ORIGINAL RESEARCH

# A 1-year Clinical and Radiographic Assessment of Regenerative Endodontic Therapy for Necrotic Primary Molars: A Randomized controlled Trial

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## Abstract

**Background:** Preservation of necrotic primary teeth is important. Pulpectomy is the gold standard treatment in this situation. Reinfection is the main cause of failure in pulpectomy. The application of regenerative endodontic therapy in mature teeth has the rationale of restoring dental-pulp-like tissue and preventing reinfection.

**Aims and objectives:** The current study was designed to clinically and radiographically assess regenerative endodontics therapy in necrotic primary molars in comparison to zinc oxide eugenol (ZOE) pulpectomy.

**Materials and methods:** A double-blinded randomized controlled trial with three parallel arms and a 1:1:1 allocation ratio was conducted. A total of 54 necrotic primary molars in 39 healthy children aged 4–7 years old were randomly allocated as follows group I—control group, in which ZOE pulpectomy was performed. Group II and III—experimental groups, in which regenerative endodontic therapy (RET) was performed. Modified triple antibiotic paste (mTAP) and Metapex™ were used as intracanal medicaments in groups II and III, respectively. Clinical and radiographic assessments were recorded at baseline, 6 and 12 months. Chi-squared and Fisher's exact tests were used to compare the qualitative data, while Friedman's test was used to study the changes by time within each group.

**Results:** Nonstatistically significant differences were reported between the three groups at the 6 and 12 months follow-ups regarding the clinical or radiographic assessment ($p$-value = 0.327 and effect size = 0.22), ($p$-value = 0.055 and effect size = 0.118), respectively.

**Conclusion:** Regenerative endodontic therapy (RET) yielded comparable results to pulpectomy. However, the use of 5 mg/mL mTAP in RET represented the highest level of clinical as well as radiographic insignificant failure.

**Clinical significance:** Regenerative endodontic therapy (RET) provides an acceptable biological alternative to pulpectomy.

**Trial registration:** The protocol was registered at ClinicalTrial.gov with the registration number (NCT04190914). 12/5/2019.

**Keywords:** Canal irrigants, Canal medication, Nonvital primary teeth, Pulpectomy, Randomized control trial, Regenerative endodontic procedure.

*International Journal of Clinical Pediatric Dentistry* (2023): 10.5005/jp-journals-10005-2536

## Introduction

A pulpectomy is a gold standard and the most practiced nonvital pulp therapy in pediatric dentistry.[1] The rationale of the pulpectomy procedure depends on canal disinfection through chemomechanical preparation for the root canal system and antibacterial obturation material to prevent reinfection.[2,3] However, pulpectomy in primary teeth is a controversial procedure due to the complexity of the root canal system and the unavailability of an obturation material that exhibits ideal properties with an adequate rate of resorption.[4]

With the great advances in dental tissue regeneration techniques, many studies have begun investigating the application of RET as a biological alternative to conventional root canal treatment in necrotic mature permanent teeth and, to a lesser extent, in primary teeth.[5–7] Application of RET achieves the objectives of pulpectomy in addition to several biological benefits such as restoring innate immunity and obtaining pulp-like tissue obturation materials.[8,9]

Canal disinfection using intracanal medications is a main step in RET to provide the required, ideal environment either for healing or for the regeneration of new biological tissues.[10,11] Although calcium hydroxide [$Ca(OH)_2$] and antibiotics are among the most commonly used intracanal medications, there is no evidence for the ideal material that provides the optimum antibacterial effect, preservation to stem cells vitality, and safe concentration.[12–14]

The American Association of Endodontics (AAE) has recommended the use of $Ca(OH)_2$ or a low concentration of TAP, considering mTAP as a possible alternative.[11]

Due to the limited antibacterial effect of $Ca(OH)_2$ against *E. faecalis*,[15,16] different substances have been combined with $Ca(OH)_2$ as chlorhexidine, iodoform (Metapex TM), and propylene glycol to improve its antibacterial effect and consistency.[17] Metapex

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**How to cite this article:** Abdelmoneim DD, Abdelaziz AM, Allam GG, et *al.* A 1-year Clinical and Radiographic Assessment of Regenerative Endodontic Therapy for Necrotic Primary Molars: A Randomized controlled Trial. Int J Clin Pediatr Dent 2023;16(2):295–301.

