, which was less noticeable in the CPP ACP group.

It has shown that fl increases enamel hardness and renders it less permeable, explaining why the fl group participants had better shade stability.

The results confirmed that the application of Na F or CPP ACP or gel without desensitizing agent does not hinder the whitening efficacy of bleaching agents like hydrogen peroxide as the shade recorded on day 1 was approximately the same as recorded on day 14.

FLOWCHART



DESIGNS OF THE INCLUDED STUDIES

AUTHOR	YEAR	STUDY DSGIN	DESENSITIZING MATERIALS USED	EVALUATION METHOD
Manoj Singh etal	2017	Randomized clinical trials	NAF CPP-ACP	Clinical [pulp vitality tests] & radiological examination [dentin bridge thickness]
Nadeem Tarique	2017	Randomized clinical trials	NAF & KNO3 CPP-ACP	Clinical [pulp vitality tests] & radiological examination[dentin bridge thickness]
Jyothi Kashi etal	2016	Randomized clinical trials	KNO3 & NAMFP CPP-ACP	Clinical [pulp vitality tests] & radiological examination[dentin bridge thickness]
Larissa dias alexandrino etal	2016	Randomized clinical trials	NOVAMIN CPP-ACP	Clinical[pulp vitality tests] & radiological examination [formation of dentin bridge and its thickness]
GA Maghaireh etal	2014	Randomized controlled trial	NAF CPP-ACP	Clinical[pulp vitality tests] & radiological examination [formation of dentin bridge and its thickness]

STUDY CHARECTERISTICS TABLE

AUTHOR	YEAR	NUMBER OF PATIENTS	MATRIALS USED	FOLLOW UP PERIOD	OUTCOME
Manoj Singh etal	2017	45	GROUP I NAF GROUP II CPP-ACP	Day 1 Day 14	Pain evaluation by Visual Analog Scale Tooth shade evaluation using vitapan shade guide
Nadeem Tarique	2017	30	GROUP I NAF & KNO3 GROUP II CPP-ACP	Day-10 Day 20 Day- 30	Pain evaluation by Visual Analog Scale
Jyothi Kashi etal	2016	66	GROUP I KNO3 & NAMFP GROUP II CPP-ACP	Day 1, Day 7 Day 14	Pain evaluation by visual analog scale sensitivity was evaluated by scaffe's scale
Larissa dias alexandrino etal	2016	60	GROUPI NOVAMIN GROUP II CPP-ACP	Day-7 Day-14 Day-21	Pain evaluation by Visual Analog Scale Shade evaluation by spectrophotometer
GA Maghaireh etal	2014	51	GROUP I NAF GROUP II CPP-ACP	Day 3 Day 7 Day 14	Pain evaluation by Visual Analog Scale Tooth shade evaluation using vitapan shade guide

RISK OF BIAS – MAJOR CRITERIA

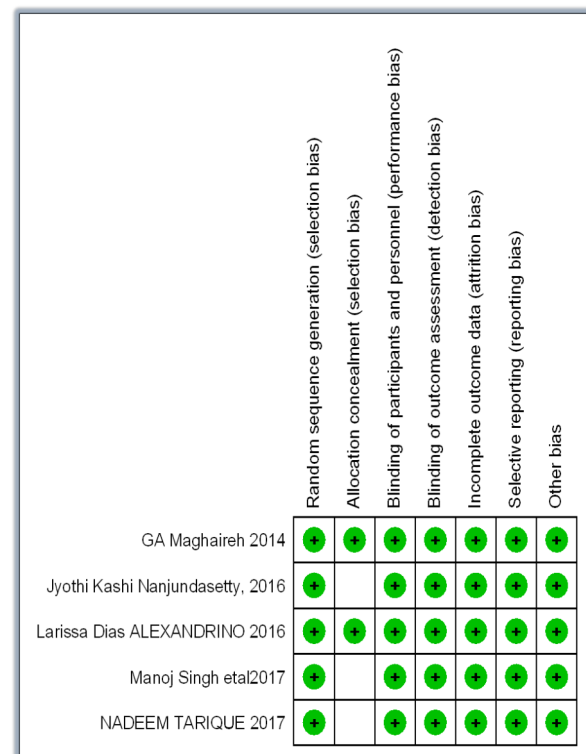
STUDY	RANDOMIZATION	ALLOCATION CONCEALED	ASSESSOR BLINDING	DROPOUTS DESCRIBED	RISK OF BIAS
Manoj Singh etal 2017	YES	NO	YES	NONE	MODERATE
Nadeem Tarique 2017	YES	NO	YES	NONE	MODERATE
Jyothi Kashi etal 2016	YES	NO	YES	YES	MODERATE
Larissa dias alexandrino etal 2016	YES	YES	YES	YES	LOW
GA Maghaireh etal 2014	YES	YES	YES	NONE	LOW

