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ORIGINAL ARTICLE

A randomized clinical trial of hyaluronic acid gel pulpotomy in primary molars with 1 year follow-up

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ABSTRACT

Objective: This randomized clinical study aimed to evaluate the success of hyaluronic acid (HA) as a pulpotomy medicament of human primary molars and to compare it with formocresol (FC) and ferric sulphate (FS) pulpotomy treatments up to 12 months.

Materials and methods: The study was conducted with 130 primary molars of 44 children. The ethical approval and registration to clinical trials (No: NCT04115358) were completed. After the removal of all the coronal pulp tissue, a 0.5% HA gel, or a FC, or a 20% FS solution were applied randomly to the radicular pulp tissues of the primary molars. Then, the pulp chambers were filled with a zinc oxide eugenol cement and restored either with a composite filling material or with a stainless-steel crown. The treatment success rates of the 3 groups were followed and compared clinically and radiographically at 1st-, 3rd-, 6th- and 12th-months.

Results: Primary molars treated with FC, FS and HA dressings were clinically successful 77.5%, 86.8% and 87.5% respectively after 12th-month follow-up ($p > .05$). Radiographic successes of FC, FS and HA groups were lower than clinical successes (57.6%, 68.8%, 57.9% respectively at the 12th-month) but the difference between the groups was not statistically significant ($p > .05$). Equivalence analysis assuming not more than 10% difference between the materials suggested that HA was not inferior to FC or FS.

Conclusions: Within the limitations of this study, our randomized clinical trial shows that HA is a promising pulpotomy medicament in primary molars. However, further studies are justified to further improve the HA material success.

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Formocresol; ferric sulphate; hyaluronic acid; paediatric endodontics; vital pulp therapies

Introduction

Pulpotomy is the most widely used endodontic treatment technique in primary dentition. Several agents, including calcium hydroxide (CH), formocresol (FC), ferric sulphate (FS), glutaraldehyde (GA), mineral trioxide aggregate (MTA), sodium hypochlorite (NaOCL), biodentine (BD), various lasers and electrosurgery have been used in primary molars [1,2]. FC has been used in paediatric dental clinics over 80 years for pulpotomy of primary teeth and established in trials as a 'gold standard' control [3]. FC was initially used in paediatric endodontics to mummify the remaining vital or necrotic pulpal tissue of primary teeth after the removal of the inflamed pulp chamber. FC is easy to use, cheap, has formaldehyde to exert bactericidal properties and reversibly inhibits enzymes in the inflammation, so it provides successful results [4]; however, its success is controversial for its safety concerns. Lewis [5] stated FC as problematic because of its toxicity, carcinogenicity, and genotoxicity. FS is a common haemostatic agent in dentistry. FS reacts with the pulp tissue upon its coverage and creates a shallow protective iron-protein layer complex. It reduces the risk of chronic inflammation and internal resorption but is not a regenerative material [6].

An ideal pulpotomy material in primary teeth differs from permanent teeth because it should preserve or heal the radicular pulp and not interfere with the physiologic root resorption and, also must be bactericidal but causes no harm to the surrounding tissues including the permanent successor. There are conflicting results about the pulpotomy agents and techniques in the literature and as novel materials become available, an 'ideal' pulp dressing material is still under investigation [2].

Hyaluronic acid (HA) is a non-sulphated glycosaminoglycan (GAG) that is composed of D-glucuronic acid and N-acetyl-D-glucosamine repeating polymeric disaccharides connected by a glucuronidic β (1→3) bond. HA is found naturally in the skin, representing 50% of the total body HA, synovial fluid, the umbilical cord, and the eye vitreous, however it is also found throughout the body, such as the lung, skeletal tissues, the aorta, heart valves. Mesenchymal cells mostly produce HA, but other cell types also can. Some of the functions of HA are joint lubrication, hydration, and a space filling capacity. HA is synthesized more when there is tissue injury and wound healing and also controls tissue repair [7]. The size of HA seems to be of great importance

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due to its functions. HA is antiangiogenic and immunosuppressive with high molecular size, exceeding 1,000 kDa. However smaller HA polymers are distress signals and may induce inflammation and angiogenesis [7].

HA has been used in dentistry for the treatment of gingivitis and chronic periodontitis, healing of intraoral ulcers, surgical operations, and the management of teething symptoms [8,9]. HA was also studied experimentally in stem cell tissues for regenerative endodontic treatment [10].

We hypothesized that HA gel might have a healing potential in injured pulp tissue of the primary molars. This randomized clinical trial aimed to evaluate the application of HA gel dressing for the pulpotomy treatment of primary molars and assess its clinical and radiographic successes as compared to FC or FS materials.

