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Original Article

Clinical and Radiographic Evaluation of Vital Pulpotomy in Primary Molars using Antioxidant Mix as a Novel Pulpotomy Medication versus Formocresol: A Randomized Clinical Trial.

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Abstract

Background: Formocresol (FC) reported high success rates when used in pulpotomy of primary molars , however many concerns have been raised regarding its mutagenicity, carcinogenicity, its local toxicity,
Objectives: to assess the success rates of Antioxidant mix and FC, used as pulpotopmy agents in vital primary molars, both clinically and radiographically.
Materials and Methods: Randomized clinical trial. Fifty-two (52) primary mandibular molars in thirty-five (35) children ranging in age from four to eight years were included in the study. Molars were divided into two equal groups (n= 26), Antioxidant mix (group 1) & FC (group 2) as a pulp medicament. All pulpotomized teeth were finally restored with stainless steel crowns. Subjects were monitored clinically & radiographically at three, six and nine months.
Results: The clinical and radiographic success rates of Antioxidant mix & FC by the end of the nine months were [(84.6 & 46.2%) & (88.4 & 84.6%)] respectively.
Conclusion: Antioxidant mix may not provide a reliable biological method for vital pulp therapy in primary molars.

Key words: Antioxidant mix; Formocresol; Primary molars; Pulpotomy.

Introduction

Irreversible damage to the dental pulp due to dental caries is one of the major causes that lead to premature loss of a primary tooth. The most important goal in pediatric dentistry is to preserve primary teeth until the time of eruption of their permanent successors. [1]

The most commonly used technique to preserve cariously involved primary molars that would be otherwise extracted is pulpotomy. This technique involves amputation of the coronal pulp tissue with preservation of the vitality and health of radicular pulp tissue by covering it with a suitable medicament.[2]

In pulpotomy, many materials were used over the years but the ideal material should meet certain criteria, such as it should be bactericidal, harmless to the pulpal tissue and surrounding structures, promote healing of the radicular pulp, does not interfere with normal physiological root resorption, and preserve the radicular pulp without any clinical or radiographic symptoms. [3]

In 1930, Formocresol (FC) was first introduced by sweet and for many years it was the most commonly used material in pulpotomy. [4] FC is both a bactericidal and a devitalizing agent. It kills off and converts bacteria and pulp tissue into inert compounds. Despite being recommended for use by AAPD [5] and still successfully used in developing countries, concerns have been raised about FC regarding its mutagenicity, carcinogenicity, its local toxicity, its potential damage to a permanent successor, systemic toxicity and finally its antigenicity. So, a search for an ideal alternative agent that is more biocompatible than FC is mandatory. [6, 7]

Nowadays, the introduction of new Bio-inductive materials resulted in the shift of the concept of preservation of radicular pulp tissue to regeneration. [8] Restoration of the anatomical continuity of damaged tissue and disturbed functional status of the radicular pulp tissue require appropriate method of wound healing which includes well-organized, biochemical and cellular events, leading to the growth and regeneration of injured radicular tissue in a special manner. [9]

Antioxidants counter the excess proteases and reactive oxygen species (ROS) often formed by neutrophil accumulation in the wounded area and protect protease inhibitors from oxidative damage. These excess ROS kills fibroblast and other cells, also antioxidants have both anti- inflammatory and anticarcinogenic effects [10], Thus this study aims to evaluate the clinical and radiographic success rate of antioxidant mix versus FC as a pulpotomy agent in primary molars.

Subjects and Methods:

Thirty- five (35) patients with fifty-two (52) mandibular primary molars indicated for vital pulp therapy were recruited to participate in this study.

PICO:

P: mandibular primary molars.

I: pulpotomy using Anti-oxidant mix.

C: pulpotomy using Formocresol.

O: clinical success rate.

Research question: Is pulpotomy procedure in primary molars using Anti-oxidant mix more clinically successful than Formocresol?

Ethics approval:

The research protocol was approved by Research Ethics Committee, Faculty of Dentistry, Cairo University with the reference code (4 5 2015).