**Source of support:** Nil

**Conflict of interest:** None

TM is considered one of the most popular $Ca(OH)_2$-based materials that have been used in pediatric dentistry; unfortunately, its use as an intracanal medication has not been evaluated sufficiently.

Therefore, this RCT was designed to evaluate RET in necrotic primary molars with two different intracanal medications in comparison to conventional ZOE pulpectomy. The null hypothesis was established as there is no difference between the three treatment groups.

## Materials and Methods

This study was designed as a single center, double-blinded (participant and statistician) prospective three parallel arms randomized controlled trial, testing the equivalence of experimental interventions with an allocation ratio 1:1:1. The study was designed, conducted and reported following the Consolidation Standards of Reporting Trials (CONSORT) statement.

The ethical approval was obtained from the Faculty of Dentistry Ain Shams University Research Ethics Committee (FDASU-REC) Cairo, Egypt, with approval number (#691).

The protocol was registered at ClinicalTrial.gov with the registration number (NCT04190914).

This randomized control trial was conducted in the outpatient clinic of the Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Ain Shams University, Cairo, Egypt, from September 2020 to 2021.

### Sample Size Calculations

Based on the results of previous studies[18,19] and by setting α error at 5% and power at 90%, the needed sample was calculated to be 16 primary molars per group. Considering the 10% dropout rate, the needed sample size was increased to 18 per group. Sample size calculation was performed using G*Power software version 3.1.9.4 for Microsoft Windows, Franz Faul, Kiel University, Germany.

### Randomization and Blinding

The computer-generated simple randomization list was prepared by the outcome evaluator using Excel- Microsoft Office. In order to ensure allocation concealment, sequentially numbered, opaque, sealed envelopes were prepared based on the preformed list, and then each patient chose one numbered envelope. Each envelope enclosed the corresponding treatment group to which the molar was allocated. Allocation was performed by the operator.

The operator could not be blinded due to the different steps in each treatment and the different materials used.

The outcome evaluator could not be completely blinded.

- During clinical evaluation: The evaluator was completely blind, as all treated teeth were finally restored by stainless steel crowns (SSCs).
- During radiographic evaluation: The evaluator could not be blinded to the control group.

### Inclusion and Exclusion criteria

Necrotic carious primary molars were examined clinically and radiographically to assess their eligibility according to the following inclusion criteria—the presence of clinical abscess/fistula, history of swelling, sensitivity to percussion, presence of maximum grade II mobility (Grace and Smales mobility index) and adequate coronal tooth structure allows rubber dam isolation.

A radiographic examination was performed using the parallel technique to produce repeatable images. A film holder (Transmission Control Protocol X-ray holder-United States of America) and phosphor plate (ACTEON® and Fona scanner FONA ScaNeo -FONA -Italy/OrisWin DG Suite imaging software) were used.

Teeth were excluded if any of the following were detected—medically compromised children, patients allergic to any of the used materials (assessed by the detailed medical history, and nonrestorable molar (periapical radiolucency that extends to the successor follicle, pathological root resorption (internal/external >1/3 of the root length)

### Participants

A total of 39 (17 girls and 22 boys) cooperative healthy children (American Society of Anesthesiologists class I) in the age range of 4–7 years old were recruited in the study after signing the informed consent by their parents. Recruited children provided a total of 54 necrotic primary molars. Clinical and radiographic evaluation criteria were recorded for each case at baseline, after 6 months, and after 12 months for evaluation and follow-up.

### Irrigation and mTAP Preparation

A concentration of 1.5% sodium hypochlorite solution (NaOCl) was freshly prepared. The solution was prepared using (5% JK Dental vision -ARE, India purity active ingredients, and distilled water).

### mTAP Preparation

A mix of ciprofloxacin 500 mg, metronidazole 500 mg, and amoxicillin 500 mg with a ratio of 1:1:1 and a concentration of 5 mg/mL was prepared in a local pharmacy with a shelf life of 1 month. The prepared mix was stored in a cold dark place.

