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An evidence-based assessment of the clinical guidelines for replanted avulsed teeth. Part I: timing of pulp extirpation

Susan Elisabeth Hinckfuss, Louise Brearley Messer

Paediatric Dentistry, School of Dental Science, University of Melbourne, Melbourne, Australia

Correspondence to: Professor Louise Brearley Messer, Emeritus Professor, School of Dental Science, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, 720 Swanston Street, Victoria, 3010, Australia Tel.: +61 3 9341 1473 Fax: +61 3 9341 1595 e-mail: ljbm@unimelb.edu.au Accepted 21 May, 2008 Abstract – Background: Clinical guidelines for the management of avulsed teeth recommend pulp extirpation (PE) within 10 to 14 days of replantation. The principles of evidence-based dentistry can be used to assess whether this is the best approach based on currently-available evidence. The objective of this study was to use the principles of evidence-based dentistry to answer the PICO Question: (P) For a replanted avulsed permanent tooth, (I) is early PE within 10 to 14 days of replantation, (C) compared with delayed pulp extirpation, (O) associated with an increased likelihood of successful periodontal healing after tooth replantation? Materials and methods: A literature search was performed across four internet databases for relevant citations (n = 38400). Limiting citations to those in English and removing duplicates produced a set of titles (n = 14729) which were sieved. Relevant titles were selected for abstract assessment (n = 628), and then papers were selected for examination (n = 84). Inclusion criteria were applied and six papers (total 236 teeth) met the final criteria for meta-analysis. Results: Meta-analyses found a statistically significant association between PE performed after 14 days and the development of inflammatory resorption [common odds ratio (COR) = 0.37, standard error (se) = 0.50, 95% confidence interval (CI): 0.14-0.98]. Pulp extirpation within 10 days of replantation was not significantly associated with a decreased likelihood of developing inflammatory resorption. There were no statistically significant differences in PE times for functional healing, acceptable healing without progressive resorption, or the development of replacement resorption. Conclusion: There is clinical evidence for an association between PE performed after 14 days following replantation and the development of inflammatory resorption. This investigation supports the current clinical guidelines for PE within 10 to 14 days of replantation.

Timing of pulp extirpation (PE) of a replanted avulsed tooth depends on tooth maturity and, if immature, the extraoral time. Unless the tooth is immature and has been replanted almost immediately, PE is generally recommended within 7 to 14 days (1–8); 7 to 10 days (1, 3, 6, 9); or 10 days post-replantation (2). Calcium hydroxide (CH) is recommended generally as the intracanal medicament (3), which may be preceded by an antibacterial intracanal dressing placed for 1 to 2 weeks (2). Extraoral endodontic treatment is contraindicated as this extends extraoral time, further damaging periodontal ligament cells (2), although this has been recommended for teeth with extended extraoral dry times (1, 6, 10).

The frequency of revascularization of a replanted immature incisor has been reported as 18% (of 72 teeth) (11) and 34% (of 94 teeth) (12); this is influenced by extraoral time. Maintaining pulp vitality in immature teeth is unlikely if the extraoral time exceeds 45 min; extended extraoral dry time beyond 45 min was associated with incomplete and arrested root formation (13). Clinical guidelines recommend avoiding PE of immature teeth unless obvious signs of non-revascularization are present (3, 6), or the extraoral period is brief (time unspecified) (2). Elective PE for immature teeth with an extraoral time exceeding 60 min has been recommended (4, 6). Extirpation may be delayed in immature teeth if there is a chance that pulp vitality has been maintained; root growth may then continue but delayed extirpation requires careful monitoring (2, 3).

The optimal time for PE after replantation has not been established from human clinical studies. Timing of PE may influence the development of inflammatory resorption (14–17), which may be prevented by early PE (2). Inflammatory resorption in replanted monkey teeth markedly increased when PE was delayed from 2 to 4 weeks (18), prompting the recommendation that endodontic treatment should be commenced 2 weeks after replantation (18). Adequate endodontic treatment has been shown to prevent or eliminate inflammatory resorption in replanted monkey teeth (15, 16, 19–21). Pulp removal immediately before replantation can reduce inflammatory resorption (14), but may be associated with increased development of replacement resorption (22).

Clinical findings indicate PE timing has no significant effect on replantation success, development of root resorption, or rate of root resorption (23–26). Although not influencing the rate of resorption, a higher frequency of inflammatory resorption was found when PE was delayed beyond 3 weeks (17, 23). For teeth replanted within 15 min, late endodontic therapy tended to increase the rate of resorption, although the difference was not statistically significant (27). These findings suggest that PE should be performed within the first 3 weeks to prevent development of inflammatory resorption.