Materials and methods

Study population

The study was initially carried out on 136 primary molars of 47 children, (28 girls, 19 boys aged between 5 and 9), who applied to the Paediatric Dentistry Department at Marmara University, Istanbul, Turkey. Ethical approval of the study was obtained from the Clinical Research Ethics Committee, Faculty of Dentistry at Marmara University (No: 2019/288) in accordance with the Declaration of Helsinki. The study was registered as a randomized clinical trial to the database of the US National Library of Medicine (Ref No: NCT04115358). Sample size calculation performed with a power analysis using survival scores from a similar study and showed that 40 teeth in each group were required initially to detect a two-sided 5% significance level with 80% power [11]. We also checked online databases for clinical trials of Power calculator for binary outcome equivalence trial. Thus, if there is truly no difference between the standard and experimental treatment (70% in both groups), then 120 teeth are required (40 for each study material) to be 80% sure that the limits of a two-sided 90% confidence interval will exclude a difference between the standards and experimental group of more than 30% [12,13].

The recruitment was initiated in May 2019, the patients' family or legal guardians were given information about the pros and cons of the study on the relevant teeth and then a written consent was obtained. The same paediatric dentist (GCI) performed whole pulpotomy treatments and restorations of all selected teeth.

The selection criteria included children without history of systemic diseases or allergic reactions, absence of requirement for general anaesthesia or sedation and who had good cooperation according to the Frankl Behaviour Scale. The criteria for the selection of treatment of primary molar was as follows: Clinically deep caries lesions without any (1) spontaneous, continuous pain in the tooth, (2) pathological or physiological mobility, (3) abscess and/or fistula, (4) tenderness to palpation or percussion, and (5) the tooth can be restored with a stainless steel crowns (SSC) or a composite filling material after treatment; and radiographically without any (1) the physiological resorption in the tooth root not exceeding 1/3, (2) pathological resorption in the tooth root canals internally and/or externally, (3) radiolucency in the periapical or furcation regions, (4) enlargement of periodontal ligaments. Exclusion criteria were families who were not willing to join the study; children who had any disorders or spontaneous pain; no restorable primary molars or may exfoliate soon and teeth with apical periodontitis, pulp necrosis, abscess, fistula, swelling or mobility.

Treatments and follow-ups

Before the treatment, 136 primary molars were randomly distributed to three groups: 1-Formocresol group (FC), 2-Ferric sulphate group (FS) and 3-Hyaluronic acid group (HA). Pulpotomy procedure was initiated with an infiltration anaesthesia. The relevant tooth was isolated by a rubber dam (Roeko Dental Dam®, Coltene Whaledent) and a saliva ejector was inserted. Cavity preparation of the teeth was done using a high speed handpiece (KaVo Dental GmbH, Germany) and a diamond round bur (Dialom, Diamond Tools Ltd.). Carious dentine tissue was removed from the periphery to the centre using round steel burs (NTI-Kahla GmbH, Germany). The roof of the pulp chamber was removed, and the pulp chamber was cleaned with another sterile slow-speed round bur. Remaining pulp tissue was removed with a sterile sharp excavator (Carl Martin GmbH, Germany). The pulp chamber was irrigated with sterile saline solution and then dry sterile cotton pellets were placed on pulp stumps for 4 min to achieve haemostasis.

All treatment steps were identical in 3 pulpotomy groups. Three different agents, FC, FS, and HA gel were applied randomly to the radicular pulp tissues. In all three groups, it was confirmed that the hemostasis was achieved before the application of the dressing materials. In the FC group, a sterile cotton pellet soaked in FC (Prevest DenPro®, India) was placed on the orifice of the radicular pulp tissue for two minutes. In the FS group, 20% FS (ViscoStat™, Ultradent Products Inc.) soaked in a cotton pellet was placed for 15 s on the radicular pulp tissue and excess FS remaining on the cavity walls was cleaned with a dry and sterile cotton pellet. In the HA group, a commercially available 0.5% HA gel (Gengigel®Teething, Ricerfarma, Italy) was scrubbed onto a sterile cotton pellet then left on the radicular pulp tissue for two minutes. The treatment time of HA gel was estimated to be comparable to FC and the excess HA gel was removed from the pulp chamber.

After the application of the medicaments in all groups, the pulp chambers were filled with zinc oxide eugenol cement (ZOE-Kalzinol, Dentsply), and the primary molars were restored either with a composite filling material (GC Gradia Direct Posterior, Japan) in case of occlusal cavities or with a stainless-steel crown (SSC) (3 M™, Unitek™, USA) in case of proximal cavities.