### Interventions

The procedure was performed over two visits with 2 week intervals in between for all cases by the same operator.

### Group I (control): Conventional Pulpectomy Treatment

*First Visit*

under local anesthesia (1.8 mL 4% articaine hydrochloride with 1:100 000 adrenalin (Laboratories Inibsa, S.A.- Spain) and rubber dam isolation. Access cavity preparation was performed by large round bur (Komet- Germany) mounted in a high-speed contra-angled handpiece under water coolant.

After working length determination, the canals were instrumented to size# 35 manual K files (Dentsply- Dentsply Caulk -United States of America). Between each file, each canal was irrigated with 3 mL of 1.5% NaOCl using a side-vented needle. After canal dryness with a sterile paper point, then the tooth was restored by resin-reinforced ZOE as a temporary restoration (IRM-Dentsply -Caulk -United States of America). After 2 weeks, when all signs and symptoms were negative, canals were irrigated with saline and 17% ethylenediaminetetraacetic acid (EDTA) (Calix -DHARMA-United States of America) for 5 minutes, dried and obturated with ZOE (Prevest DenPro Limited -India) mixed according to the manufacturer's instructions. Finally, the tooth was restored with SSCs (KiDS CROWN. www.shinhung.co.kr) cemented by glass ionomer cement (Medicem- Promedica-Germany).

### Group II, III (experimental): Regenerative Endodontic Therapy (RET)

*First Visit*

The same previous steps of access cavity preparation were followed. Then sizes #15:25 manual k files were used for minimal canal preparation and 1.5% NaOCl 3mL/canal for irrigation. After the dryness of the canals, mTAP or Metapex TM (Meta Biomed Co. Ltd, Seoul, South Korea) were placed as intracanal medicaments in groups II and III, respectively. Then, the teeth were temporally restored with intermediate restorative material (IRM).

*Second Visit*

If all signs and symptoms are negative, a second visit RET was performed. (AAE regenerative protocol). Mineral trioxide aggregate (MTA) base (Neo-MTA-Nu-Smile-United States of America) was placed, followed by IRM and SSCs at the same visit.

## Outcomes

### Clinical and Radiographic Assessment

At baseline, 6 and 12 months follow-up visits, the assessment was performed by the same evaluator.

Success or failure was decided according to the following criteria:[19,20]

*Clinical Assessment Criteria*

The tooth was considered a failure if any of the following was assessed at 6 and 12 months—pain, pain on palpation, presence of abscesses, fistula openings, pathological mobility (more than grade I on the previously mentioned mobility index), and/or sensitivity to percussion. A binary scoring system was employed to record any failure (1 = failure, 0 = success).

*Radiographic Assessment Criteria*

Radiographic assessment was performed based on the following scores:

0 = No furcation/periapical radiolucency at baseline.
Complete healing of the radiographic lesion at follow-up.
1 = periapical/furcation radiolucency at baseline.
The static state of the radiographic lesion.
Not >1/3 root resorption at follow-up.
2 = Increase in the size of the radiographic lesion.
>1/3 root resorption and newly formed lesions.

Where 0, 1 scores were considered success and score 2 was considered a failure.

### Statistical Analysis

Qualitative data were presented as frequencies and percentages. Quantitative data were presented as mean and standard deviation values. Chi-squared and Fisher's exact test were used to compare qualitative variables in the three groups. Friedman's test was used to study the changes by time within each group, followed by Nemenyi *post hoc* test for intragroup comparison. A one-way analysis of variance formula test was used to compare mean age values in the three groups. The significance level was set at $p \leq 0.05$. Statistical analysis was performed with IBM Statistical Package for the Social Sciences statistics for windows, version 23.0. Armonk, New York: IBM.

## Results

The total numbers of enrolled, recruited, followed, and analyzed patients were represented in the flow diagram (Flowchart 1); intention to treat analysis was applied.

### Demographic Data

There was no statistically significant difference between mean age values, gender distributions, teeth distributions, and between loss of IRM between appointments in the three groups.

Baseline and follow-up data for each group were presented in (Table 1).

