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WOUND HEALING FOLLOWING THE USE OF HYALURONIC ACID AND HONEY FOR MULTIPLE EXTRACTION SOCKETS OF PRIMARY TEETH COMPARED TO SALINE IN CHILDREN: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Aim: The current randomized clinical trial (RCT) evaluated normal saline solution (NSS), hyaluronic acid (HA), and manuka honey (MH) for multiple extraction sockets under general anesthesia (GA) of primary teeth in order to assess the effects of various dressings on blood clot formation and soft tissue healing.

Material and methods: In the present RCT, 63 patients aged two to seven were involved. Under GA, several primary teeth were removed from each participant. Three groups of volunteers (n = 21 each) were randomly assigned to the study. Following tooth extraction, the group 1 primary investigator moistened a piece of gauze with NSS and placed it over the socket, covering it with one millimeter of MH. Rather than using MH on the gauze, group 2 applied HA. Group 3 had a piece of gauze soaked with NSS put to the socket wound. The parents and the patients were instructed to keep the gauze in place for 45 minutes. Assessments were made on the color of the wound tissue, the presence of pus, and the bleeding upon palpation at baseline, three, and seven days later.

Results: When comparing the MH and HA wound dressing groups to the NSS group on the third and seventh days after tooth extraction, the results revealed no differences in the color of the wound tissue, the presence of pus, or the bleeding upon palpation.

Conclusions: Wound dressings play a crucial role in mitigating clinical symptoms such bleeding and inflammation, with a noticeable reduction observed after approximately a week.

KEYWORDS: Blood clot, Multiple extractions, Primary Teeth, Soft tissue healing, Wound dressing.

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INTRODUCTION

Extractions are among the worst dental treatments for children, particularly for those who have had traumatic oral experiences [1]. Immediately following tooth extraction, the socket fills with blood, leading to the formation of a blood clot. Usually, a fibrin network entangling platelet, red blood cells, and white blood cells forms a blood clot[2-4]. Within the first seven days, granulation tissue replaces this blood clot. Granulation tissue is mostly composed of many blood vessels embedded in the connective tissue of leukocytes and mesenchymal cells [2, 5, 6].

Regularly applying saline solution to wounds that are infected has been seen to have a cleaning impact that promotes healing. However, it's crucial to remember that this therapy does not hasten postoperative recovery [7]. Because of its isotonic qualities which closely match intracellular fluid and its sterile, non-cytotoxic qualities, sterile normal saline is often used in both Western and Eastern nations. Its osmotic pressures are likewise similar to those of intracellular fluid, in addition [8, 9].

Accessibility, cost, and effectiveness are all important considerations when trying to choose the best wound dressings. By taking these factors into account, it is feasible to ensure that the dressings employed are suitable for the intended usage [10]. Honey is a safe natural substance that effectively stops the growth of germs, its use in wound care and regenerative medicine has recently gained clinical appeal [11-13]. Numerous active ingredients in honey, such as organic acids, phenolic acid, flavonoids, vitamins, and enzymes, may potentially speed up the healing of wounds [13-15].

HA is a polymer that is naturally produced by the human body. It has unique physicochemical and biological properties, such as favourable biocompatibility and biodegradability. It is an important component of the extracellular matrix and a constituent of the neural, connective, and epithelial tissues [16-19]. Among the many biological effects of HA are its functions in cell differentiation, wound healing, inflammation, embryological development, and viscoelasticity [18, 20].

Applying honey and HA to hasten the healing process following tooth extractions which might a quite advantageous [14, 21, 22]. Consequently, the current study's goal was to compare the effectiveness of NSS and hyaluronic acid and honey treatment for blood clot formation and soft tissue healing in children who had multiple primary tooth extraction sockets.

SUBJECT AND METHODS

This RCT was carried out at Cairo University's Faculty of Dentistry's Paediatric Dentistry and Public Health Department. On March 20, 2022, the Cairo University Faculty of Dentistry's Evidence-Based Committee reviewed and accepted the study request, giving it an approval code (Eth. 5-3-22). The NCT05161403 number for the study endeavour was registered on clinicaltrial.gov.