Children were recalled at 1st-, 3rd-, 6th- and 12th-month intervals, periapical x-rays (Dürr Dental, Germany) were taken. Teeth were evaluated clinically and radiographically according to the following criteria: (1) Clinical criteria: Spontaneous pain, tenderness to percussion and/or palpation, pathological

mobility and abscess or fistula, (2) Radiographic criteria: Periapical or furcal radiolucency, internal or external root resorption, loss of lamina dura, pulp canal obliteration. All evaluations were performed by two calibrated paediatric dentists (BIS and AM). The patients were blinded to the group assignments, the performing dentist (GCI) was not blinded to the treatment materials but two examiners who evaluated clinical and radiographic findings were blinded to the treatment (Intra and inter-rater reliability; 0.89, and 0.85 respectively).

Statistical analysis

Statistical analyzes in this study were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) packaged software. In the evaluation of the data, descriptive statistical methods (mean, standard deviation) as well as Independent Sample T-Test for comparison of paired groups, and Pearson's Chi-Square Test for comparison of qualitative data were used. The results were evaluated at the significance level of $p < .05$. A result suggesting treatments were not statistically different does not necessarily mean the treatments were the same. Therefore, we also determined the non-inferiority of the treatments by assuming that the difference in the number of failures between treatments would be no greater than 10% (one case in every 10).

Results

Three children (2 boys, 1 girl) did not show up in any recalls, so initially 51, 40, and 39 pulpotomies were followed in HA, FC, and FS groups respectively and the study was performed in 130 primary molars. Table 1 showed that there were no statistically significant differences between age, sex, dental arch, tooth, and final restoration types of the three groups at the beginning of the study ($p > .05$). The dropouts at 3rd-month were none in HA, FC, and FS groups. At 6th-month only 1 dropout was seen in each HA and FS groups, however they were all reached at 12th-month (Appendix Figure A1).

In the 12th-month follow-up, the appointment failure of the children increased due to the Covid-19 pandemic and periapical radiographs could not be taken in a total of 8 children (27 teeth), but they were reached *via* Zoom® and other video conferencing media to examine and record vis-a-vis clinical findings and complaints of the children so that all children in the study groups were recorded without any further dropout. On the other hand, 1 primary molar exfoliated from the FS group at 6th-month, and two from HA group at 12th-month.

Table 2 shows clinical success rates of the 3 different treatment groups at 4 different time periods and the clinical success rates of the HA, FC and FS groups were not statistically different at 1st-month ($p = .567$), 3rd-month ($p = .325$), 6th-month ($p = .244$) and 12th-month ($p = .380$). The most common clinical finding was sensitivity to the percussion at 1st-month (7 HA, 6 FC, 3 FS), 3rd-month (10 HA, 8 FC, 3 FS), 6th-month (11 HA, 8 FC, 3 FS) and 12th-month (2 HA, 6 FC, 2 FS). One tooth was extracted at 1st-month in the HA group due to abscess whereas there were not any signs of tenderness to the palpation or swelling, abscess and fistula in any group at the 3rd-, 6th-, and 12th-month follow-ups.

One primary molar exfoliated from FS group at 6th-month and two from HA group at 12th-month (Appendix Table A1). On the other hand, the success rates decreased 7.5% and 5.5% in FC and FS groups respectively from the 1st-month up to the 12th-months but increased 1.2% in HA group.

Table 2 shows similarly radiographic success rates of the 3 different treatment groups at 4 different time periods and radiographic success rates of the HA, FC and FS groups were not statistically different at 1st-month ($p = .078$), 3rd-month ($p = .901$), 6th-month ($p = .773$), and 12th-month ($p = .570$) follow-ups.

The most common radiographic findings were internal root resorptions at 1st-month (6 HA-11.76%, 4 FC-10%, 1 FS-2.56%), 3rd-month (9 HA-18%, 11 FC-27.5%, 6 FS-15.4%), 6th-month (11 HA-22.45%, 12 FC-30%, 10 FS-27%), 12th-month (11 HA-30.56%, 8 FC-25%, 5 FS-16.1%) whereas the second common features were external root resorptions at 1st-month (1 HA-1.96%, 1 FS-2.56%), 3rd-month (6 HA-12%, 1 FC-2.5%, 3 FS-7.69%), 6th-month (5 HA-10.2%, 5 FC-12.5%, 5

Table 1. Baseline characteristics of the study groups.