*Overall Clinical and Radiographic Assessment between the Three Groups*

After 6 as well as 12 months, there were no statistically significant differences between clinical success in the three groups (p-value = 0.765, effect size = 0.193) and (*p*-value = 0.327 and effect size = 0.22), respectively.

At 12 months follow-up, the clinical success was 88.9, 77.8, and 83.3% for groups I, II, and III, respectively (Fig. 1).

After 6 as well as 12 months, there was no statistically significant difference between radiographic success in the three groups (*p*-value = 0.585, effect size = 0.021) and (*p*-value = 0.055, effect size = 0.118), respectively. At 12 months follow-up, the success was 77.7, 55.5, and 77.7% for groups I, II, and III, respectively (Figs 2 and 3).

*Overall Outcome at 12 Months*

Two cases failed in group I (one tooth showed <1/3 root resorption, and the other tooth showed mobility and pain on percussion clinically and <1/3 root resorption radiographically. Eight cases failed in group II (five molars showed radiographic failure only as follows two molars with <1/3 root resorption, two molars with progression in periapical/furcation radiolucency, one molar showed both <1/3 root resorption and progression in radiolucency), clinically one molar showed pathological mobility. At the same time, two molars showed both clinical and radiographic failure (abscess—progression in radiolucency—abscess, pain, and progression in radiolucency). In group III, one single molar showed <1/3 root resorption. The difference between groups was statistically significant ($p = 0.021$), with the percentage of failed cases in group II being significantly higher than that of group III ($p < 0.05$). Table 2—complete case analysis was applied.

