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Periodontal healing following avulsion and replantation of teeth: a multi-centre randomized controlled trial to compare two root canal medicaments

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Abstract – *Background*: Non-setting calcium hydroxide (Ultracal XS®) is recommended by the International Association of Dental Traumatology as the initial medicament following avulsion and replantation for mature teeth. There is experimental evidence to suggest Ledermix®, placed as an alternative inter-visit dressing may improve periodontal healing. *Aim*: This study investigated, using a multi-centre randomized controlled trial, the effect of two root canal medicaments, Ledermix® and Ultracal XS®, on periodontal healing of avulsed and replanted teeth. *Material and methods*: Children were recruited if they fulfilled all inclusion criteria. Treatment followed a standardized protocol. Assessment of periodontal healing or ankylosis was made clinically and radiographically by an experienced, 'blinded', clinician at 12 months. *Results*: Over 200 patients were assessed for eligibility at five centres. Twenty-nine patients were eligible for inclusion. Final analysis involved 22 patients with 27 teeth. Ankylosis was detected in four of the 12 teeth in the Ledermix® group and nine of 15 in the Ultracal XS® group. No significant difference between medicaments was found in the proportion of teeth or patients showing periodontal healing. *Discussion*: There was no significant difference in periodontal healing between the two medicaments at either a tooth or patient level. The numbers recruited fell short of an estimated power calculation. For patients meeting the inclusion criteria and completing the trial, periodontal healing was seen in 52% of teeth at the 12-month assessment between both groups. The only factor found to significantly influence the periodontal outcome was dry time.

Avulsion is one of the most severe dento-alveolar injuries. This injury accounts for between 0.5% and 3% of dento-alveolar trauma to permanent teeth (1) but also carries one of the poorest outcomes for dento-alveolar trauma with 73–96% of replanted teeth being lost prematurely (1). The damage to the periodontal ligament at the time of injury, the condition of a tooth's subsequent storage and the interval prior to replantation, all profoundly influence prognosis (2–4). The evidence to support different treatment interventions provided by clinicians is limited. A recent Cochrane review (5) identified three randomized controlled trials that were eligible for inclusion. Two of the studies were at high risk, with the third categorized as moderate risk of bias. Thus, the evidence to support most treatment interventions as advised by different guidelines (6, 7) is based upon human case series, which are frequently retrospective in nature or based on animal studies. Consequently, there is a clear need to demonstrate the effectiveness of different interventions using study designs that are of low risk of bias and are carried out in humans. As avulsion injuries present relatively infrequently even to specialist centres (2, 3), a multi-centre design would be required. The Cochrane review (5) was unable to identify any multi-centre randomized controlled trials (m-cRCT) teeth.

Medicaments to promote periodontal healing following avulsion and replantation have been studied extensively in animal models. Topical medicaments applied to the tooth prior to replantation have the advantage of reduced systemic uptake and less reliance on pharmokinetics to ensure adequate concentrations are delivered to the socket and associated tooth (8, 9). One of the major problems with topical medicaments is the retention of medication in the socket and prevention of 'wash-out' during replantation and subsequent exudation. One possible solution is to place it inside the root canal. This space following endodontic treatment is avascular, and consequently, any medicament will remain *in-situ* to exert its effect. The root canal has the added benefit of

tubules that communicate between pulp and periodontal space. Following avulsion and replantation, the initial inflammatory response on the external root surface results in the removal of necrotic cementum, thereby opening the tubules (10). Medicaments, depending on their molecular size, can then pass from root canal to periodontal space (11). This is a good way to deliver medicament as these areas of damaged, necrotic cementum are exactly where active medicament needs to be released to influence the type of periodontal healing that occurs.

Following an avulsion injury, the pulpal tissue is severed from its neurovascular supply. For mature teeth, with an apical width of 1 mm or less, no revascularization was reported in two clinical case series (12, 13). Therefore, for teeth with a closed apex, the IADT guidelines (6) advise elective pulp extirpation to prevent the initiation and relentless progression of inflammatory resorption.

Current guidelines (6) advocate that pulp extirpation and disinfection take place 7–10 days following avulsion and replantation for closed apex teeth. The reason for this is that the recommended intracanal medicament, non-setting calcium hydroxide (NSCaOH), showed significant detrimental outcomes to periodontal healing in comparison with a more inert gutta percha root filling (14, 15) if placed earlier. Andreasen et al. (14) suggested waiting for 2 weeks. This they felt gave time for repair of the cementum but the use of NSCaOH at this point would prevent inflammatory resorption before it became established. The suggestion was validated by the work of Thong et al., (16). Their work showed the elimination of inflammatory resorption with an increase in surface resorption and to a lesser extent ankylosis, for teeth extirpated and dressed with NSCaOH at day 11. This small increase in ankylosis appeared acceptable for the elimination of inflammatory resorption related to the necrotic and infected pulp.