	Hyaluronic Acid n:51		Formocresol n:40		Ferric Sulphate n:39		*p* value
Mean Age±(SD)	6.65±(0.99)		6.83±(0.98)		6.67±(1.08)		.680*
Sex							
Boys	19	37.25%	15	37.5%	16	41.03%	.925**
Girls	32	62.75%	25	62.5%	23	58.97%	
Dental Arch/Tooth Type							
Upper 1st primary molars	11	21.57%	9	22.5%	7	17.95%	.786**
Upper 2nd primary molars	17	33.33%	13	32.5%	8	2.51%	
Lower 1st primary molars	14	27.45%	11	27.5%	15	38.46%	
Lower 2nd primary molars	9	17.65%	7	17.5%	9	23.08%	
Dental Arch							
Lower	23	45.10%	18	45%	24	61.54%	.227**
Upper	28	54.90%	22	55%	15	38.46%	
Tooth Type							
1st primary molars	25	49.02%	20	50%	22	56.41%	.764**
2nd primary molars	26	50.98%	20	50%	17	43.59%	
Final Restoration							
SSC	33	64.71%	28	70%	28	71.79%	.749**
Composite	18	35.29%	12	30%	11	28.21%	

*Independent Sample *T*-Test; **Pearson's Chi-Square Test; SD: Standard Deviation; SSC: Stainless Steel Crown.

FS-13.5%), 12th-month (7 HA-19.44%, 6 FC-18.75%, 5 FS-16.13%) (Figure 1). The periapical resorptions of the primary molars were also higher but not considered as failure because of the resorptive nature of these teeth. In all three groups there was no pulp canal obliteration or enlargement of PDL at any time (Appendix Table A2). Radiographic findings of all three groups were similarly significantly lower at 3rd-, 6th-, and 12th-month as compared to the 1st-month ($p < .05$).

There were no significant differences in other time frames ($p < .05$), but the success rates seemed to decrease in all groups. Differences between HA or FS and FC were never bigger than 12% in all time points, suggesting that these treatments were not inferior to FC.

Discussion

The success rate of the primary molar pulpotomy treatment depends on the therapeutic ability of the dressing material and healing capacity of the remaining pulp after the removal of part or all of the coronal pulp [14]. Two control groups; a mummifying agent FC, which has been used as a 'gold standard' in paediatric dentistry for many years, and a preserving agent FS, which has been favoured against the possible toxicity of FC in recent years, were chosen to compare clinical and radiographic successes of the treatment. All three materials were covered with the same ZOE cement to seal the pulp chamber thus allowing a better comparison of the three medicaments. MTA, another promising agent, was not used in this study due to its strict distinctness in the clinical procedure which excludes ZOE material.

Paediatric Dentistry literature is abundant with different types of medicaments in the pulpotomy treatment of the primary molars. In 2018, Smail-Faugeron et al. [1] from Cochrane Library cited 87 trials and stated that one of the four materials (FC, FS, CH, or MTA) was generally used.

Markovic et al. [15] followed clinically and radiographically the pulpotomy treatment of primary molars for 18 months and found that the radiographic success of FC, FS and CH were 84.4%, 81.1%, 76.5% respectively. While there was no statistically significant difference between the groups, CH was reported to be the most unsuccessful group. In a study by Sonmez et al. [16] although there was no statistically significant difference between the groups, the success rates of FC, FS, MTA, and CH were 76.9%, 73.3%, 66.6%, and 46.1% respectively at the end of 24 months. Erdem et al. [17] performed pulpotomy treatment on primary molars with FC, FS, MTA, and ZOE, and conducted follow-up clinically and radiographically for 24 months. While at 12th-month FC, FS and MTA showed clinically and radiographically 100% success rate and ZOE was 92% successful, at the end of the

Table 2. Clinical and radiographic success rates (%) of the study groups.

	Hyaluronic Acid	Formocresol	Ferric Sulphate	*p* values
1st Month				
Clinical	86.3%	85%	92.3%	.567*
Radiographic	78.4%	87.5%	94.9%	.078*
3rd Month				
Clinical	78%	80%	89.7%	.325*
Radiographic	68%	67.5%	71.8%	.901*
6th Month				
Clinical	76%	77.5%	89.5%	.244*
Radiographic	65.3%	60%	67.6%	.773*
12th Month				
Clinical	87.5%	77.5%	86.8%	.380*
Radiographic	57.9%	57.6%	68.8%	.570*

*Pearson's Chi-Square Test.