Calcium hydroxide is a suitable intracanal medicament because of its antibacterial properties and ability to dissolve necrotic tissue (21, 28). Hard tissue resorption seen with inflammatory resorption occurs in acidic environments (29). At high pH (2.9), CH can neutralize acid products from osteoclasts, inhibiting tooth root mineral dissolution (29), and promoting necrosis of resorptive cells at inflammation sites (30). Intracanal placement of CH increases the pH levels in tubular dentine in resorbing areas (29). Animal experimental models and human clinical studies have shown that CH placement prevents or controls inflammatory resorption (30-33), and in immature teeth with open apices, CH assists apical barrier formation (26, 34-36). Recently, mineral trioxide aggregate has been used to obturate immature avulsed incisors with open apices (37).

Although opinions vary on how long a CH dressing should remain prior to gutta percha obturation, 6–12 months is recommended generally or until the entire lamina dura is apparent radiographically (2, 3). Current clinical guidelines suggest CH placement should be delayed for at least 1 week after replantation (2), because of a possible ankylosis and replacement resorption in the teeth treated immediately with CH (21, 32). However, replacement resorption is expected after an extended extraoral dry time, so the development of ankylosis and replacement resorption may not be an effect of CH (21, 32).

The medicament Ledermix[®] (Lederle Pharmaceuticals, Wolfratshausen, Germany) has been proposed following PE (4). The anti-inflammatory (corticosteroid) and antibiotic (tetracycline) actions may be advantageous (38, 39) and Ledermix[®] may decrease root resorption by directly inhibiting resorptive cells (40). To date, no human clinical studies have compared the effectiveness of Ledermix[®] and CH as intracanal medicaments.

This paper is the first in a two-paper series using the principles of evidence-based dentistry to assess whether the clinical guidelines for managing replanted permanent avulsed teeth (2, 3, 6–8) reflect the best approaches according to currently-available evidence. This study assessed the evidence for timing of PE as recommended in the clinical guidelines to determine if early PE within 10 or 14 days of replantation is associated with an increased likelihood of a successful periodontal healing outcome.

Materials and methods

The PICO question

The research question was expressed as a PICO Question: (P) for a replanted avulsed permanent tooth, (I) is early PE within 10 to 14 days of replantation, (C) compared with delayed pulp extirpation, (O) associated with an increased likelihood of successful periodontal healing after tooth replantation?

Searching the literature

The evidence-based assessment process has been described previously (41). A search was performed (April 2004) across four databases, Ovid Medline (42), Cochrane Library (43), PubMed (44) and Web of Science (45), for citations relevant to the PICO Question resulting in 38 400 citations (Table 1). Limiting to articles written in English and removing duplicates reduced the list to 14 729 citations.

Limitation criteria

Inclusion/exclusion criteria were applied in examining titles of papers, retaining human studies and investigations of permanent anterior teeth (Table 1). Excluded were animal or laboratory studies, studies on primary or permanent posterior teeth, reviews, position papers, letters, editorials and meeting abstracts. This sieve retained 628 papers with abstracts that were searched via libraries and databases, re-applying the criteria and adding more exclusions (intentional extraction, transplantion, luxations). Abstracts addressing *exarticulation* and *avulsion* were retained.

Developing an evidence hierarchy

Evidence categories were assigned to papers based on the abstracts and ranked. For papers without abstracts, the *introduction* and *materials and methods* sections were read to determine relevance and assign a category. Examining titles and abstracts of the 628 papers found that 231 were irrelevant to the PICO Question, 129 were case reports, and 84 papers (66 clinical studies, 18 case series) were retained (Table 1).

Appraisal and ranking of evidence

Full texts of the 84 papers were examined. Of these, 49 papers were irrelevant (one position paper, four case series, 10 case reports, five prevalence studies, 18 on trauma but not avulsion, one on risk factors, one on history taking for avulsed teeth, one on revascularization, one on orthodontic management of avulsed teeth, one on treatment of ankylosis, six on intentional extraction/transplantation), three papers were grey literature and 32 papers remained. Data were extracted from the 32 papers and each study was appraised critically using forms adapted from checklists (46–49).

Excluded then were 28 papers describing clinical studies as follows: four papers describing a single study

Sequence of steps	Procedure	Limitation (inclusion) criteria applied	Results of search and sieve (no. papers)
 Initial search (Ovid Medline, PubMed, Cochrane Library, Web of Science) 	Keywords Boolean operators	None	38 400
2. Initial removal of duplicate citations	Keywords Boolean operators	Written in English No duplicate citations across database results	23 608
3. Development of single set of citations	Search strings keywords Boolean operators	No duplicate citations in database results	14 729
4. Preliminary sieve	Paper titles examined	Human studies Actual studies Permanent anterior teeth Relevant to PICO question	628
5. Secondary sieve	Abstracts examined	Above criteria reapplied Clinical studies and case series	84
6. Appraisal and ranking of evidence	Papers examined	Relevant prospective and retrospective clinical studies	32
7. Final assessment for meta-analysis	Data extraction and critical appraisal	Early and late pulp extirpation in same study Periodontal healing outcomes described in relation to pulp extirpation timing Replantation conforms to current clinical guidelines Teeth representative of typical avulsed tooth	6

Table 1. Sequence of steps, procedures and results of evidence-based assessment

plus two additional studies where all teeth received early PE, or all mature teeth received early PE without comparative group data; 14 studies not specifying PE timing; three studies not reporting periodontal healing outcomes with respect to PE timing; one study with incomplete data on periodontal outcomes after PE; one study on pulpal healing; and four studies with unsuitable cohorts (teeth with extended extraoral times, sample included primary teeth, or management dissimilar to the clinical guidelines). One prospective cohort study and three retrospective clinical audits were retained, providing data for early PE within 10 days (\leq 10 days) or within 14 days (\leq 14 days), and delayed PE (>10 days, or >14 days) in relation to periodontal healing outcomes (17, 24, 26, 27).