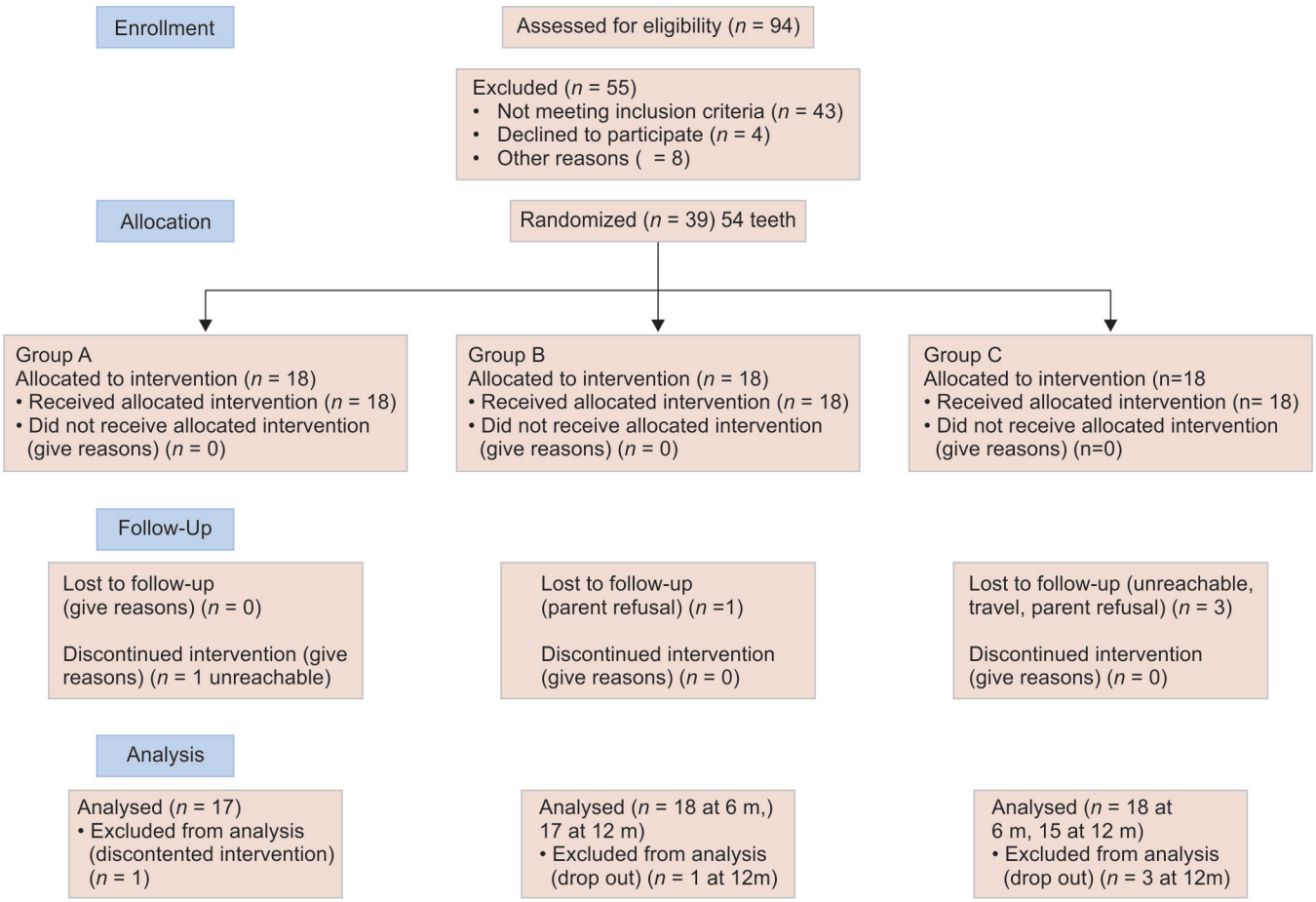
## Discussion

Premature loss of necrotic primary teeth by extraction does not only affect the oral cavity but also affects many aspects of a child's development. Therefore, pulpectomy is considered the last treatment option to keep necrotic primary molars without root resorption in place functional and asymptomatic.[21] Root canal branching and ramifications in the root canal system of primary teeth usually complicate the disinfection process and do not eliminate the probability of reinfection.[22] Therefore, the search for alternatives has been the focus of research for many years. The cutting-edge technology in root canal treatment nowadays is the application of RET in mature teeth.[23,24] So, the aim of this study was to assess RET in necrotic primary teeth.

Clinical and radiographic inclusion criteria were adopted based on the indications criteria of nonvital pulpectomy suggested by the American Academy of Pediatric Dentistry to ensure proper case selection.[25] In this RCT, the first and second primary molars were included in the study since there is no difference in pulpectomy prognosis between the first and second primary molars.[26]

Since there is no evidence of the superiority of ZOE over zinc oxide mixed with $Ca(OH)_2$/iodoform,[27,28] ZOE as an obturation

**Flowchart 1:** CONSORT 2010 Flow




material was chosen in group I due to its availability and the presence of the manufacturer's instructions. In this study, group I was reported with 88.2% overall success. The results agreed with several studies (Pandranki et al.)[29] reported 89% in 12 months clinical success rate of ZOE pulpectomy (Reddy et al.),[30] reported 97% clinical and radiographic success, (Mortazavi and Mesbahi)[31] reported 78.5 overall success for ZOE pulpectomy, and (Gupta and Das)[32] reported 85.7% success rate, that may be due to using the standard protocol of pulpectomy.

Chemical irrigations and intracanal medications are among the most used methods for canal disinfection. In this study, a concentration of 1.5% NaOCl and 17% EDTA were used in irrigation because several studies have recommended and reported the effectiveness of using EDTA in pulpectomy. As well as to follow the AAE recommendations in RET.[33,34] For intracanal medications, an interval of 2 weeks was applied because several studies reported it to be enough for complete canal disinfection. Also, intracanal medications become diluted and of less effect, if left for a longer duration.[35]

A concentration of 5 mg/mL of mTAP was chosen because it provides a higher antibacterial effect (dose depended on effect) and nonstatistically significantly higher toxicity than 1 mg/mL. While in the other experimental group (group III), Metapex TM was chosen as it is a $Ca(OH)_2$-based material that has a better antibacterial effect.[17,36]

Different approaches are available for dental pulp regeneration, from which the blood clot technique was selected due to the high cost and complexity of other techniques, which is not suitable for practical application in pediatric dentistry. Furthermore, this technique is adequate for achieving the targeted primary aim of RET, which is repair rather than regeneration.[5]

One of the main factors that affect the success of nonvital pulp therapy is an optimal coronal seal. Therefore, SSCs were chosen for the final restoration in the three groups as it provides the best coronal seal.[37]

In group II, the highest number of failures reported that maybe due to the used concentration of antibiotics that may have a toxic effect on the stem cells or due to its liquid consistency, which is difficult in the clinical application and might result in a lower antibacterial effect.