One intervention that has demonstrated positive benefits in a number of animal studies (16–20) over other medicaments is the use of Ledermix placed within the root canal shortly after the replantation of an avulsed tooth. Ledermix® is a water soluble paste containing 1% triamcinolone, a corticosteroid, and 3% demeclocycline, a tetracycline. To date, there has been one case series of 27 avulsed and replanted teeth that were treated with pulp extirpation and dressing with Ledermix® at day 7–10 (21). This study used multiple medicaments, and therefore, it is not possible to identify the beneficial effect of each.

One of the main effects of Ledermix®, in experimental studies (16–20), was the reduction in inflammatory resorption compared with the control medicaments. The explanation suggested for this effect was the presence of the corticosteroid in Ledermix® and its ability to dampen the inflammatory response during the healing of the periodontal apparatus. Chen et al. (18) investigated the effect of each of the constituents, triamcinolone and demeclocycline, at the concentrations present in Ledermix®. They found that triamcinolone on its own was almost as effective as Ledermix® and was significantly more effective than demeclocycline on its own. Consequently, it appeared, from this single experimental study, that the main active ingredient of Ledermix® for avulsed teeth was the steroid, triamcinolone.

Therefore, the aim of our study was to investigate using a m-cRCT design, the effect of two root canal medicaments (Ledermix® and a NSCaOH paste called Ultracal XS®) on periodontal healing of avulsed and replanted teeth.

Materials and method

Before the study could commence, a number of research approvals were secured, including ethical approval (04/Q1205/145), MHRA (CTA 16767/0203/001-0001, Eudract Number: 2004-005188-12) and registration of the trial with ISRCTN (58467151). Informed consent was obtained from all patients recruited to the study. The description of the methodology and results will follow CONSORT guidelines (22) for the transparent reporting of the randomized controlled trial.

Five specialist paediatric dentistry centres participated in the study. These were Eastman Dental Institute, Glasgow Dental Hospital, Leeds Dental Institute, Newcastle Dental Hospital and Royal Belfast Hospital for Sick Children.

Inclusion criteria

To be eligible for inclusion in the trial, the child had to satisfy the following criteria:

1 To have suffered an avulsion of a permanent tooth or teeth.
2 To be aged < 16 years old.
3 Have a completed root length with or without an open apex.
4 A maximum of 20 min dry extra-alveolar storage time prior to replantation.
5 A maximum of 60 min extra-alveolar time, prior to replantation, where the tooth was kept in milk or another appropriate storage media. For example, these scenarios were acceptable: 50 min in milk, 5 min dry time or 20 min dry and 40 min in milk.
6 No previous endodontic treatment.

Children were accepted into the study in two ways: acute presentation (Fig. 1a), where all the treatment (replantation, splinting and endodontics) was carried out in the specialist unit or delayed presentation (Fig. 1b), where emergency treatment (replantation and splinting) was provided 'outside' the specialist unit. Patients were only eligible via the delayed presentation route, if all the required details could be obtained of the emergency treatment provided by the health care professional, parent or bystander. In addition, they must have presented at the specialist centre within 10 days of the injury being sustained.

Interventions, randomization and allocation concealment

All children fulfilling these criteria were invited to enrol. The recruitment was carried out by the senior clinician assessing the patient. Following informed consent, the patients were randomly allocated to one of two groups.