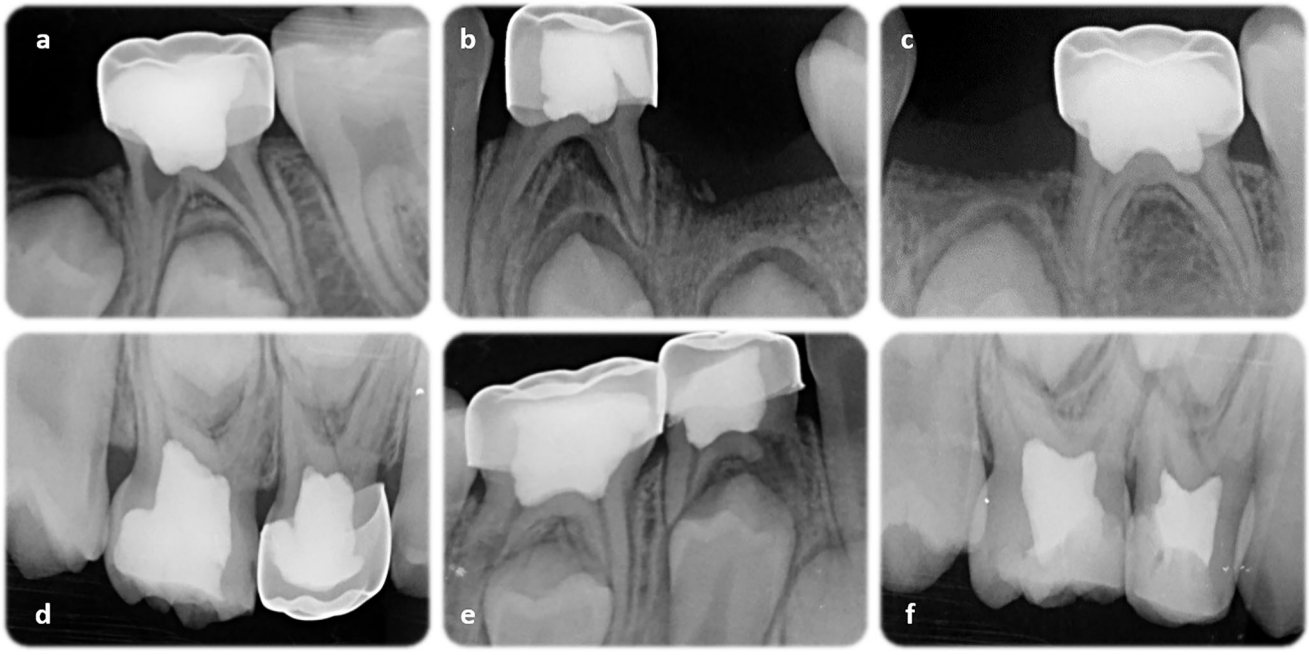

Figure 1. (a) Internal root resorption without perforation at 6th-month with Formocresol. (b) External root resorption and furcal radiolucency at 3rd-month with Ferric Sulphate. (c) No radiographic finding at 12th-month with Hyaluronic acid. (d) Internal root resorption of the 1st primary molar root with Formocresol and no radiographic finding on the 2nd primary molar with Hyaluronic acid at 12th-month. (e) Internal root resorption with perforation on the 1st primary molar with Formocresol, internal root resorption on the 2nd primary molar with Hyaluronic acid at 12th-month. (f) No radiographic finding on the 1st primary molar with Formocresol and external root resorption on the 2nd primary molar with Ferric Sulphate at 12th-month.

24 months, MTA, FC, FS and ZOE was 96%, 88%, 88%, 68% respectively. Fernandez et al. [18] reported that at the end of 24 months, clinical success of FC, FS, MTA and NaOCL groups were 100%, 92%, 100%, 96% respectively. Radiographic successes on the other hand were 95%, 100%, 93%, 75% respectively. There was no significant difference between the groups both clinically and radiographically. Havale et al. [19] found that clinical success in FC, FS and GA groups were 86.7%, 96.7%, 100% respectively and radiographic success were 56.7%, 63.3%, 83.3% respectively at the end of 12 months. Durmus and Tanboga [20] showed that diode laser had 75%, FC 87% and FS 79% radiographic success at the end of 12 months. Juneja and Kulkarni [21] reported the radiographic success rates in FC, MTA, and BD pulpotomy treatments as 73.3%, 100% and 86.6% respectively in the 18th month. Jamali et al. [22] used FC, MTA, and a combination of simvastatin and 3Mix antibiotic (3Mixtatin), as pulpotomy medicaments. At the end of 24 months, they reported that the overall success rate was 78.9% for FC, 90.5% for 3Mixtatin and 88.1% for MTA group. This novel endodontic biomaterial (3Mixtatin) was also successfully used as a direct pulp capping material in primary molars and the treatment medicament for the inflammatory root resorption in primary molars with furcation lesions [23,24]. In 2018 Junqueira et al. [25] reported a remarkably high rate of success for both FS and MTA, at the end of 18 months follow-up. Recently El Meligy et al. [12] found higher success of the pulpotomy treatment on primary molars with DFC (Diluted formocresol) and BD clinically and radiographically at 12th-month.