The sample size calculation showed that the study required a minimum of 19 participants in each group at a power of 0.8. The Type I error probability for this test of the null hypothesis is 0.05. In order to accommodate for the 15% dropout rate, each group's total sample size was increased to 21 patients based on a prior study by Mokhtari et al [22].

Thirty-three healthy Egyptian children, aged two to seven years, of both genders were selected for this randomized controlled trial (RCT). Out of the 63 samples in total, three groups of 21 samples each were assigned to either the control group (NSS), intervention 1 (MH), or intervention 2 (HA). The child's guardian agreed verbally and subsequently signed an official informed consent form to accept the therapeutic treatments.

Under GA, severely damaged primary teeth were extracted. To stop the bleeding before the kid heals, the extraction sockets were cleansed and

replaced with simple cotton plugs (Figure 1-a). After the kid had fully recovered, the principal investigator worked with each group on the following assignments: The lead investigator in group 1 applied one millimeter of MH (Manuka honey, THE TRUE HONEY CO., New Zealand) on a gauze piece that had been moistened with NSS (Sodium Chloride 0.9%, ADWIC Co., Egypt) after the tooth was extracted (Figure 1-b). In group 2, wet gauze was treated with HA (0.2% HA, GENGIGEL, RICERFARMA Co., Milano (Lombardia), Italy) rather than MH (Figure 1-c). Group 3 (control group) received a piece of gauze soaked with NSS placed to the socket incision (Figure 1-d).

The lead investigator watched each patient for 45 minutes while they left the gauze in place for all groups. All groups received postoperative instructions telling them to rinse their lips with water to remove any remaining gauze. Additionally, they were instructed not to use mouthwash for the first seven days following the extraction of their teeth [7, 22-24].

The study variables included tissue colour (recorded as either normal gingival colour or as red (inflamed)), bleeding upon palpation (recorded as either presence or absence of bleeding on palpation), and pus presence (recorded as either presence or absence of pus), were noted using the Landry, Turnbull, and Howley standardized index for every participant in every group at baseline (the day after the tooth was extracted but before the gauze piece was placed), as well as on the third and seventh day after the tooth was out. After that, these data were included to a diagnostic chart that was specifically created [25].