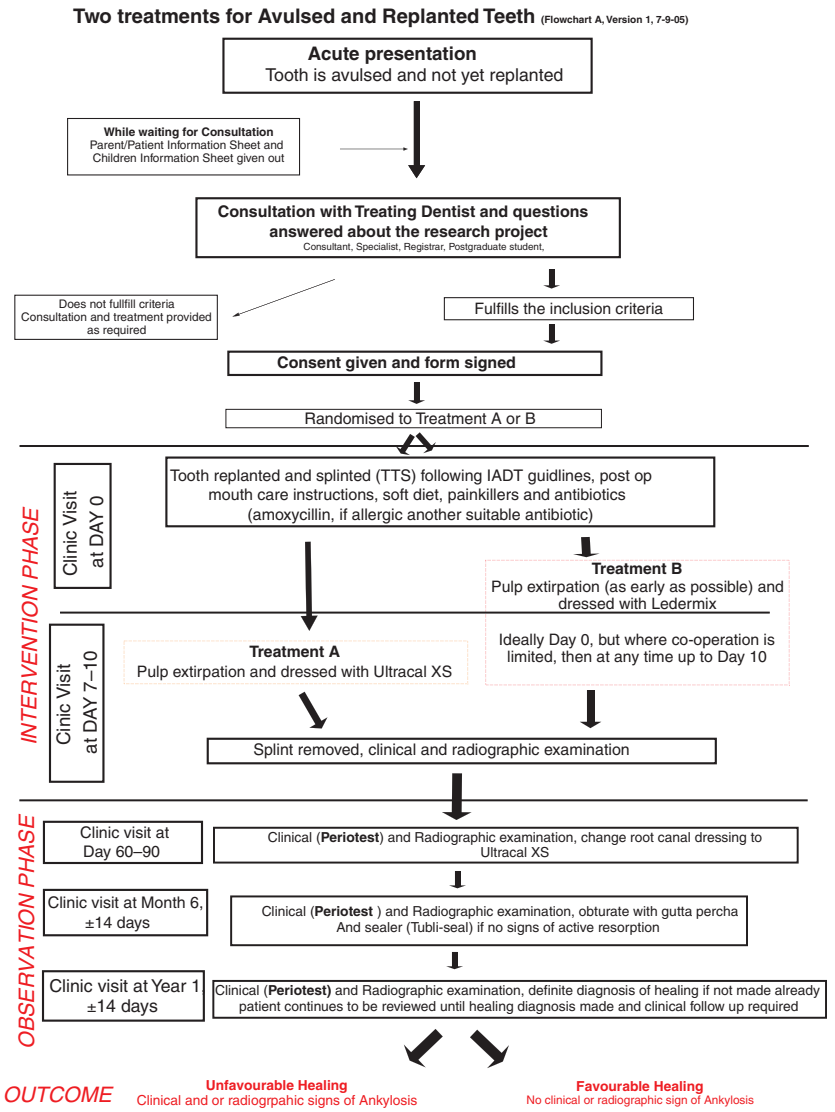

Fig. 1. (a) The acute treatment flowchart for patients recruited to a m-cRCT following tooth avulsion and replantation, where all treatment was provided by the specialist centre. (b) The delayed treatment flowchart for patients recruited to a m-cRCT following tooth avulsion and replantation, where emergency care was provided outside the specialist centre.

1 Replantation followed by pulp extirpation (root canal treatment) and intra-canal dressing with Ledermix® as soon as possible (within the first 10 days) or
2 Replantation followed by pulp extirpation (root canal treatment) at day 7–10 and intra-canal dressing with UltraCal XS® (Optident, UK), a non-setting calcium hydroxide paste.

To ensure uniformity of application, a standard syringe and applicator, Navitip, were used for both medicaments to facilitate the filling of the entire root canal.

Patients were assessed for eligibility, recruited and consented, and only at this point was a randomization envelope opened. The randomization process was carried out by the Biostatistics Department, University of Leeds. A block randomization method was used to generate a randomization sequence for each of the centres. Randomization codes were sealed within opaque envelopes, by the department secretary, with a sequential number placed on the outside. The randomization envelopes were then grouped into numerical order and placed within the avulsion treatment box that was located in a secure area of each clinic.

Standardization of replantation technique and publicity to increase recruitment

Where possible, the replantation technique was standardized and followed IADT guidelines (23). The author tried to ensure uniformity of replantation and splinting technique by being involved in multiple teaching courses to dentists within the Yorkshire region and local Accident and Emergency departments and Oral and Maxillofacial staff. Education of the same personnel was provided in other units by the primary author, the local principal investigator or their staff. This publicity, including the advertisement flyers, aimed to increase the number of children recruited, to heighten the awareness of the trial amongst local dentists and medical staff and to improve the acute treatment provided for patients.