Study design:

The study is a randomized clinical trial (RCT) where 2 arm parallel groups with a 1:1 allocation ratio were compared. The child participants and the legal guardian of each participating child and the statistician were blinded. Blinding of the investigators was not feasible due to the apparent physical characteristics of the used materials both clinically and radiographically (Antioxidant mix is radiolucent).

Sample size estimation:

The sample size was estimated using power and sample size calculations program (Sealed Envelope, London, UK).

Calculation was based on the formula:
$n = f(\alpha/2, \beta) \times [p1 \times (100 - p1) + p2 \times (100 - p2)] / (p2 - p1)2$
Where p1 and p2 are the percent 'clinical success' in the control and experimental group respectively, and $f(\alpha, \beta) = [\Phi\text{-}1(\alpha) + \Phi\text{-}1(\beta)]2$ Φ-1 is the cumulative distribution function of a standardized normal deviate.
Adjustment for cross-overs based on formula: nadj = n × 10,000 / (100 - c1 - c2)2 where c1 and c2 are the percent cross-over in the control and experimental group
Since no numerical data could be taken from previous studies a preliminary estimation of research size was designated to 52 molars (including a dropout rate of 20%) , which were required to have an 80% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 67% clinical success rate in the control group according to ***Sabbarini et al.,2008*** work ``Comparison of Enamel Matrix Derivative Versus Formocresol as Pulpotomy Agents in the Primary Dentition``[11] and to 97% clinical success rate in the experimental group according to ***Reddy et al.,2014*** work `` Antioxidant mix: A novel pulpotomy medicament: A scanning electron microscopy evaluation``. [12]

Study setting:

The study was conducted at Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Cairo University, Egypt.

Trial Registration:

The study was registered by the main investigator with clinicaltrials.gov under the title: `` Clinical and Radiographic Evaluation of Vital Pulpotomy in Primary Molar Using Antioxidant Mix as A Novel Pulotomy Medication Versus Formcresol: A Randomized Clinical Trial ``, with an identifier: PACTR201711002568284.

Subjects selection:

Fifty-two (52) mandibular primary molars in thirty-five (35) children ranging in age from 4 to 8 years were recruited to participate in this study. Children were selected independent of their gender from the outpatient clinic of the Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Cairo University.

Eligibility criteria:

The eligibility criteria were set according to the guidelines of *AAPD, 2015* .[5]

Inclusion criteria

Mandibular primary molars with no spontaneous or provoked pain.
Primary molars with at least two-thirds of the root length were still present.
Primary molars with no sign of internal or other kinds of root or bone resorption.

Exclusion criteria

Patients with systemic diseases (congenital or rheumatic heart disease, hepatitis, nephritis, tumor, cyclic neutropenia, leukemia, and children on long term corticosteroid therapy).
Un-cooperative patients.
Un-restorable primary molars (Grossly broken-down primary molars that have decay extending way under the gingiva and tooth with root caries).

Randomization & allocation concealment:

Simple randomization was done, to allocate the molars, using computer sequence generation (www.random.org) by the third investigator with 1:1 allocation ratio into two groups (n=26) based on the dressing materials. group (1) designated for Antioxidant-mix and group (2) designated for FC as pulp medicaments. Allocation concealment was done using opaque envelopes.

Sequence generation:

Sequence generation was done for the molars number (1 to 52; 26 numbers in each group) by the third investigator using computer sequence generation (www.random.org).

Allocation concealment mechanism:

Each of the 52 papers numbered from 1 to 52, was individually packed by the third investigator in an opaque envelope after folding each paper eight folds. Each patient was asked to pick an envelope, after their enrollment in the study and before the beginning of treatment. The numbers in the envelopes determined the group assigned for each molar.

Informed Consent:

The procedure, their benefits, and risks were fully explained to the parents of the participants, and approval was taken by the main investigator through written informed consent.

Intraoperative procedure:

All intraoperative procedures were performed by the main investigator. Each tooth was locally anesthetized using topical anesthesia (20 % benzocaine gel, Deepak, Miami, USA) followed by, nerve block injection using Articaine HCI 4% with 1:100,000 epinephrine (Septanest, Saint-Maurdes-Fosses, France), then the tooth was isolated using a rubber dam.