Searching reference lists added one study (50). The PubMed search was updated with the keyword 'avulsion'

(May 2006); limiting citations to papers in 2004–2006 resulted in 117 citations. Titles of these papers were assessed for relevance and one prospective cohort study was added, giving six papers for meta-analysis (17, 24, 26, 27, 39, 50; Table 1).

Studies investigating the effect of timing of pulp extirpation

Three retrospective clinical audits (24, 26, 27) and three prospective cohort studies (17, 39, 50) met the inclusion criteria for the effect of PE timing on periodontal healing outcome (Table 2). Reporting on 24 teeth, Cvek et al. stated 'root resorption associated with radiolucency in the bone can be avoided in reimplanted incisors given adequate endodontic treatment of pulpal necrosis' (26). Andersson and Bodin reported a nonsignificant 'tendency that late endodontic treatment

Table 2. Descriptions of six studies for effect of timing of pulp extirpation on periodontal healing outcomes

Study and study type	No. Patients	Patient age (years)	No. teeth	Timing of pulp extirpation	Follow up	Diagnosis of periodontal healing outcome
Retrospective clinical audits:						
Cvek et al. (26)	33	6–17 Av. 11	36	≤14 days: 21 >14 days: 3	22 to 78 months	Radiographic and clinical
Andersson and Bodin (27)	18	7–29	21	Exact day tabulated for each tooth within paper	Av 5 years	Radiographic (root resorption index)
Mackie and Worthington (24)	36	6–14	46	≤14 days: 17 >14 days: 29	1–7 years	Radiographic, high percussion note, reduced mobility, infraocclusion
Prospective cohort studies:						
Andreasen (50)	35	7–39	40	7–14 days: 18 >14 days: 18	Up to 1 year	Radiographic (resorption), mobility, percussion
Kinirons et al. (17)	71	6–16	84	4-10 days: 28 11-19 days: 24 ≥ 20 days: 23 Not extirpated: 9	Min 2 years	Radiographic, high percussion note, reduced mobility, periodontal ligament space loss
Chappius and von Arx (39)	34	6–48 Av 21	45	7–10 days: 27 >10 days: 10 Not extirpated: 8	1 year	Radiographic and clinical

increased the rate of root resorption' (27). Mackie and Worthington reported no statistically significant difference in success of treatment or replacement resorption when PE occurred within 14 days compared with teeth with PE delayed until there were obvious signs of loss of vitality (24). Kinirons et al. proposed an increase in root resorption could be expected if PE was delayed for more than 20 days (17). Two papers tabulated periodontal healing outcomes in relation to PE timing (39, 50).

Direct comparisons of early and late pulp extirpation

Six studies directly compared early and late PE (Table 3). Some teeth were excluded because of inadequate follow-up periods (less than 1 year), reducing sample sizes. Meta-analyses included assessment of periodontal healing outcomes with PE within 14 days or within 10 days of replantation. Teeth in one paper (39) were included for both time periods where early PE was defined as within 7–10 days, and delayed PE was inferred as beyond 14 days. Teeth without PE were excluded. A total of 236 teeth (PE within 14 days: 113; PE beyond 14 days: 99; PE within 10 days: 112; PE beyond 10 days: 124) were metaanalysed.

All six studies described periodontal healing outcomes (Table 3). Favourable periodontal healing outcomes (defined by the present investigators as: periodontal healing, normal healing, transient replacement resorption, no resorption, non-progressive resorption, inflammatory resorption absent, surface resorption) after PE within 14 days varied markedly between studies as follows: 8 of 21 teeth (26); 6 of 18 teeth (50); 2 of 2 teeth (27); 6 of 17 teeth (24); 21 of 28 teeth (17); 16 of 27 teeth (39). Favourable periodontal healing outcomes (defined as: periodontal healing, normal healing, transient replacement resorption, no resorption, non-progressive resorption, inflammatory resorption absent, surface resorption) following PE after 14 days also varied: 2 of 3 teeth (26); 4 of 18 teeth (50); 10 of 16 teeth (27); 16 of 29 teeth (24); 14 of 23 teeth (17); 6 of 10 teeth (39).