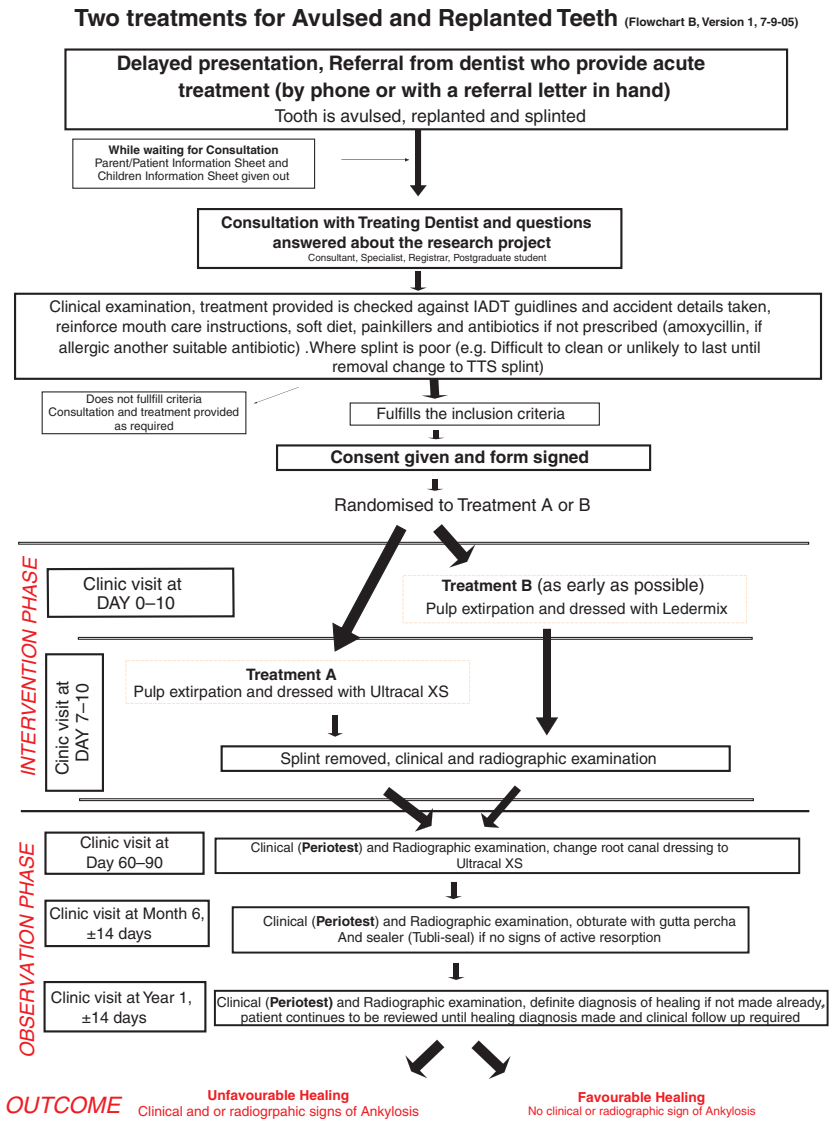

Fig. 1.(Continued)

Acute treatment followed the IADT guidelines (23) except for the prescription of amoxycillin rather than doxycycline. Where the patient was allergic to penicillin, another suitable antibiotic was prescribed. Splinting was standardized to the use of one specific splint (TTS, Medartis, Switzerland) where the patient presented directly to a specialist centre. A TTS splint was used for delayed presentation cases, where the original splint was unsatisfactory.

Standardization of endodontic technique and assessment at review visits

To be included in the clinical trial, all endodontic treatment had to be carried out by the specialist centre. The author visited each unit and provided training, including didactic lectures, to clinicians involved, to ensure the protocol was followed (Fig. 1a,b). At the day 60–90 appointment, the root canal medicament in both Ledermix® and UltraCal XS® group was flushed away using a standard debridement technique with copious sodium hypochlorite and gentle hand instrumentation. UltraCal XS® was then placed within the root canal of both groups until the 6 month appointment. At this appointment, where there was no sign of infection or active resorption, cold lateral condensation with gutta percha and Tubliseal® was used for definitive obturation.

At each visit for endodontic treatment, the avulsed tooth or teeth were assessed for signs of favourable or unfavourable periodontal healing. These assessments coincided with the day 60–90 and 6-month treatment appointments and the 12-month review appointment. Clinical assessment included examinations of colour, signs of infection, periodontal support, signs of infra-occlusion, percussion note and tooth mobility. Radiographic evaluations were standardized to a long-cone periapical centred over the avulsed tooth. Data collection sheets were developed for each of the initial

and review appointments for this information to be recorded.

Assessment of periodontal outcome and blinding

Periodontal healing (regeneration of periodontal ligament) was a diagnosis made by the exclusion of healing by ankylosis. At 12 months, where ankylosis could not be detected either clinically or radiographically, the periodontal healing was assumed to have occurred. Ankylosis was detected by specific characteristics clinically and radiographically frequently in comparison with an non-avulsed adjacent tooth (24, 25). These included the followings:

1. a high percussion note (tested by tapping the tooth in a vertical and horizontal direction with the handle of a mirror),
2. reduced mobility (tested by moving a tooth in a labiolingual direction with finger pressure),
3. progressive infra-occlusion,
4. radiographically, the disappearance of the normal periodontal space with replacement by bone in association with an uneven contour of the root and, or the loss of lamina dura.

A positive recording of ankylosis either clinically or radiographically resulted in the tooth being classified as ankylosed. Although the treating clinician was aware of the group the patient was allocated to, at 12 months or sooner, assessment of periodontal healing was carried out by a second senior paediatric dentist (who had not provided treatment). They were blinded to the patient's randomization and carried out their assessment without conferring with the original treating dentist. Only following this were diagnoses compared. Any disagreement between the two examiners led to an outcome of ankylosis being recorded.

Statistical methods and power calculation

All data were entered onto SPSS spreadsheet (Statistical Package for the Social Sciences – version 16.1; SPSS Inc, Chicago, IL, USA) for data analysis. Continuous data were assessed for whether it was normally distributed using a Shapiro–Wilk test. Appropriate descriptive analysis and simple statistical tests were used to examine the effect of the two medicaments on the periodontal outcome seen.