Dental caries was removed with a large slow-speed round bur. Then access to the pulp chamber was obtained with no. 330 carbide bur, followed by amputation of the coronal pulp with a sharp spoon excavator. Stasis at the orifice of the radicular pulp was achieved with a moist cotton pellet placed on orifices under pressure for three min. If hemorrhage persisted, pulpectomy was performed and the tooth was eliminated from the study.

After stasis, in group (1) standard consistency of freshly prepared Antioxidant- mix (Pfizer Canada Inc, Montreal, Canada) was introduced in the pulp chamber using dental spatula and condensed over the orifice with the aid of a suitable size condenser over a moist cotton pellet followed by a layer of reinforced Zinc Oxide Eugenol (ZOE) (Prevest Denpro limited, Digiana, India), while in group (2) a sterile cotton pellet lightly moistened with a 1:5 dilution of Buckley's FC (Prevest Denpro limited, Digiana, India) was placed against the pulpal stumps for three- five minutes, then removed. A layer of reinforced ZOE was condensed against the orifices using a suitable size condenser over a moist cotton pellet.

In both groups, molars were finally restored with stainless steel crown (3M, ESPE, USA), which was cemented by glass ionomer cement (Ningbo Gaoju Imp. & Exp. Co., Ltd, Zhejiang, China). Finally, postoperative periapical radiographs of the treated teeth were taken using size two periapical film (Kodak, Carestream Health, Inc., NY, USA) and considered as a baseline, Fig (1, 2).

Strategies to improve adherence to the intervention

Face to face session with the patients' parents by the main investigator was held to stress on the importance of follow up. The main investigator ensured that the follow-up appointments are obligatory to assess the outcome of initial treatment and to discuss other treatment options if this treatment failed to meet expected goals.

Follow-up protocol & Assessments of the outcomes:

All treated molars were followed up by the second and third investigators at three, six and nine months for clinical and radiographic evaluation. Blinding was not feasible as Antioxidant-mix appears radiolucent in the radiographs.

The intraexaminer consistency was confirmed, between the two examiners, through repeated clinical examinations and radiographic interpretation for 10 molars. Kappa test showed that the intraexaminer and interexaminer consistencies were 100 % and 99%, respectively.

Molars were judged as clinically successful if they met the following criteria: Absence of sensitivity, pain, tenderness to percussion, abscess, fistula, or tooth mobility. Radiographic failure was defined according to the radiographic failure score according to *Memarpour et al., 2016.* [13]