In our study, FC, FS and HA were 77.5%, 86.8% and 87.5% clinically successful at the end of 12 months respectively and the difference was not statistically significant ($p > .05$). These rates were similar to most previous studies and lower than some recent studies as mentioned above. The tenderness to percussion which was the primary clinical complaint in our study suggests the possibility that children may give a false positive response to the pulpal condition of the treated tooth in the clinical setting and if we exclude these findings, the rate of success increases dramatically. Camp [26] pointed out that children's psychological status also affected how they would respond to percussion symptoms. All tender teeth survived for 12 months without any other clinical symptoms in our study so that positivity to percussion alone could not be considered a clinical failure like in other studies [25].

Previous studies [1,2] found that the radiographic success rates of pulpotomies were lower than clinical success. Similarly in our study radiographic success of FC, FS and HA groups were 57.6%, 68.8%, 57.9% respectively at the 12th-month and although not significant they were lower than clinical success ($p > .05$). Sonmez et al. [16] reported that the most common radiographic findings were external root resorption and pulp canal obliteration. We found the most common radiographic finding to be internal root resorption, and overall rates were highest from FC (23.12%) to HA (20.69%) and FS (15.26%).

Some studies indicated the pulp canal obliteration as a common finding in FC [27], 1/5 diluted FC [28], and FS [29] pulpotomies, whereas there was no sign of pulp canal obliteration in any tooth in the present study. In our study, we did not use MTA as a control pulpotomy agent because the treatment steps differ in this material, the examiners can easily differentiate the material in radiographs and interfere with the blinding of the study.

There are a limited number of *in vitro* and *in vivo* animal studies [30,31] showing the effect of HA on dental pulp. Sasaki and Kawamata-Kido [32] performed pulpotomy of molar teeth in female Sprague-Dawley rats. They suggest that high molecular weight HA may provide an environment suitable for reparative dentine formation owing to mesenchymal cell differentiation during healing of the partial or total pulpotomies. Bogovic et al. [31] performed direct pulp capping using HA, CH, and dentine adhesive on the pulp tissue of Sprague-Dawley rats. They showed that HA was most efficient and the least toxic for direct pulp capping.

A recent study used a 1:1 mixture of high molecular weight HA gel and ZOE cement as a pulpotomy filling material in primary molars and found that the success of this mixture was comparable to FC pulpotomy after 12 months [33]. Authors stated that HA gel could easily be mixed with the ZOE powder, however the release of the HA from the cement or the setting mechanism of the mixture could not be evaluated from the study. In our study, a commercially available product containing 0.5% HA gel was used for ethical reasons [9] and, the HA gel applied directly to the pulp tissue as a pulpotomy dressing material, the application time was two minutes (similar to FC solution) and then the pulp chamber was filled with ZOE cement. This procedure allows us to assess accurately the applicability as well as the similarity in the success of the HA gel as compared to FC or FS solutions, because the same technique is designed to apply equally for both control materials.

In our results, the success rates of HA were similar to the control FC or FS groups in both clinical and radiographic findings at 1st-, 3rd-, 6th-, and 12th-months. On the other hand, the clinical success rate of the HA group seemed to be improved compared to the FC and FS group in the 12th-month (Table 2). Recent *in vitro* studies concentrated the potential of HA hydrogels on dental pulp stem cell behaviour and regeneration [34,35]. These studies showed promising healing potential of HA on dental pulp. However, our study showed that the internal resorption seen in primary molar teeth was higher in HA gel group than FS or FC groups without any significant difference. The resorptive nature of roots of the primary molars may interfere with the regeneration of the dental pulp, and histological studies are needed to explore the healing nature or potential of HA in the primary dental pulp.

The manufacturer of the product 'Gengigel' claims that they add choline alfoscerate to improve adhesion property and film forming activity of the aqueous gel of HA and the synergic action of the two compounds leads to greater therapeutic efficacy of HA gel, but these arguments need to be investigated further histologically and experimentally.