The effects of the two root canal medicaments used in this trial had been investigated by Bryson *et al*. (17) using a dog model. In this study, teeth were extracted and exposed to 60 min dry time prior to replantation. During this period, the pulp was extirpated and either NSCaOH or Ledermix® placed as an inter-visit root canal dressing. A power calculation based on an $\alpha = 0.05$ and $1 - \beta = 0.90$ estimated the need for 19 patients per group. Minimal drop out of patients was expected before the 12 month assessment of periodontal outcome.

To investigate the effect of other factors that may influence the periodontal outcome, teeth from both the Ledermix® and NSCaOH groups were combined and then divided up dependent on whether they healed by ankylosis or periodontal healing.

Results

The flow of participants in the study is reported in Fig. 2. Over 200 children were assessed for eligibility at the five centres over the recruitment period (July 05 – December 08, 42 months). All had suffered an avulsion injury to one or more permanent teeth. Of these, only 29 met the inclusion criteria. One patient declined, and the remaining 28 consented and were randomized. Subsequently, five were found to be ineligible, not meeting inclusion criteria. This left 23 patients who were recruited. One patient declined follow up. This left a total of 10 patients (12 teeth) in the Ledermix® group and 12 patients (15 teeth) in the Ultracal XS® group. The location of patients recruited and available for analysis was three from Centre 1, one from Centres 2 and 3, 17 from Centre 4 and none from Centre 5. Over three-quarters of patients were recruited by Centre 4, where the primary author works. Only one patient presented to a specialist centre for all treatment (acute presentation flowchart, Fig. 1a); the other 21 had emergency treatment provided by a third party prior to being referred for treatment (delayed presentation flowchart, Fig. 1b).

When the two groups were compared, there was no significant difference in any of the parameters previously reported to influence periodontal outcome. The various baseline parameters of the two groups are shown in Table 1. As a result of the protocol, there was a significant difference (Mann–Whitney *U*-test, $P = 0.02$) between the two groups for the timing of pulp extirpation and placement of medicament.

The results were analyzed at both tooth and patient level. This was carried out as one patient in the Ultracal XS® group injured two teeth that healed in different ways (one by periodontal healing and the other by ankylosis). When the results were analyzed at tooth level, Table 2, there was no significant difference between the two medicaments.

At a patient level, analysis was carried out for the worst and best scenario for the two groups. The one patient lost to follow up in the Ledermix® group was included. For both scenarios, one tooth per patient was taken. Two of the patients, suffering injuries to more than one tooth, healed with the same periodontal outcome. With the third patient (two teeth) in the Ultracal XS® group, one tooth healed by periodontal healing and the other by ankylosis. The best and worst scenarios are presented in Table 3, neither analysis showed a significant difference between groups.

One variable from those listed in Table 1 was found to significantly influence the type of periodontal outcome when both the Ledermix® and Ultracal XS® groups were combined at a tooth level and analyzed. This was dry storage time, prior to replantation (Mann–Whitney *U*-test, $P = 0.006$). The median and interquartile range was 5 min and five for the periodontal healing group compared with 10 min and 12 for the ankylosis group.

There were no suspected unexpected severe adverse reactions or severe adverse events from either medicament during the trial. The only adverse effect of the medicaments was discolouration. This outcome is reported in a separate article (26).