Classification of periodontal healing outcomes

In pooling the teeth from the six studies (Table 3), the periodontal healing outcomes were reclassified by the present authors as functional healing, acceptable healing, development of replacement resorption and development of inflammatory resorption. Functional healing was defined to include periodontal healing (26, 39), normal healing (50) and no root resorption (27). Acceptable healing was defined as including periodontal healing (26), normal healing and transient replacement resorption (50), non-progressive root resorption and no root resorption (27), absence of root resorption (24), absence of inflammatory resorption (17) and periodontal healing or surface resorption (39). The development of replacement resorption was defined as including ankylosis (26), permanent replacement resorption (50) and replacement resorption (39). Teeth diagnosed with transient replacement resorption (initial reduced mobility returned to normal) were categorized as having no replacement resorption (50). Inflammatory resorption was defined to include progressive root resorption (27), inflammatory resorption (17, 50) and infection-related resorption (39).

Table 3. Periodontal healing outcomes in six studies reporting on effect of early and late pulp extirpation and providing teeth for meta-analysis

Study and study type	Meta-analysis (no. teeth)	Early pulp extirpation (no. teeth)	Periodontal healing outcome after early pulp extirpation (no. teeth)	Late pulp extirpation (no. teeth)	Periodontal healing outcome after late pulp extirpation (no. teeth)
Retrospective clinical audits:					
Cvek et al. (26)	24	21	Periodontal healing (8) Ankylosis (13)	3	Periodontal healing (2) Ankylosis (1)
Andersson and Bodin (27)	18	2, 1*	No root resorption (2, 1) Non-progressive root resorption (0, 0) Progressive root resorption (0, 0)	16, <i>17</i>	No root resorption $(4, 5)$ Non-progressive root resorption $(6, 6)$ Progressive root resorption $(6,6)$
Mackie and Worthington (24)	46	17	No root resorption (6) Root resorption (11)	29	No root resorption (16) Root resorption (13)
Prospective cohort studies:					
Andreasen (50)	36	18	Normal healing (2) Transient replacement resorption (4) Permanent replacement resorption (12) Inflammatory resorption (0)	18	Normal healing (2) Transient replacement resorption (2) Permanent replacement resorption (7) Inflammatory resorption (6)
Kinirons et al. (17)	51, <i>75</i>	28, <i>28</i>	Inflammatory resorption absent (21, 21) resorption $(7, 7)$	23, <i>47</i>	Inflammatory resorption absent (14, 33) Inflammatory resorption (9, 14)
Chappius and von Arx (39)	37	27, <i>27</i>	Periodontal healing (15, <i>15</i>) Surface resorption (1, <i>1</i>) Replacement resorption (10, <i>10</i>) Infection related resorption (1, <i>1</i>)	10, <i>10</i>	Periodontal healing (5, 5) Surface resorption (1, 1) Replacement resorption (3, 3) Infection related resorption (1, 1)
Totals	212, <i>236</i>	113, <i>112</i>	,	99, <i>124</i>	
*Numbers in italics refer to nun	nber of teeth wh	en early pulp	extirpation is defined as within 10 days.		

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Statistical analysis

Meta-analyses and forest plots were created using REVMAN 4.2 statistical software (RevMan Analyses, Version 4.2 for Windows, The Nordic Centre, The Cochrane Collaboration 2003, Copenhagen) (51, 52), examining data as dichotomous (i.e. the outcome did or did not occur), and calculating odds ratios (ORs), standard errors (se) and 95% confidence intervals (CI) as described previously (41). Study ORs were weighted, common odds ratios (CORs) were calculated for an overall estimate of effect; the random effects model was used in combining data (51). The overall effect of early vs delayed PE on periodontal healing outcomes was examined by the z statistic (alpha = 0.05). Between-study heterogeneity was assessed by the Chi squared test as Cochran's Q(51). Inconsistency because of heterogeneity (as opposed to sampling error) was assessed by the I^2 statistic (values > 56% show marked heterogeneity; values < 31% show less significant heterogeneity), followed by sensitivity analysis for heterogeneity sources (53).

Results

Functional healing and pulp extirpation within 14 days

Functional healing was determined by pooling data from four studies (26, 27, 39, 50; Table 3), and assembling 115 teeth (PE \leq 14 days: 68; PE > 14 days: 47). Functional healing occurred as follows: PE \leq 14 days: 27 teeth (40%); and PE > 14 days: 13 teeth (28%).

Odds ratios and study weightings

Study ORs for the effect of PE within 14 days on functional healing (Fig. 1a) were not statistically significant: 0.31 (se = 1.30; CI = 0.02-3.97) (26); 1.00 (se = 1.06; CI = 0.13 - 8.00) (50); 13.89 (se = 1.64; CI = 0.55-348.27) (27); and 1.25 (se = 0.74; CI =0.29-5.35) (39). A non-significant COR of 1.22 (se = 0.56; CI = 0.40-3.69), suggested PE within 14 days of replantation was not associated with increased likelihood of functional healing. Study weights and contributions to the overall estimate of effect were: 0.55, 17.4% (26); 0.80, 25.3% (50); 0.35, 11.3 (27); and 1.49, 46.0% (39). The non-significant overall effect (z = 0.34; P = 0.73), indicated a lack of effect of PE within 14 days on functional healing. No between-study heterogeneity was found ($\chi^2 = 3.36$; P = 0.34), but the I^2 statistic (10.7%) noted inconsistency.