A cost analysis was not done because of great variability of prices in different countries but the easy availability and reasonable cost of this product also make it a good choice or alternative for the pulpotomy treatment in primary molars.

The limitations of this study included the unfortunate Covid-19 pandemic that interfered with the radiographic results of our study at 12th-month and complicated the follow-up results up to 24 months. But clinical assessments that could be considered success of the treatment were effectively completed *via* visual communication devices. Moreover, since we observed some interesting variations on the HA gel results, the application time and/or the concentration of the HA gel material has to be investigated further for better effects on the pulp tissue. In future trials, HA gels may offer the potential and capacity to treat injured dental pulp tissues of the primary as well as the immature and/or mature permanent teeth.

Conclusion

Within the limitations of this study, the results of our randomized clinical trial show that 0.5% HA gel is a promising pulpotomy medicament in the pulpotomy treatment of primary molars and can be advised as an alternative to FC or FS materials. However further clinical, and histological studies are needed to improve the HA gel material and increase its success.

Disclosure statement

The authors report no conflict of interest.

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Appendix

Table A1. Clinical findings observed (*n*) and rates (%) of the 3 study groups from the 1st month up to 12th month.

	Hyaluronic Acid		Formocresol		Ferric Sulphate		*p* value
Mobility							
1st Month	1	1.96%	0	0.00%	0	0.00%	.458*
3rd Month	1	2.00%	0	0.00%	1	2.56%	.619*
6th Month	3	6.00%	2	5.00%	1	2.63%	.755*
12th Month	4	8.33%	4	10.00%	3	7.89%	.940*
Percussion							
1st Month	7	13.73%	6	15.00%	3	7.69%	.567*
3rd Month	10	20.00%	8	20.00%	3	7.69%	.220*
6th Month	11	22.00%	8	20.00%	3	7.89%	.188*
12th Month	2	4.17%	6	15.00%	2	5.26%	.133*
Palpation							
1st Month	1	1.96%	0	0.00%	0	0.00%	.458*
3rd Month	0	0.00%	0	0.00%	0	0.00%	–
6th Month	0	0.00%	0	0.00%	0	0.00%	–
12th Month	0	0.00%	0	0.00%	0	0.00%	–
Abscess							
1st Month	1	1.96%	0	0.00%	0	0.00%	.458*
3rd Month	0	0.00%	0	0.00%	0	0.00%	–
6th Month	0	0.00%	0	0.00%	0	0.00%	–
12th Month	0	0.00%	0	0.00%	0	0.00%	–
Fistula							
1st Month	1	1.96%	0	0.00%	0	0.00%	.458*
3rd Month	0	0.00%	0	0.00%	0	0.00%	–
6th Month	0	0.00%	0	0.00%	0	0.00%	–
12th Month	0	0.00%	0	0.00%	0	0.00%	–
Exfoliation							
1st Month	0	0.00%	0	0.00%	0	0.00%	–
3rd Month	0	0.00%	0	0.00%	0	0.00%	–
6th Month	0	0.00%	0	0.00%	1	2.56%	.313*
12th Month	2	4.00%	0	0.00%	0	0.00%	.205*

*Pearson's Chi-Square Test.

Table A2. Radiographic findings observed (n) and rates (%) of the 3 study groups from the 1st month up to 12th month.

	Hyaluronic Acid		Formocresol		Ferric Sulphate		*p* value
Periapical Radiolucency							
1st Month	2	3.92%	0	0.00%	1	2.56%	.462*
3rd Month	0	0.00%	0	0.00%	1	2.56%	.313*
6th Month	0	0.00%	0	0.00%	1	2.70%	.298*
12th Month	0	0.00%	0	0.00%	1	3.23%	.330*
Periapical Resorption							
1st Month	1	1.96%	1	2.50%	2	5.13%	.668*
3rd Month	2	4.00%	3	7.50%	4	10.26%	.510*
6th Month	7	14.29%	5	12.50%	5	13.51%	.970*
12th Month	12	31.58%	8	24.24%	15	46.88%	.145*
Internal Resorption							
1st Month	6	11.76%	4	10.00%	1	2.56%	.274*
3rd Month	9	18.00%	11	27.50%	6	15.38%	.361*
6th Month	11	22.45%	12	30.00%	10	27.03%	.716*
12th Month	11	30.56%	8	25.00%	5	16.13%	.386*
External Resorption							
1st Month	1	1.96%	0	0.00%	1	2.56%	.620*
3rd Month	6	12.00%	1	2.50%	3	7.69%	.246*
6th Month	5	10.20%	5	12.50%	5	13.51%	.887*
12th Month	7	19.44%	6	18.75%	5	16.13%	.936*
Furcal Radiolucency							
1st Month	3	5.88%	1	2.50%	0	0.00%	.269*
3rd Month	7	14.00%	3	7.50%	3	7.69%	.501*
6th Month	4	8.16%	4	10.00%	3	8.11%	.942*
12th Month	4	11.11%	4	12.50%	2	6.45%	.705*

*Pearson's Chi-Square Test.