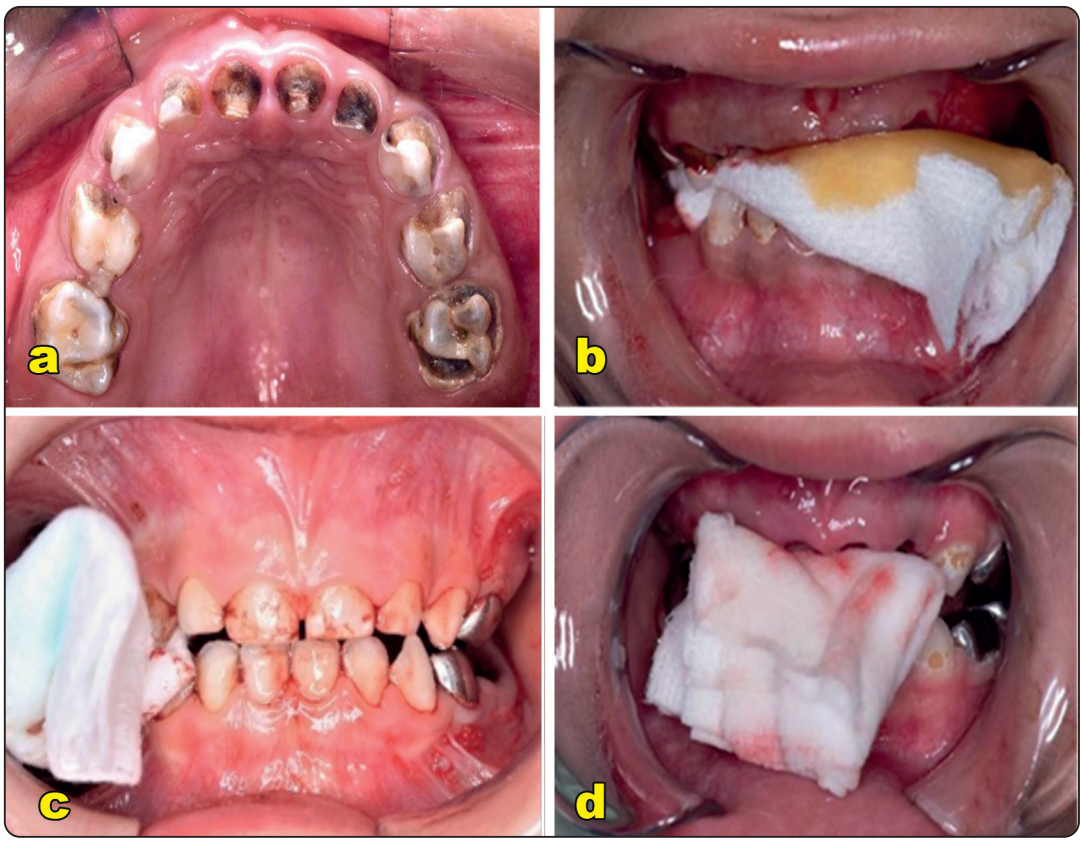

Fig. (1) (a) Preoperative photograph of badly decayed primary teeth; (b) Extraction sockets packed with a gauze soaked with MH; (c) Extraction sockets packed with a gauze soaked with HA; (d) Extraction sockets packed with a gauze soaked with NSS.

The Kolmogorov Smirnov test was used to check numerical data for consistency with the normal assumption. Non-normal data was analysed using the Kruskal Wallis test. Freidman's test was used to compare numerical variables within groups. The Chi-square test was used to compare categorical data. P values that were less than 0.05 on both sides were deemed statistically significant. All statistical analyses were performed using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS

Comparison of age using Kruskal Wallis test revealed insignificant difference among the three groups (Table 1). The chi-square test findings for gender showed no significant difference between the three groups (Table 2).

TABLE (1) Mean and standard deviation of age among the study population

Groups	Age (Mean± SD)	P-value
NSS	4.8±1.3	
MH	5.3±1.3	0.373 NS
HA	4.8±1.3	

In relation to the tissue colour, each of the extraction sockets had a red colour at baseline, while after that they displayed a normal colour on the third and the seventh days. No comparison could be done because there were no variations in the results of the three groups over the study time period; all extraction sockets for the three groups had red colour at baseline, and normal colour at the third and seventh days of the extraction (Table 3).

All patients had bleeding at the baseline. On the third day of the study, four patients (6.8%) in the saline group, five patients (5.9%) in the manuka honey group, and three patients (4.7%) in the hyaluronic acid group continued to have bleeding. By the seventh day, there were no instances of bleeding seen in any of the three groups. There was no statistically significant difference between the three groups on the third day of the study. No comparison could be done between the three groups at the baseline and on the seventh day due to the lack of variation in the results (Table 4).

In an attempt to compare t the presence of pus among the three groups over the study time points, it was found that no case had pus at any time point. No comparison could be done because there were no variations in the results of the three groups over the study time period (Table 5).

TABLE (2) Number and percentages of gender distribution among the study population

Gender	Groups			P-value
	NSS (n = 21)	MH (n = 21)	HA (n = 21)	
Male [n, (%)]	12 (57.1%)	15 (71.4%)	15 (71.4%)	0.526 NS
Female [n, (%)]	9 (42.9%)	6 (28.6%)	6 (28.6%)	

TABLE (3) Tissue color in number and percentage among the three groups at baseline and on the third and seventh days after extraction of teeth.

	Tissue color	NSS	MH	HA	P-value
Baseline	Red (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	NC
	Normal (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Day 3	Red (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NC
	Normal (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	
Day 7	Red (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NC
	Normal (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	
P-value		NC	NC	NC	

NC; Not computed.

TABLE (4) Comparison of bleeding on palpation in number and percentage between the three groups at baseline and on the third and seventh days after extraction of teeth

	Bleeding on palpation	NSS	MH	HA	P-value
Baseline	Bleeding (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	NC
	No bleeding (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Day 3	Bleeding (N, %)	4 (6.8%)	5 (5.9%)	3 (4.7%)	0.882 NS
	No bleeding (N, %)	55 (93.2%)	80 (94.1%)	61 (95.3%)	
Day 7	Bleeding (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NC
	No bleeding (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	
P-value		NC	NC	NC	

NC; Not computed. NS; non-significant.