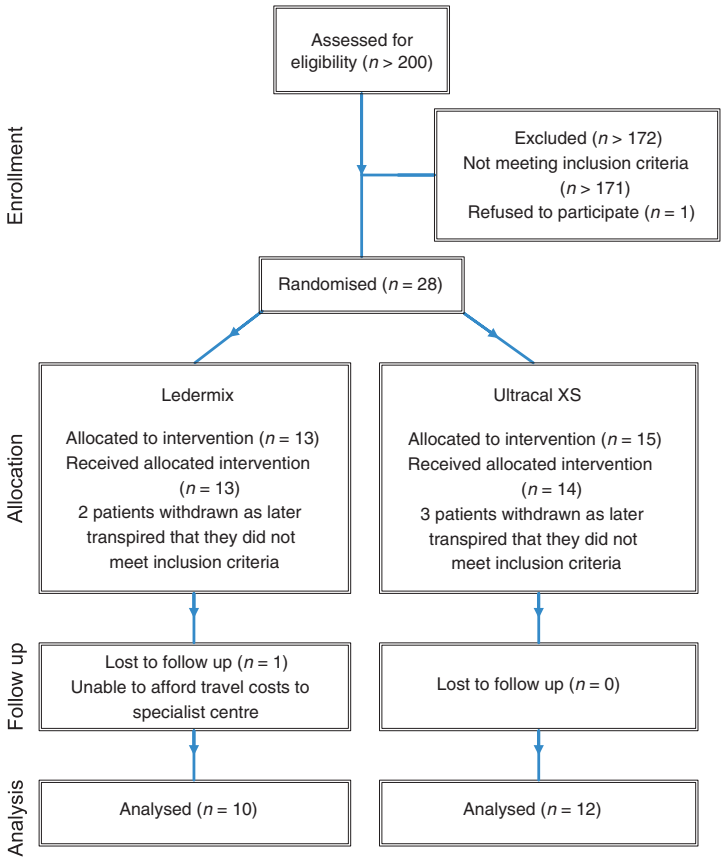

Fig. 2. The flow of participants assessed for eligibility, enrolled, allocated, lost to follow up and analyzed for a m-cRCT to compare two root canal medicaments for avulsed and replanted teeth.

Discussion

This study is the first to use a multi-centre randomized controlled trial design (m-cRCT) to investigate the efficacy of two interventions, following avulsion and replantation, of a permanent anterior tooth. The randomization technique used ensured that every patient had an equal chance of being randomized to either treatment group. A block randomization design was used to ensure that even with small numbers, a similar group size would be achieved. The block size was unknown to any clinician involved in the study, and the multi-centre design ensured clinicians had no influence over randomization in other centres. This, together with the use of sealed, opaque randomization envelopes ensured clinicians had no way of predicting what the next randomization code would be, prior to recruiting the next patient.

A detailed protocol for the endodontic treatment was required because the IADT guidelines (23) were not as prescriptive as was required. From histological studies (27–29), it was felt that the initial medicament should remain within the root canal while the periodontal ligament and cementum were healing. This has been estimated to be completed by 8 weeks (29, 30) for monkeys, and consequently, this was the minimum duration of the first medicament. This was achieved with a mean duration of placement of 70 days. There was no significant difference in the duration of application between the medicaments. Sodium hypochlorite was the standard root canal irrigant for disinfection. There were concerns that Ledermix when used as the only inter-visit canal medicament would not kill all bacteria within the root canal, and therefore, a period of NSCaOH was required to ensure disinfection. As noted by Spangberg and Haapasalo, NSCaOH is 'the intra-canal dressing of choice in contemporary endodontic practice' (31). Therefore, a further period of time with NSCaOH *in-situ* was required. As reported by Nguyen et al. (32), there is a considerable cost for the family unit in time, and therefore, it was felt important to minimize the number of appointments required by combining periodontal healing assessment and treatment provision. Therefore, the duration of placement of NSCaOH was for a further 3 months. At the time that the trial was designed and started, the concerns over the long-term use of NSCaOH were still in their infancy (33) and the effectiveness of Ledermix® as the only inter-visit root canal medicament to facilitate disinfection were still to be reported (34).

Patient recruitment

Over 200 patients who were under 16 years old and had avulsed one or more of their front teeth were assessed for eligibility. Unfortunately, only 10% of patients fulfilled inclusion criteria. These were designed to ensure that the periodontal ligament had a chance of periodontal healing. There was little point in recruiting patients to the trial where these chances were minimal. The need to allow patients to access the trial both through acute and delayed pathways was essential to maximize recruitment. Only one patient was recruited through the acute

Table 1. The distribution of baseline prognostic variables for 22 patients (27 teeth) seen in a m-cRCT for children suffering avulsion injuries and replantation

	Ledermix® 10 pts (12 teeth)	Ultracal XS® 12pts (15 teeth)	Statistical tests
Mean age in years (SD)	12.8 years (±2.2)	12.0 years (±1.9)	Independent *t*-test (NS, CI -13.1 to 31.3)
Gender	5 Males	8 Males	Fisher's exact test (NS)
Tooth type (all maxillary teeth)	9 central incisors 1 lateral incisor 2 canines	15 central incisors	
Apical status	2 convergent (complete root length open apex) 10 complete	4 convergent (complete root length open apex) 11 complete	Fisher's exact test (NS)
Antibiotics	9 patients received either penicillinbased (7) or erythromycin or metronidazole	11 of 12 patients received at least one antibiotic all penicillin based with 2 patients receiving a second antibiotic of metronidazole or clindamycin	
Extra-alveolar time (mins), median, (inter quartile range; 25th and 75th centile)	40 (32; 27.5, 60)	55 (30; 30, 60)	Mann–Whitney *U*-test (NS)
Extra-alveolar dry time (mins), median, (inter quartile range; 25th and 75th centile)	10 (8; 5, 12.5)	5 (5; 5, 10)	Mann–Whitney *U*-test (NS)
Storage medium	8 patients (8 teeth) milk 1 patient (3 teeth) saliva 1 patient no storage medium	11 patients (14 teeth) milk 1 patient (1 tooth) saliva	
Contamination	1	4 (5 teeth) were contaminated with up to a third of root surface	Fisher's exact test (NS)
Washing prior to replantation (saline or tap water)	3 (3 teeth)	6 (8 teeth)	Fisher's exact test (NS)
Time to extirpation (days), median, (inter quartile range; 25th and 75th centile)	7 (1; 6.3, 7.3)	9 (3; 7, 10)	Mann–Whitney *U*-test $P = 0.02$
Duration of splinting (days), median, (inter quartile range; 25th and 75th centile)	7 (5; 6, 10.8)	9 (2; 7.5, 10)	Mann–Whitney *U*-test (NS)
Duration of first inter canal dressing (days), mean (±standard deviation)	70 (12.2)	74 (21.4)	Independent *t*-test NS (CI −20.6 to 11.3)