Forest plot

In plotting the effect of PE within 14 days on functional healing, all study lines (26, 27, 39, 50) cross the vertical line (no effect) at one, indicating the non-significant ORs (Fig. 1a). Diamond placement slightly right and crossing the vertical line favours PE within 14 days, but without statistical significance.

^(a)Influence of pulp extirpation within 14 days of replantation on a functional periodontal healing outcome

Study or sub-category	Pulpectomy <10 days <i>n</i> /N	Extirpation >14days <i>n</i> /N	OR (random) 95% Cl	Weight %	OR (random) 95% Cl
Cvek et al	8/21	2/3		17.39	0.31 [0.02, 3.97]
Andreasen	2/18	2/18 —	+	25.27	1.00 [0.13, 8.00]
Andersson and Bodin	2/2	4/16		11.29	13.89 [0.55, 348.27]
Chappius and von Arx	15/27	5/10		46.05	1.25 [0.29, 5.35]
Total (95% CI)	68	47		100.00	1.22 [0.40, 3.69]
Total events: 27 (Pulpe Test for heterogeneity: Test for overall effect:	ectomy < 14 days), 13 (Ext $\chi^2 = 3.36$, df = 3 ($P = 0.34$ Z = 0.34 ($P = 0.73$)	irpation >14 days) I), <i>I</i> ² = 10.7%			

^(b)Influence of pulp extirpation within 10 days of replantation on a functional periodontal healing outcome

Review: Comparison: Outcome:	Pulp extirpation time 02 Pulp extirpation 10 da 01 Functional periodonta	ys or less compared with p I healing	ulp extirpation after 10 d	lays	
Study or sub-category	Pulpectomy <10 days <i>n</i> /N	Pulpectomy >10 days n/N	OR (random) 95% Cl	Weight %	OR (random) 95% Cl
Andersson and Bodir Chappius and von Ar	n 1/1 rx 15/27	5/17 5/10		15.81 84.19	6.82 [0.24, 195.13] 1.25 [0.29, 5.35]
Total (95% CI) Total events: 16 (Pulp Test for heterogeneity Test for overall effect:	28 bectomy <10 days), 10 (Po 2^{2} χ^{2} = 0.83, df = 1 (P = 0.3 Z = 0.72 (P = 0.47)	27 ulpectomy >10 days) 36), $l^2 = 0\%$		100.00	1.63 [0.43, 6.20]
		0.1	0.2 0.5 1 2	5 10	

Fig. 1. (a) Influence of pulp extirpation within 14 days of replantation on a functional periodontal healing outcome. (b) Influence of pulp extirpation within 10 days of replantation on a functional periodontal healing outcome.

Sensitivity analysis

As the I^2 value showed between-study inconsistency, the meta-analysis was repeated excluding one study with a wide CI (27). Of note, this study had only two teeth with PE within 14 days and 18 teeth were replanted within 15 min (27). There were 97 teeth remaining (PE \leq 14 days: 66; PE > 14 days: 31). Functional healing occurred as follows: $PE \le 14$ days: 25 teeth (38%); PE > 14 days: 9 teeth (29%). Pooling three studies (26, 39, 50), the COR for effect of early PE on functional healing was 0.92 (se = 0.55, CI = 0.31-2.70; Fig. 1b). This statistically non-significant result confirmed the previous finding that PE within 14 days was not associated with an increased likelihood of functional healing. Study weights and contributions to the overall effect were: 0.59, 17.8% (26); 0.89, 27.0% (50); and 1.82, 55.2% (39). The overall effect (z = 0.16; P = 0.87), was not statistically significant, showing a lack of effect for early PE within 14 days on functional healing. No between-study heterogeneity was noted ($\chi^2 = 0.88$; $P = 0.64; I^2 = 0\%$).

Functional healing with pulp extirpation within 10 days

Functional healing was determined by pooling data from two studies (27, 39; Table 3), and assembling 55 teeth (PE \leq 10 days: 28; PE > 14 days: 27). Functional healing occurred as follows: PE \leq 14 days: 16 teeth (57%); PE > 14 days: 10 teeth (37%).

Odds ratios and study weightings

Study ORs for functional healing after PE within 10 days were not statistically significant: 6.82 (se = 1.71; CI = 0.24–195.13) (27); and 1.25 (se = 0.74; CI = 0.29–5.35) (39) (Fig. 1b). A non-significant COR of 1.63 (se = 0.68; CI = 0.43–6.20), suggested that PE within 10 days is not associated with an increased likelihood of functional healing. Study weights and contributions to the overall estimate of effect were: 0.34, 15.8% (27); and 1.82, 84.2% (39). The non-significant overall effect (z = 0.72; P = 0.47), indicated a lack of effect for PE within 10 days. No between-study heterogeneity was found ($\chi^2 = 0.83$; P = 0.36; $I^2 = 0\%$).