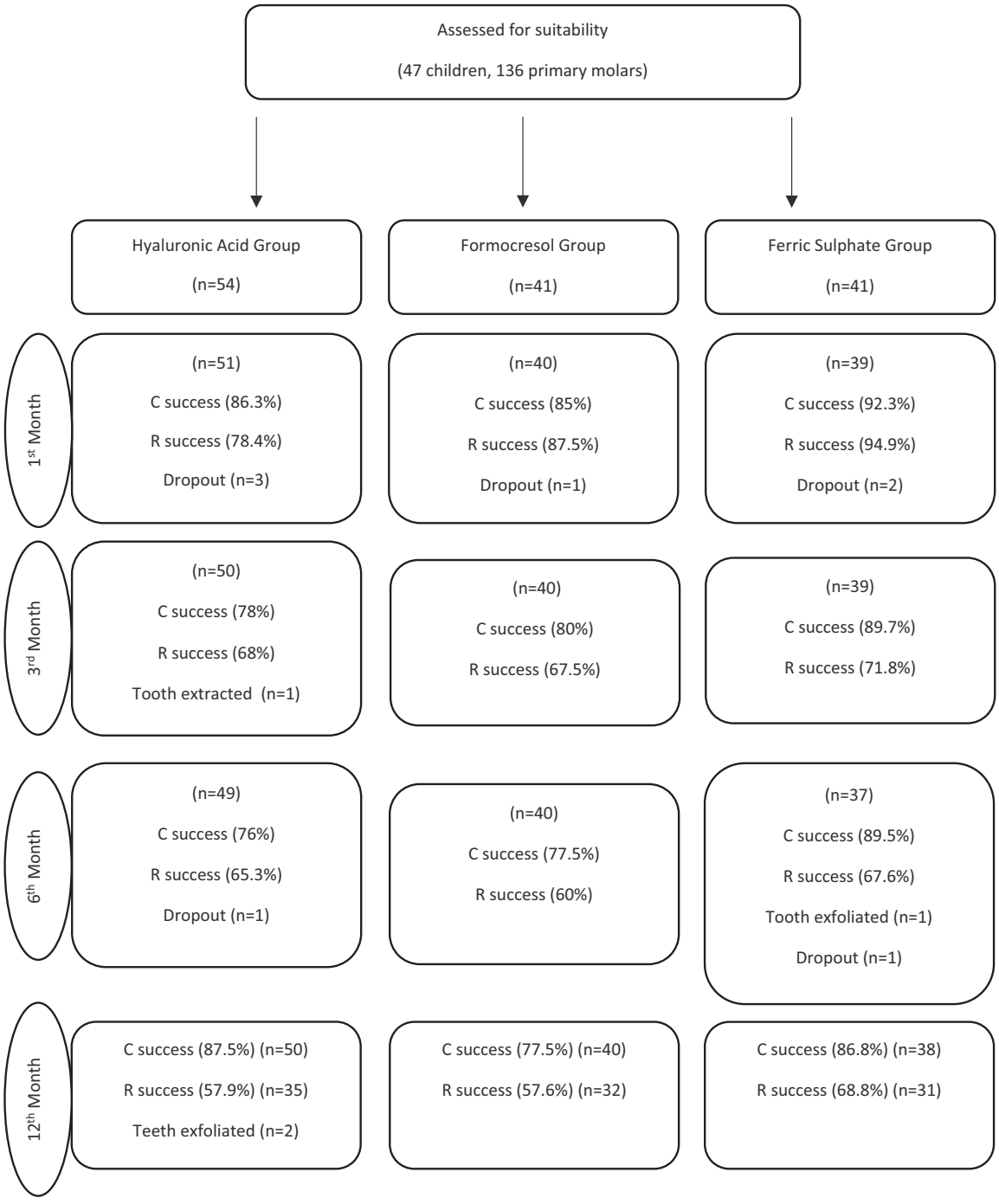

Figure A1. Flow chart of number of patients and clinical/radiographic success rates (C: Clinical, R: Radiographic).