Table (5). Presence of pus among the three groups at baseline and on the third and seventh days after extraction of teeth.

	Presence of pus	NSS	MH	HA	P-value
Baseline	Pus (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NC
	No Pus (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	
Day 3	Pus (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NC
	No Pus (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	
Day 7	Pus (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NC
	No Pus (N, %)	59 (100.0%)	85 (100.0%)	64 (100.0%)	
P-value		NC	NC	NC	

NC; Not computed.

DISCUSSION

According on how they are treated, wounds heal more quickly and alter in appearance. Nonetheless, the development of chronic wounds that do not heal might be the result of an interference with the normal healing process [15]. Because of this, this study examined how NSS and HA and MH affected the blood clot formation and soft tissue healing in kids with multiple primary teeth extraction sockets.

Because regular saline dressing improves blood circulation and acts as an anti-inflammatory, it efficiently heals infected wounds and was utilized as the control dressing in this RCT [9]. Because utilizing 0.9% to 1.8% NaCl solution three times a day for two minutes each time can aid to increase extracellular matrix formation and the migration of human gingival fibroblasts, we used NSS with a concentration of 0.9% in this RCT.

Children between the ages of two and seven were selected to take part in this RCT based on a certain inclusion criterion. The group that has GA the most commonly falls within this age range, which is why it was chosen. This is mostly due to the low cognitive and understanding abilities of children in this age range [26].

honey was particularly used as a wound dressing in this RCT because of its antibacterial qualities, which allow it to successfully treat a variety of pathogens including fungus as well as aerobic, anaerobic, gram-positive, and gram-negative bacteria [11]. Furthermore, due to the rising incidence of multidrug-resistant infections and the availability of an alternative treatment without known bacterial resistance, honey is becoming a preferred choice for treating infected wounds with antibiotic resistance [12].

Hyaluronic acid has been selected as the preferred alternative therapy for wound healing in this RCT due to its favourable effects on many types of wounds in human medicine. This is due to the fact that it has been demonstrated to be more effective than alternative therapies, especially when it comes to displaying distinct histological characteristics and noticeably reducing the healing period of wounds [16, 18, 20].

In the current RCT, participants were instructed to retain the gauze piece in the socket for 45 minutes in an effort to prevent and absorb any potential bleeding that could occur while a blood clot was building, in accordance with the methods used by Mokhtari et al [22]. Following extraction, this RCT had a follow-up period that lasted from the third to the seventh day. This was because most surgical procedures generate some edema or swelling, which typically results in difficulty opening the mouth. The edema is observed to peak one to two days following the surgery, and vanish by the end of the first week [24].

The null hypothesis of the trial is that there would be no discernible difference between HA or MH and NSS in the healing of multiple primary tooth extraction sockets in a sample of children aged two to seven. The results of this RCT showed that at three and seven days, there was no statistically significant difference between the groups that received NSS and the other two groups (MH and AH). Consequently, the null hypothesis was approved.

The improvement in in tissue colour, and absence of bleeding upon palpation, or pus formation with MH at the third and seventh day could be attributed to its antibacterial, and anti-inflammatory properties. Moreover, it aids in granulation and epithelialization, and sheds necrotic tissue [12, 13]. Because HA acts as a scavenger and gets rid of mediators like prostaglandins and metalloproteinases that encourage inflammatory activity, wound healing is much improved by HA on the third and seventh day.

The results of the study indicate that there was no statistically significant difference between the groups that received MH and HA. This might be explained by HA and MH's ability to promote granulation formation and epithelization in addition to inducing an anti-inflammatory response.

Furthermore, the little difference in the rate of wound healing between MH and HA in this RCT may be attributable to their use, since our investigation suggested that the administration of HA or MH at high concentrations may enhance their ability for wound healing [12].

CONCLUSIONS

When applied to wound sockets, wound dressings have a crucial role in reducing clinical symptoms such bleeding and inflammation, with a noticeable improvement observed after approximately a week.

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