Forest plot

Plotting the effect of PE within 10 days on functional healing, both study lines (27, 39) cross the vertical line indicating non-significant ORs (Fig. 1b). Diamond placement to the right and crossing the vertical line favours (without significance) PE within 10 days.

Acceptable healing and pulp extirpation within 14 days

Acceptable periodontal healing was determined from six studies (17, 24, 26, 27, 39, 50; Table 3), assembling 212 teeth (PE \leq 14 days: 113; PE > 14 days: 99). Acceptable healing occurred as follows: PE \leq 14 days: 59 teeth (52%); PE > 14 days: 52 teeth (53%).

Odds ratios and study weightings

Study ORs for the effect of PE within 14 days on acceptable healing (Fig. 2a) were not statistically signif-

icant: 0.31 (se = 1.30; CI = 0.02–3.97) (26); 1.75 (se = 0.76; CI = 0.40–7.70) (50); 3.10 (se = 1.63; CI = 0.13–75.18) (27); 0.44 (se = 0.63; CI = 0.13– 1.52) (24); 1.93 (se = 0.61; CI = 2.08–22.81) (17); and 0.97 (se = 0.76; CI = 0.22–4.26) (39). A non-significant COR of 1.04 (se = 0.32; CI = 0.55–1.95), suggested PE within 14 days was not associated with an increased likelihood of acceptable healing. Study weights and contributions to the overall estimate of effect were: 0.59, 6.1% (26); 1.75, 18.1% (50); 0.38, 3.9% (27); 2.52, 26.1% (24); 2.68, 27.7% (17) and 1.75, 18.1% (39). The nonsignificant overall effect (z = 0.12; P = 0.91), indicated no effect for PE within 14 days on acceptable healing. No between-study heterogeneity was found ($\chi^2 = 4.66$; P = 0.46; $I^2 = 0\%$).

Forest plot

Plotting the effect of PE within 14 days on acceptable healing, all study lines (17, 24, 26, 27, 39, 50) cross the vertical line, indicating no statistically significant ORs (Fig. 2a). Diamond placement at approximately 1 favours neither early nor late PE timing.

Acceptable healing and pulp extirpation within 10 days

Acceptable healing in relation to PE within 10 days was determined from three studies (17, 27, 39; Table 3), assembling 130 teeth (PE \leq 10 days: 56; PE > 10 days: 74). Acceptable healing occurred as follows: PE \leq 10 days: 38 teeth (68%); PE > 10 days: 50 teeth (68%).

Odds ratios and study weightings

Study ORs for the effect of PE within 10 days on acceptable healing (Fig. 2b) were not statistically significant: 1.70 (se = 1.71; CI = 0.06–47.95) (27); 1.27 (se = 0.54; CI = 0.44–3.67) (17); and 0.97 (se = 0.76; CI = 0.22–4.26) (39). A non-significant COR of 1.19 (se = 0.43; CI = 0.52–2.74), suggested PE within 10 days is not associated with an increased likelihood of acceptable healing. Study weights and contributions to the overall estimate of effect were: 0.34, 6.2% (27), 3.42, 62.0% (17), and 1.75, 31.8% (39). The non-significant overall effect (z = 0.41; P = 0.93), indicated no effect for PE within 10 days on acceptable healing. No between-study heterogeneity was noted ($\chi^2 = 0.13$; P = 0.76; $I^2 = 0\%$).

Forest plot

In plotting the effect of PE within 10 days on acceptable healing, all study lines (17, 27, 39) cross the vertical line, indicating no OR was statistically significant (Fig. 2b). Diamond placement slightly right and crossing the vertical line favours (without significance) PE within 10 days.

Replacement resorption and pulp extirpation within 14 days

Three studies reported data on replacement resorption (26, 39, 50; Table 3), providing data on 97 teeth (PE \leq 14 days: 66; PE > 14 days: 31). Replacement resorption occurred as follows: PE \leq 14 days: 35 teeth (53%); PE > 14 days: 11 teeth (35%).