RISK OF BIAS – MINOR CRITERIA

STUDY	SAMPLE JUSTIFIED	BASLINE COMPARISION	INCLUSION & EXCLUSION CRITERIA	METHOD ERROR
Manoj Singh etal 2017	YES	YES	YES	No
Nadeem Tarique 2017	YES	YES	YES	NO
Jyothi Kashi etal 2016	YES	YES	YES	NO
Larissa dias alexandrino etal 2016	YES	YES	YES	NO
GA Maghaireh etal 2014	YES	YES	YES	NO

RESULTS

S NO	AUTHOR AND YEAR	GROUPS	PARAMETERS	STATISCICAL ANALYSIS	P VALUE
1	Manoj Singh etal 2017	GROUP I NAF GROUP II CPP-ACP	PAIN & SENSITIVITY EVALUATION TOOTH SHADE EVALUATION	SPSS ANOVA CHI SQUARE TEST KENDALL'S TAU TEST	P<0.05
2	Nadeem Tarique 2017	GROUP I NAF & KNO3 GROUP II CPP-ACP	PAIN & SENSITIVITY EVALUATION	SPSS ANOVA	P<_0.05
3	Jyothi Kashi etal 2016	GROUP I KNO3 & NAMFP GROUP II CPP-ACP	PAIN & SENSITIVITY EVALUATION	SPSS ANOVA	P<_0.05
4	Larissa dias alexandrino etal 2016	GROUPI NOVAMIN GROUP II CPP-ACP	PAIN & SENSITIVITY EVALUATION TOOTH SHADE EVALUATION	BIOESTAT ANOVA TUKEY'S TEST	P>0.05
5	GA Maghaireh etal 2014	GROUP I NAF GROUP II CPP-ACP	PAIN & SENSITIVITY EVALUATION TOOTH SHADE EVALUATION	SPSS ANOVA	P<_0.05



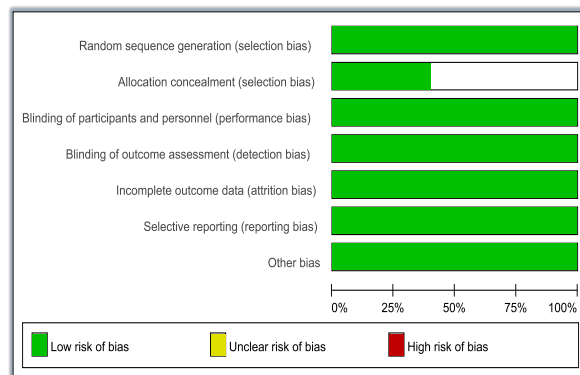
RISK OF BIAS SUMMARY

Overall completeness and applicability of evidence GRADE PRO SOFTWARE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	inconsistency	Indirectness	Imprecision	Other considerations	[intervention] CPP-ACP	NAF [comparison]	Relative (95% CI)	Absolute (95% CI)		
New Outcome												
5	Randomised trials	Not serious	Not serious	Not serious	Not serious		80	80	-	MD 160 higher (0 to 0)	-	IMPORTANT

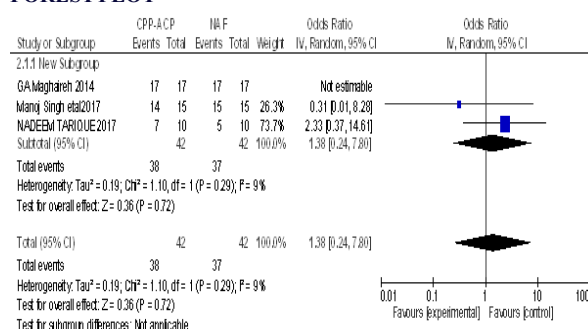
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Risk of bias graphical representation

FOREST PLOT



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