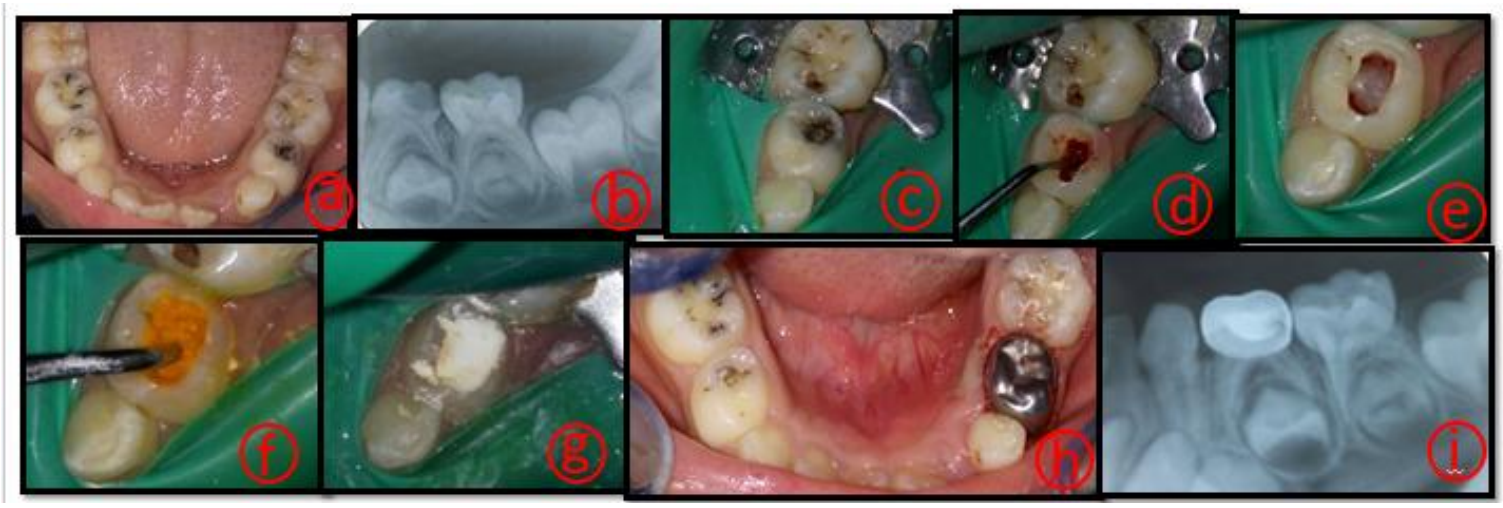

Fig 1 :Antioxidant-mix: a - Preoperative photograph. b-Preoperative radiograph. c- Rubber dam isolation. d- Access cavity. e- Stasis of amputated pulp. f- Placement of Antioxidant- mix. g- Reinforced ZOE dressing. h- Postoperative photograph. i- Postoperative radiograph.

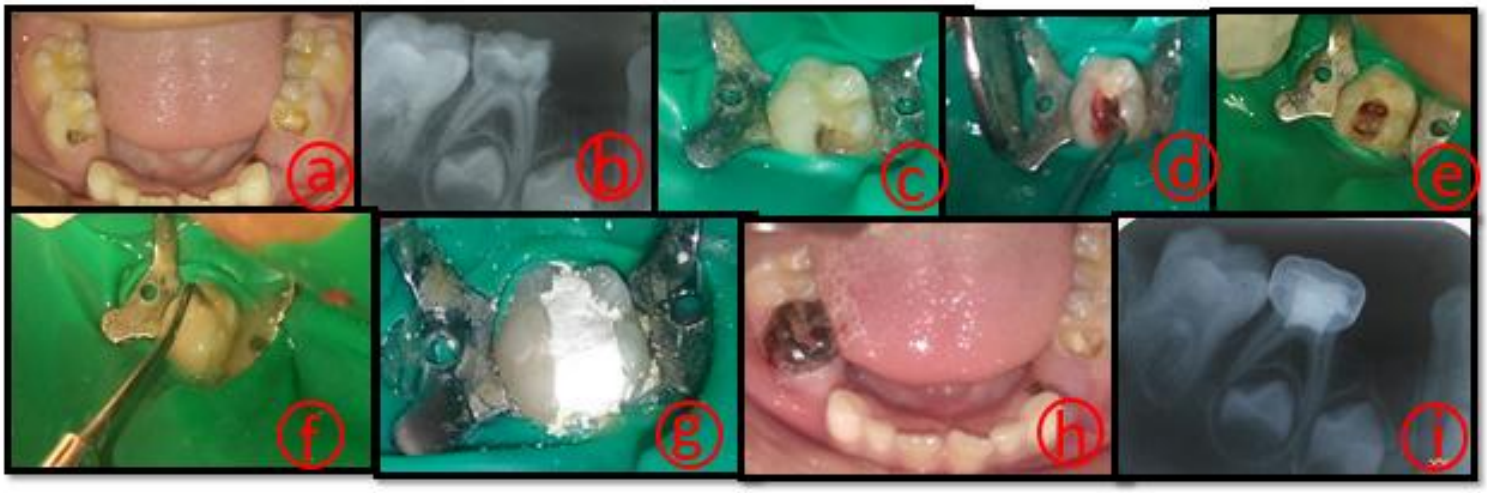

Fig 2 (FC): a -Preoperative photograph. b-Preoperative radiograph. c- Rubber dam isolation. d- Access cavity. e- Stasis of amputated pulp. f- Cotton pellet with FC. g- Reinforced ZOE dressing. h- Postoperative photograph. i- Postoperative radiograph.