While group III showed the highest clinical and radiographic success, which might return to the high antibacterial effect of Metapex TM and the less toxicity and positive effect of its $Ca(OH)_2$ component upon the survival, proliferation, and differentiation of the stem cells. The use of Metapex TM provided very promising results and caused the results of the RET to be comparable to pulpectomy. These results might be due to its difficult removal and the prolonged antibacterial effect of its remnant.

The results of RET in this study are in line with the results that were reported in the case series Ulusoy and Cehreli. A tendency to shorten and foundation of root apexes was reported in the four treated teeth in the case series but not in the current study. This may be due to the difference in the technique used, as in the case series, no instrumentation was performed on the root canals, while in this study, minimal instrumentation was performed on the first visit.[6]

**Table 1:** Clinical and radiographic criteria for the three groups at baseline, 6 and 12 months follow-up—Friedman`s test for the changes by time within each group followed by Nemenyi *post hoc* test for intragroup comparison

| | *Group I (N)%* | | | | *Group II (N)%* | | | | *Group III (N)%* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Signs/symptoms* | *Baseline (n = 18)* | *6m (n = 17)* | *12m (n = 17)* | *p-value* | *Baseline (n = 18)* | *6m (n = 18)* | *12m (n = 17)* | *p-value* | *Baseline (n = 18)* | *6m (n = 18)* | *12m (n = 15)* | *p-value* |
| Clinical findings | | | | | | | | | | | | |
| Pain on palpation | (7) 38.9% | (0) 0% | (0) 0% | 0.002* | (7) 38.9% | (0) 0% | (0) 0% | 0.001* | (6) 33.3% | (0) 0% | (0) 0% | 0.049* |
| Pain on percussion | (13) 72.2% | (0) 0% | (1) 5.9% | 0.001* | (6) 55.6% | (0) 0% | (2) 11.8% | 0.001* | (12) 66.7% | (0) 0% | (0) 0% | 0.0001* |
| Abscess | (8) 44.4% | (0) 0% | (0) 0% | 0.001* | (14) 77.8% | (1) 5.6% | (2) 11.8% | 0.0001* | (12) 66.7% | (0) 0% | (0) 0% | 0.0001* |
| Mobility | (6) 33.3% | (0) 0% | (1) 5.6% | 0.006* | (10) 55.6% | (1) 5.6% | (1) 5.9% | 0.001* | (7) 38.9% | (0) 0% | (0) 0% | 0.002* |
| Pain | (17) 94.4% | (0) 0% | (0) 0% | 0.001* | (17) 94.4% | (0) 0% | (1) 5.9% | 0.001* | (16) 88.9% | (1) 5.6% | (0) 0% | 0.0001* |
| Radiographic findings | | | | | | | | | | | | |
| No root resorption | (16)88.9% | (15)88.2% | (14)82.4% | 0.368 | (14) 77.8% | (12) 66.7% | (9) 52.9% | 0.006* | (17) 94.4% | (16) 88.9% | (12) 80% | 0.097 |
| <1/3 root resorption | (2) 11.1% | (1) 5.9% | (1)5.9% | | (4) 22.2% | (6) 33.3% | (5) 29.4% | | (1) 5.6% | (1) 5.6% | (2) 13.3% | |
| >1/3 root resorption | (0) 0% | (1) 5.9% | (2)11.2% | | (0) 0% | (0) 0% | (3) 17.6% | | (0) 0% | (1) 5.6% | (1) 5.7 | |
| no periapical/ furcation radiolucency | (13) 72.2% | (16) 94.1% | (15) 88.2% | 0.202 | (9) 50% | (17) 94.4% | (11) 64.7% | 0.02* | (10) 55.6% | (16) 88.9% | (13) 86.7% | 0.007* |
| radiolucency at baseline/static | (5) 27.8% | (1) 5.9% | (1) 5.9% | | (9) 50% | (1) 5.6% | (1) 5.6% | | (8) 44.4% | (2) 11.1% | (2) 13.3% | |
| progression in size of the Periapical/ furcation radiolucency | (0) 0% | (0) 0% | (1) 5.9% | | (0) 0% | 0% | (5) 29.4% | | (0) 0% | (0) 0% | (0) 0% | |