Table 2. The periodontal healing for 27 teeth that suffered an avulsion injury and replantation. These teeth were part of a m-cRCT and were randomized to one of two inter-visit root canal medicaments

	Ledermix® (12 teeth)	Ultracal XS® (15 teeth)
Periodontal healing	8	6
Ankylosis	4	9

Fisher's exact test ($P = 0.17$).

pathway. An important issue that becomes obvious from this 'failure to recruit more patients' stems from the poor levels of access to emergency dental care and treatment, the failure of accident and emergency departments to prioritize these injuries and public ignorance of the appropriate treatments for an avulsed tooth.

Recruitment difficulties have resulted in delays of 1–6 months in over half the clinical trials in the United States (35), and this failure to recruit sufficient patients into a trial is part of a common phenomenon. There was an uneven level of recruitment from the five centres involved in the trial. Although the host centre is expected to recruit the most patients, other centres have struggled to recruit any. On discussion with each centre, a number of barriers were identified. These included: many patients being referred outside the 10-day period, the maturity of the root canal needed, patients' lack of access to emergency care and the patchy standard of this care with teeth rarely replanted within 60 min and the lack of knowledge of the general public. Unfortunately, many of these barriers were outside the control of those involved in the trial. This was despite significant efforts made to publicize the trial in the five regions. The primary author over the recruitment period gave over 40 lectures on the subject, and adverts were sent out to all dentists in local regions on multiple occasions.

Comparability of groups

The effect of the randomization process showed that there was no significant difference in the distribution of variables that have been reported to influence periodontal outcomes between the two groups. The duration of splinting was relatively short at 7–10 days. For three patients, the avulsed tooth showed excessive mobility at their day 7–10 appointment, and a further short period of splinting was instigated. For the majority of teeth, this short splinting period allowed sufficient time for gingival and periodontal attachment to start. Although it has been shown in a primate model to take up to 14 days for

Table 3. A patient-based assessment of periodontal outcome for Ledermix® and Ultracal XS® groups showing the best and worst case scenarios for each medicament. This includes the one patient in the Ledermix® group that was lost to follow up and for the Ultracal XS® group taking the one patient who avulsed two teeth and had two different healing outcomes. In the best case Ledermix® scenario the patient lost to follow up was deemed to have healed by periodontal healing and ankylosed tooth was selected for the Ultracal XS® patient. For the best case Ultracal XS® scenario the opposite choices were made

	Ledermix® (11 patients) best case scenario	Ultracal XS® (12 patients) worst case scenario	Ledermix® (11 patients) worst case scenario	Ultracal XS® (12 patients) best case scenario
	Fisher's exact test ($P = 0.41$)		Fisher's exact test ($P = 0.83$)	
Periodontal healing	7	5	6	6
Ankylosis	4	7	5	6

the periodontal ligament to regain 60% of its original strength, no untoward effects were noted (36). Certainly, early splint removal allowed the patient better access for cleaning with the possible reduction of bacterial ingress into the injured area.

The time to pulp extirpation was significantly different between the two groups. For the Ultracal XS® group, there was a 4 day window for pulp extirpation, between day 7 and 10, and all other patients were successfully treated in this period. For the Ledermix® group, this was to be placed between day 0 and 10, with the aim of placing the medicament as quickly as possible. The time to extirpation was still longer than expected as the most beneficial effect of Ledermix® appears from experimental models to be following replantation at day 0 (17, 18, 20). The time to extirpation therefore reflects that, for almost all patients, the acute treatment was not provided at specialist centres. Frequently swelling and tenderness around the injured teeth was worse over following days, and therefore, it was very difficult to justify a traumatic visit, when around day 7 treatment can be provided in a more comfortable manner often without local anaesthetic.