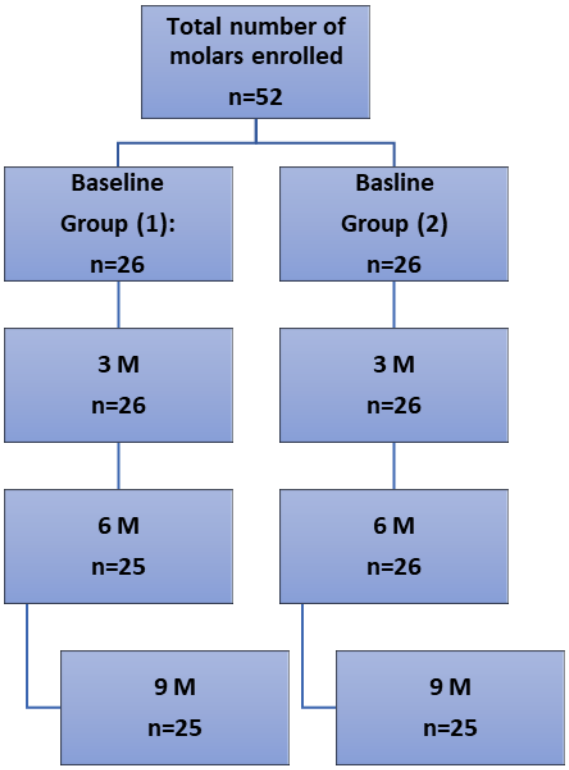

Fig 3: A Consort diagram of the treated molars.

Criteria for discontinuing or modifying intervention :

In case of the presence of adverse clinical signs (pain, abscess, etc…) the case was managed by pulpectomy or extraction and considered as failure.

Statistical analysis:

All data were tabulated and refereed to the statistician blindly. Statistical analysis was performed using SPSS statistical version 19 (Statistics Statistical Procedures Companion, Chicago, IL, USA. Chi-square test was used for comparison of all binary outcome data at different times points and T-test was used to compare the mean age in both groups. The Significance level was set at p <0.05.

Results

The mean age of anti-oxidant group and FC group were 6.08 ±1.1 and 5.9±1.35 respectively. The antioxidant group included 14 males (53.8%) and 12 females (46.2%), whereas FC group included 50% males & 50% females. The Antioxidant group consisted of 15 D (57.7%) & 11 E (42.3%), whereas FC group consisted of 11 D (42.3%) & 15 E (57.7%), with no statistically significant difference between the two groups regarding age, sex and type of treated molar. One case dropped out from group (1) & another one from group (2), Table (1-3), Fig. 1.

Results of clinical findings at different follow-up periods showed no statistically significant difference between the two groups in terms of

Table (1): Comparison of age in both groups (t- test)

	Mean	±SD	Min	Max	t	*p*
Group 1	6.08	1.1	4	7.5	0.5271	0.6005^{ns}
Group 2	5.9	1.35	1.15	7.5		

Significance level ***p*** <0.05, ns=non-significant

Table (2): Gender distribution in both groups (Chi- square test)

Groups	Male		Female		X^2	*P*
	No.	%	No.	%		
Group 1	14	53.8	12	46.2	0.077	0.781^{ns}
Group 2	13	50	13	50		

Significance level ***p*** <0.05, ns=non-significant

Table (3): Treated teeth in both groups (Chi- square test)

Groups	D		E		X^2	*P*
	No.	%	No.	%		
Group 1	15	57.7	11	42.3	1.231	0.267^{ns}
Group 2	11	42.3	15	57.7		

Significance level ***p*** <0.05, ns=non-significant

pain, swelling, mobility, and sinus or fistula, Table (4).

Regarding the incidence of radiographic signs, external root resorption, and periapical and furcal radiolucencies revealed significantly higher incidences in group (1) at 3, 6, and 9 months, Table (5). Radiographic Failure score showed a significantly higher incidence of Score 0 (26 cases=100%) in group (2) at 3 months and 6 months, Table (6).

The clinical & radiographic success rates of Antioxidant-mix & FC, among the study sample, by the end of the study were [(84.6 & 46.2%) & (88.4 & 84.6%)] respectively, Table (7).