(a) Influence of pulp extirpation within 14 days of replantation of avulsed teeth on an acceptable healing outcome

Review: Pulp extirpation time

Comparison: 01 Pulp extirpation 14 days or less compared to pulp extirpation after 14 days

Outcome: 04 Acceptable periodontal healing vs unacceptable periodontal healing

Study	Pulpectomy <14 days P	ulpectomy >14 days	OR (random)	Weight	OR (random)
or sub-category	<i>n</i> /N	<i>n</i> /N	95% Cl	%	95% Cl
Cvek et al	8/21	2/3		6.08	0.31 [0.02, 3.97]
Andreasen	6/18	4/18			1.75 [0.40, 7.70]
Andersson and Bodir	n 2/2	10/16	-	3.90	3.10 [0.13, 75.18]
Mackie & Worthington	n 6/17	16/29		26.05	0.44 [0.13, 1.52]
Kinirons et al	21/28	14/23		27.73	1.93 [0.58, 6.38]
Chappius and von Ar	x 16/27	6/10		18.14	0.97 [0.22, 4.26]
Total (95% CI) Total events: 59 (Pulp Test for heterogeneity Test for overall effect:	113 ectomy <14 days), 52 (P $\chi^2 = 4.66$, df = 5 (P = 0. Z = 0.12 (P = 0.91)	99 ulpectomy >14 days) .46), $I^2 = 0\%$	-	100.00	1.04 [0.55, 1.95]
		0.1 0	.2 0.5 1 2 5	5 10	

Favours >14 days Favours <14 days

. . .

(b) Influence of pulp extirpation within 10 days of replantation of avulsed teeth on an acceptable healing outcome

 Review:
 Pulp extirpation time

 Comparison:
 02 Pulp extirpation 10 days or less compared with pulp extirpation after 10 days

 Outcome:
 03 Acceptable periodontal healing vs unacceptable periodontal healing

Fig. 2. (a) Influence of pulp extirpation within 14 days of replantation of avulsed teeth on an acceptable healing outcome. (b) Influence of pulp extirpation within 10 days of replantation of avulsed teeth on an acceptable healing outcome.

Odds ratios and study weightings

Study ORs for the effect of PE within 14 days on the development of replacement resorption (Fig. 3) were not statistically significant: 3.25 (se = 1.30; CI = 0.25–41.91) (26); 3.14 (se = 0.70; CI = 0.80–12.28) (50); and 1.37 (se = 0.80; CI = 0.29–6.54) (39). A non-significant COR of 2.32 (se = 0.48; CI = 0.89–6.02), suggested PE within 14 days is not associated with a decreased likelihood of replacement resorption. Study weights and contributions to the overall estimate of effect were: 0.59, 13.9% (26); 2.07, 48.9% (50) and 1.57, 37.2% (39). The non-significant overall effect (z = 1.73;

P = 0.08), indicated no effect of PE within 14 days on development of replacement resorption. No betweenstudy heterogeneity was seen ($\chi^2 = 0.69$; P = 0.71; $I^2 = 0\%$).

Forest plot

In plotting the effect of PE within 14 days on development of replacement resorption, all study lines (26, 39, 50) cross the vertical line, indicating no statistically significant ORs (Fig. 3). Diamond placement to the right but crossing the vertical line favours PE later than 14 days (but without statistical significance).

Influence of pulp extirpation within 14 days of replantation on the development of replacement root resorption Review: Pulp extirpation time

Review:Pulp extirpation timeComparison:01 Pulp extirpation 14 days or less compared to pulp extirpation after 14 daysOutcome:05 Replacement resorption vs no replacement resorption

Study	Pulpectomy <14 days	Pulpectomy >14 days	OR (random)	Weight	OR (random)
or sub-category	n/N	n/N	95% Cl	%	95% Cl
Cvek et al	13/21	1/3 -		13.89	3.25 [0.25, 41.91]
Andreasen	12/18	7/18		48.87	3.14 [0.80, 12.28]
Chappius and von Ar	10/27	3/10		37.23	1.37 [0.29, 6.54]
Total (95% CI) Total events: 35 (Pulp Test for heterogeneity Test for overall effect:	66 ectomy <14 days), 11 : $\chi^2 = 0.69$, df = 2 (P = Z = 1.73 (P = 0.08)	(Pulpectomy >14 days) 0.71), $I^2 = 0\%$. 100.00	2.32 [0.89, 6.02]
		0.1 0.2 Favours	0.5 1 2 5 <14 days Favours >	10 14 days	



Outcome: Weight Study Pulpectomy <10 days Pulpectomy >10 days OR (random) OR (random) or sub-category n/N n/N 95% CI 95% CI % 1/1 11/17 6.23 1.70 [0.06, 47.95] Andersson and Bodin 21/28 33/47 61.99 1.27 Kinirons et al [0.44, 3.67] Chappius and von Arx 16/27 6/10 31.78 0.97 [0.22, 4.26] Total (95% CI) 56 74 100.00 1.19 [0.52, 2.74] Total events: 38 (Pulpectomy <10 days), 50 (Pulpectomy >10 days) Test for heterogeneity: $\chi^2 = 0.13$, df = 2 (P = 0.94), $l^2 = 0\%$ Test for overall effect: Z = 0.41 (P = 0.69) 0.1 0.2 0.5 1 ż 10 5 Favours >10 days Favours <10 days

Inflammatory resorption and pulp extirpation within 14 days

Inflammatory resorption in relation to PE time was determined from four studies (17, 27, 39, 50), assembling 142 teeth (PE \leq 14 days: 75; PE > 14 days: 67). Inflammatory resorption occurred as follows: PE \leq 14 days: 8 teeth (11%); PE > 14 days: 22 teeth (36%).