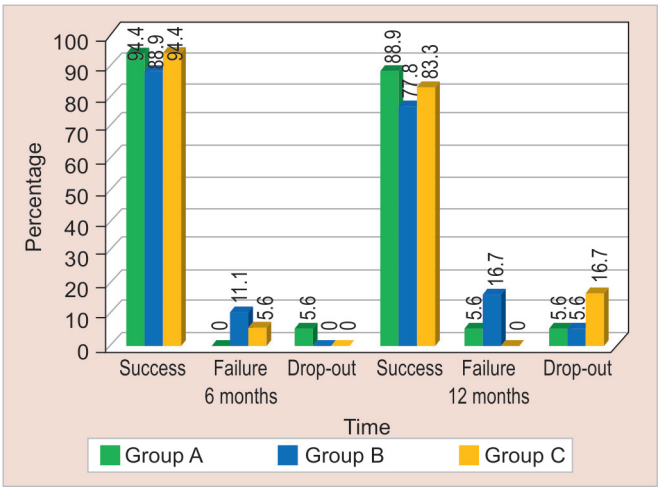



**Fig. 1:** Bar chart representing overall clinical success in the three groups

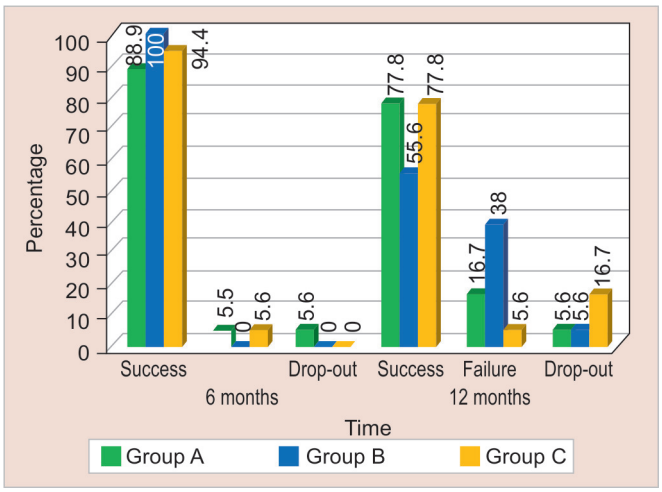



**Fig. 2:** Bar chart representing overall radiographic outcome in the three groups

On the contrary, the results of the current study were in disagreement with the finding of Rawi,[38] who reported 100% success of Regenerative Endodontic Procedure (REP) in nonvital mature primary teeth using TAP as an intracanal medication; this disagreement may be due to the different combination of antibiotics used, and the use of 5.25% concentration of NaOCl. To our knowledge, there are no other studies that evaluated RET in primary teeth.

The lack of tooth sensibility assessment is one of the limitations of the current study. Using SSCs as a final restoration did not allow sensibility testing. However, the use of SSCs was mandatory to obtain the maximum coronal seal. Moreover, regaining vitality was not a necessity and is unpredictable as it is considered a third aim of REP. The study also lacks the histological examination of the regenerated tissue in the pulp space as the participants' age group didn't allow this investigation. Lack of bone healing monitoring through bone density assessment and lack of intraexaminer reliability could also be listed among the limitations.

## Conclusion

Based on the findings of this study, it can be concluded that RET can be a successful treatment modality in nonvital primary molars with results comparable to pulpectomy when using Metapex TM as an intracanal medication; it is recommended to conduct further RCTs with longer follow-up periods. And to test the antibacterial and stem cells' friendly concentration as well as the consistency of different intracanal medications.