Discussion

Formocresol pulpotomy has enjoyed long-term clinical use and success. In the past, it was considered as the gold standard dressing agent for pulpotomy of primary molars, but concerns over its effect in devitalizing the remaining radicular tissue, toxicity and mutagenicity have prompted research into other biocompatible alternatives accelerating the recovery of remaining radicular pulp tissue to a healthy physiologic state. [14]

Pulp vitality, as well as, its physiologic function has been claimed as being preserved when pulp has been treated with Antioxidant-mix in few earlier investigations; in addition to its biocompatibility, wound healing ability,

Table (4): Incidence of clinical signs in both groups (Chi-square test)

Clinical signs	Time	Groups	Present		Absent		Extraction/ Dropouts		X^2	*P*
			No.	%	No.	%	No.	%		
Pain	3 M	**Group 1**	1	3.8	25	96.2	0	0	1.02	0.31^{ns}
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	2	7.7	22	84.6	2	7.7	4.33	0.114^{ns}
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	0	0	22	84.6	4	15.4	3.822	0.147^{ns}
		Group 2	2	7.7	23	88.5	1	3.8		
Swelling	3 M	**Group 1**	0	0	26	100	0	0	0	1^{ns}
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	1	3.8	23	88.5	2	7.7	3.18	3.183^{ns}
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	0	0	22	84.6	4	15.4	1.99	0.369^{ns}
		Group 2	0	0	25	96.2	1	3.8		
Mobility	3 M	**Group 1**	0	0	26	100	0	0	0	1^{ns}
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	2	7.7	22	84.6	2	7.7	4.33	0.114^{ns}
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	0	0	22	84.6	4	15.4	2.89	0.236^{ns}
		Group 2	1	3.8	24	92.3	1	3.8		
Sinus /Fistula	3 M	**Group 1**	1	3.8	25	96.2	0	0	1.02	0.31^{ns}
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	1	3.8	23	88.5	2	7.7	3.184	0.204^{ns}
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	0	0	22	15.4	4	15.4	1.991	0.158^{ns}
		Group 2	0	0	25	96.2	1	3.8		

availability and cheapness, all these advantages make antioxidant a promising substitute to FC.[12,15] So, this study was done to evaluate the success of antioxidant mix versus FC as pulpotomy materials in primary molars.

Children of the present study were selected with age ranging between four and eight years. This age is the most favorable chronological age with considerable root length where, resorption of the roots not yet started or may be minimal and to ensure patient cooperation .[16]

The child participants and the legal guardian of each participating child and the statistician were blinded to avoid information bias. Blinding of the investigators was not feasible due to the apparent physical characteristics of the used materials both clinically and radiographically (Antioxidant- mix is radiolucent).

Only mandibular primary molars were selected because of the ease of visualization and the less overlapping of permanent tooth buds onto roots and furcations of lower primary molars in comparison to the maxillary molars which enables the investigator to identify the radiographic pathology and healing more clearly [17].

Randomization of the selected molars were done

Table (5): Incidence of radiographic signs in both groups (Chi- square test)

Clinical signs	Time	Groups	Present		absent		Extraction /Dropouts		X^2	*P*
			No.	%	No.	%	No.	%		
Internal resorption	**3 M**	**Group 1**	0	0	26	100	0	0	0	1^{ns}
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	1	3.8	23	88.5	2	7.7	3.184	0.204^{ns}
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	2	7.7	20	76.9	4	15.4	4.356	0.113^{ns}
		Group 2	0	0	25	96.2	1	3.8		
External resorption	**3 M**	**Group 1**	5	19.2	21	80.8	0	0	5.532	0.019*
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	6	23.1	18	69.2	2	7.7	9.455	0.009*
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	6	23.1	16	61.5	4	15.4	6.971	0.031*
		Group 2	1	3.8	24	92.3	1	3.8		
Periapical / Furcal radiolucencies	**3 M**	**Group 1**	4	15.4	22	84.6	0	0	4.333	0.037*
		Group 2	0	0	26	100	0	0		
	6 M	**Group 1**	5	19.2	19	73.1	2	7.7	8.089	0.018*
		Group 2	0	0	26	100	0	0		
	9 M	**Group 1**	4	15.4	18	69.2	4	15.4	6.94	0.031*
		Group 2	0	0	25	96.2	1	3.8		

Table (6): Comparison of radiographic Failure score in both groups (Chi- square test)