Periodontal outcome

Twenty-two patients completed the trial. There was no significant difference in periodontal outcome between the two groups at a tooth level. Although many studies have investigated the outcome of treatment interventions on a tooth basis, this is rarely a valid statistical method. This is because each tooth is not an individual variable unless they each come from a different patient. Each tooth evaluated from the same patient is subject to the same host response, oral micro-flora, pharmacokinetics and other variables and are therefore not truly independent. If the assumption was made that all teeth were independent and an appropriate single level statistic was used, there is an increased risk of a type I error occurring. If the opposite approach is taken as a summary measure, for example using only one avulsed tooth per patient, this would lead to a greater potential for a type II error. The analysis carried out in Tables 2 and 3 allows the reader to assess the best and worst case scenario with respect to periodontal healing for the two medicaments at a tooth and patient level.

This study has shown no difference between the two medicaments. Two conclusions can be drawn: first, there is no difference in effect on periodontal healing between the two materials or second, a type II error has occurred because of the insufficient recruitment of patients to the trial. The power calculation estimated the need for a minimum of 19 patients per group, and this was probably an underestimation for two reasons. First, NSCaOH was placed on Day 0 in this experiment that differs from the recommendations of the IADT guidelines (23). This certainly exacerbated the inflammatory effect of NSCaOH and therefore contributed to the high proportion of unfavourable healing seen in this group. Second, in this study, although it was planned to extirpate the pulp and dress with Ledermix® as soon after replantation as possible, this rarely occurred before day 7 and may have reduced the benefit of Ledermix® application.

Trial retention of patients was excellent with only 10% of patients failing to attend their 12-month review. One patient attended their day 60–90 review where ankylosis was already detected, so the loss of this patient did not affect the results for the periodontal outcome. It has been reported that up to 25% of patients failed to complete clinical trials in USA (35). This retention rate showed that once patients were identified, the close interaction with the staff involved and the clear explanation of the number of visits required helped families to understand the mechanics of the trial and the commitment required.

Although patients followed a strict protocol once recruited to the trial, as soon as ankylosis was detected, adherence to this only continued if this was in the best interest of the patient. One tooth in the Ultracal XS® group was extracted 16 months after their avulsion and replantation. This was because of the persistent symptomatic infection of the root canal despite attempted retreatment. This tooth was ankylosed but the cause was not identified. Persistent infection, given time, leads to extensive bone loss that will only hinder subsequent restorative options. Three other avulsed and replanted teeth, all exhibiting ankylosis, were extracted as part of a premolar transplantation programme. Despite the care taken at 12 months to identify the periodontal outcome, worries persist that ankylosis may take longer to appear as a result of the careful adherence to the IADT guidelines (23) and the anti inflammatory effect of Ledermix®. Therefore, all patients with favourable healing are being followed up to ascertain if the diagnosis made at 12 months was premature. Seven of these patients have begun or are close to starting orthodontic treatment that will provide further evidence of the periodontal outcome.

Although some authors (37) have argued that it is not possible to run m-cRCT to assess treatment intervention following dento-alveolar trauma, this trial has demonstrated it is possible. Better feasibility assessment and external grant funding to allow dedicated time to be devoted at each centre would both have helped in ensuring the trial met its power calculation.

Periodontal healing of both groups combined

When the periodontal outcomes for both groups are combined, this trial reports a periodontal healing rate at 12 months of 52%. The m-cRCT reported here has shown that the pessimistic outcome predicted for 'all teeth not replanted within five minutes' is unfounded (38). This level of periodontal healing exceeds almost all previous reports for teeth suffering an avulsion and replantation (1). The only study that reports a similar level of periodontal healing (58%) at 12 months is Chappuis and von Arx (21). Therefore, the strict inclusion criteria of <60 min total time when stored in an appropriate medium e.g. milk prior to replantation may have been excessive. Teeth when stored appropriately with minimal dry time may still have a chance of periodontal healing at time points >60 min. A longer time period with respect to this inclusion criterion may have made a significant difference in eligibility numbers.

Only one variable was found significantly to influence the type of periodontal outcome when the periodontal outcome of both groups was combined at a tooth level. This was dry storage time, prior to replantation. This is in agreement with a number of other human case series (2, 3, 21) and confirms the pre-eminence of this prognostic factor in determining the type of periodontal outcome. A longer time period for this inclusion criterion to increase patient recruitment would appear counterproductive as it would result in little or no effect in increasing the number of teeth demonstrating periodontal healing. It is interesting to note that the dry time inclusion criteria differed in this study from current guidelines (6), e.g. 20 vs 60 min.

Conclusions

There was no difference in periodontal healing between the two medicaments. No conclusive opinion between the medicaments can be expressed confidently as the recruitment of subjects into the trial fell short of what had been determined by the initial power calculation. For those patients who met the inclusion criteria and completed the trial, periodontal healing was seen in 52% of teeth at 12 months. Dry storage time prior to replantation was the only factor significantly related to periodontal outcome.

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