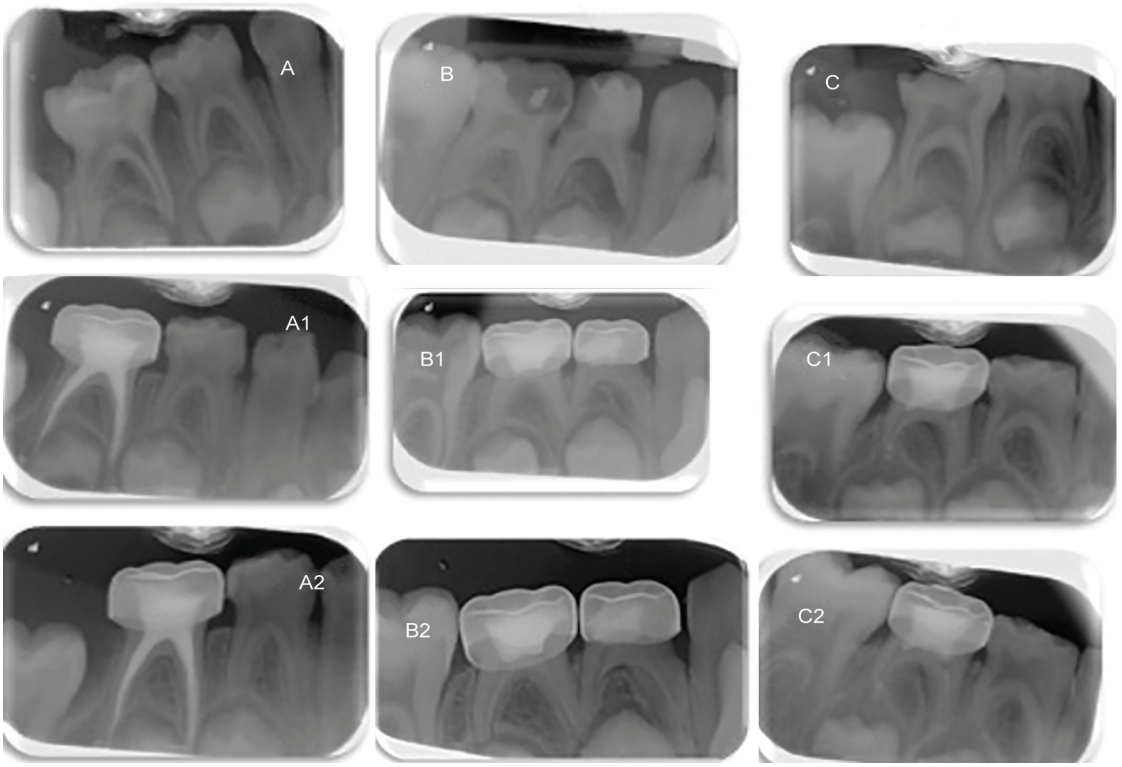



**Fig. 3:** Showing a successful case of each treatment group. A, B, and C showing the radiographic evaluation at baseline for the corresponding treatment group. Where A1, B1, and C1 were at 6 months, follow-up and A2, B2, and C2 at 12 months follow-up

**Table 2:** Frequency and percentage values for overall outcome in different groups at 12 months

| *Parameter* | | *Group I* | *Group II* | *Group III* | *p-value* |
|---|---|---|---|---|---|
| Failure | *n* | $2^{AB}$ | $8^{A}$ | $1^{B}$ | **0.021*** |
| | % | 11.8% | 47.1% | 6.7% | |
| Success | *n* | 15 | 9 | 14 | |
| | % | 88.2% | 52.9% | 93.3% | |

Different superscript letters indicate a statistically significant difference within the same horizontal row *; significant ($p \leq 0.05$); ns, nonsignificant ($p > 0.05$)

### Clinical Significance

Regenerative endodontic treatment may provide a more successful and biological treatment option for necrotic primary teeth and a way to get rid of the adverse effect of synthetic obturation materials.

## Ethics Approval

This research was approved by the ethical committee of the Faculty of Dentistry, Ain Shams University, Egypt (#691–23/5/2018). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Compliance with "Ethical Standards" when submitting a paper—research involving human participants.

## Patient Consent Statement

The authors have obtained written informed consent from the patient's parents/legal guardians for the publication of the case report details and related images.

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