Time	Groups	Score 0		Score 1		Score 2		Score 3		Extraction /Dropouts		X^2	*P*
		No.	%	No.	%	No.	%	No.	%	No.	%		
3 M	**Group 1**	18	69.2	1	3.8	0	0	7	26.9	0	0	9.46	0.024*
	Group 2	26	100	0	0	0	0	0	0	0	0		
6 M	**Group 1**	16	61.5	1	3.8	0	0	7	26.9	2	7.7	10.32	0.016*
	Group 2	26	100	0	0	0	0	0	0	-	-		
9 M	**Group 1**	14	53.8	1	3.8	0	0	7	26.9	4	15.4	8.35	0.079^{ns}
	Group 2	22	84.6	0	0	1	3.8	2	7.7	1	3.8		

Table (7): Comparison of clinical and radiographic success and failure (Chi- **square test)**

Time	Group	Clinical success		Clinical failure		Radio-graphic success		Radio-graphic failure		X^2	*P*
		No.	%	No.	%	No.	%	No.	%		
3 M	**Group 1**	25	96.2	1	3.8	15	57.7	11	42.3	10.833	0.0009*
	Group 2	26	100	0	0	26	100	0	0	0	1 ns
6 M	**Group 1**	22	84.6	3	11.5	13	50	12	46.2	7.714	0.005*
	Group 2	26	100	0	0	26	100	0	0	0	1 ns
9 M	**Group 1**	22	84.6	3	11.5	12	46.2	13	50	9.191	0.002*
	Group 2	23	88.4	2	7.7	22	84.6	3	11.5	0.222	0.637 ns

to ensure that every molar has equal chances to be recruited to both groups to avoid selection bias. Blinding of children and their guardians were adopted to avoid information bias.

Radiographic examination was performed using periapical radiographs, since it is considered the practical detection method for root resorption, periapical tissue, periodontal status, osseous defects and any changes in the surrounding structures.[18] The treated molars were isolated with rubber dam to ensure adequate isolation which is necessary to prevent salivary and bacterial contamination. [19]

Data were referred to the statistician in the form of labelled groups to avoid information bias.

In the present study, no statistically significant differences between comparison groups were found for age, gender and type of treated molar, fortunately all these findings favor linear comparison in which both groups were nearly similar with the major difference remaining being their exposure to different materials.

Results of clinical findings at different follow-up periods showed no statistically significant difference between the two groups in terms of pain, swelling, mobility, and sinus or fistula. However, the incidence of radiographic signs, external root resorption, and periapical and furcal radiolucencies revealed significantly higher incidences in group (1) at 3, 6, and 9 months. This may be explained on the basis that chroinc signs of radiographic failure take longer periods of time to be expressed clinically.

The present study showed relatively high clinical success rate (84.6 %) in the Antioxidant group, however radiographic success was evident only in only (46.2%) of the molars. The previous studies by Yildiz & Tosun, 2014 [20]; Reddy et al., 2014 [12] & Kumar et al., 2017 [15] reported high clinical and radiographic success rates of antioxidant mix and attributed that to its strong Antioxidant property, binding to the free radicals transforming them into non-damaging compounds, stimulating antibody production (first line of defense), healing of remaining radicular pulp by collagen formation and angiogenesis [12].

A possible explanation for the high failure rates shown by a considerable amount of external bone and root resorption observed in group (1) may be attributed to the different type of the Antioxidant-mix used in this study. Unknown irritation from any of the component of the material may cause pulpal inflammation and subsequent pulpal necrosis with root and bone resorption.

On the other side FC treated molars showed high clinical and radiographic success rates. This was in

accordance with Ibricevic & Al-Jame, 2003 [21] and Alolofi et al., 2016. [22] This is attributed to its well-documented bactericidal and fixative properties. [23]

Conclusion:

Formocresol is still the material of choice as pulpotomy agent in primary molars in developing countries. Antioxidant- mix may not provide a reliable biological method for vital pulp of primary molars. Understanding tissue uptake metabolism, biochemical interactions, and biomechanical properties of various antioxidants on pulpal response is mandatory before its use.

Limitation of the study:

-Antioxidant-mix products specially designed to be used as pulpotomy agents in primary molars are not available in the market yet.

-The use of radiographic stents for standardization of radiographic imaging was planned but this was not feasible due to frequent lack of acceptance by participants.

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