Odds ratios and study weightings

Study ORs for the effect of PE within 14 days on the development of inflammatory resorption (Fig. 4a) were not statistically significant: 0.05 (se = 1.51; CI = 0.00-1.01) (50); 0.32 (se = 1.63; CI = 0.01-7.77) (27); 0.52 (se = 0.61; CI = 0.16-1.72) (17); and 0.35 (se = 1.47; CI = 0.02-6.13) (39). A significant COR of 0.37 (se = 0.50; CI = 0.14-0.98), indicated PE within 14 days is associated with a decreased likelihood of developing inflammatory resorption. Study weightings and contributions to the overall estimate of effect were: 0.44, 11.0% (50); 0.38, 9.5% (27); 2.68, 67.7% (17); and 0.47, 11.8% (39). The overall estimate of effect (z = 2.00; P = 0.05), indicated a statistically significant association of PE within 14 days and periodontal healing without inflammatory resorption. No between-study heterogeneity was found ($\chi^2 = 2.11$; $P = 0.55; I^2 = 0\%$).

Forest plot

In plotting the effect of PE within 14 days on inflammatory resorption, the study OR of 0.05 (50) is located beyond the scale of the graph and the CI excludes the value of one (Fig. 4a). As all study lines cross the vertical line, the ORs were not statistically significant. Diamond placement to the left but not crossing the vertical line, in association with a CI excluding the value of one, indicates a statistically significant association of PE within 14 days in preventing development of inflammatory resorption.

Inflammatory resorption and pulp extirpation within 10 days

Three studies reported the development of inflammatory resorption for PE within 10 days and after 10 days (17, 27, 39; Table 3). Additional teeth excluded from one study (17) in the previous meta-analysis were now included, assembling 130 teeth (PE \leq 10 days: 56; PE > 10 days: 74). Inflammatory resorption occurred as follows: PE \leq 10 days: eight teeth (14%); PE > 10 days: 21 teeth (28%).

Odds ratios and study weightings

Study ORs for the effect of PE within 10 days on the development of inflammatory resorption (Fig. 4b) were not statistically significant: 0.59 (se = 1.71; CI = 0.02–16.68) (27); 0.79 (se = 0.54; CI = 0.27–2.27) (17); and 0.35 (se = 0.47; CI = 0.02–6.13) (39). A non-significant COR of 0.70 (se = 0.49; CI = 0.27–1.82), suggested PE within 10 days is not associated with a decreased likelihood of inflammatory resorption. Study weightings and contributions to the overall estimate of effect were: 0.34, 8.1% (27); 3.42, 80.9% (17); and 0.47, 11.0% (39).

(a) Influence of pulp extirpation within 14 days of replantation on the development of inflammatory resorption

Review: Comparison: Outcome:	Pulp extirpation time 01 Pulp extirpation 14 c 06 Inflammatory resorp	lays or less compared to pu tion vs no inflammatory res	ulp extirpation after 14 orption	4 days	
Study or sub-category	Pulpectomy <14 days n/N	Pulpectomy >14 days <i>n</i> /N	OR (random) 95% Cl	Weight %	OR (random) 95% Cl
Andreasen Andersson and I Kinirons et al Chappius and vo	0/18 Bodin 0/2 7/28 on Arx 1/27	6/18 6/16 9/23 1/10	•	11.04 9.53 67.69 11.75	0.05 [0.00, 1.01] 0.32 [0.01, 7.85] 0.52 [0.16, 1.72] 0.35 [0.02, 6.13]
Total (95% CI) Total events: 8 (F Test for heteroge Test for overall e	⁷⁵ Pulpectomy <14 days), 2 neity: χ^2 = 2.11, df = 3 (ffect: Z = 2.00 (P = 0.05)	2 (Pulpectomy >14 days) $P = 0.55$), $I^2 = 0\%$		100.00	0.37 [0.14, 0.98]
				10	
nfluence of pulp of Baview:	extirpation within 10 da	0.1 0.2 Favours < ays of replantation on the	2 0.5 1 2 5 14 days Favours > development of infl	10 •14 days ammatory res	orption
nfluence of pulp of Review: Comparison: Outcome:	extirpation within 10 da Pulp extirpation time 02 Pulp extirpation 10 (04 Inflammatory resorp	0.1 0.2 Favours < hys of replantation on the days or less compared with tion vs no inflammatory res	2 0.5 1 2 5 14 days Favours > development of infl pulp extirpation after corption	10 14 days ammatory res 10 days	orption
nfluence of pulp of Review: Comparison: Outcome: Study or sub-category	extirpation within 10 da Pulp extirpation time 02 Pulp extirpation 10 (04 Inflammatory resorp Pulpectomy <10 days n/N	0.1 0.2 Favours < ays of replantation on the days or less compared with tion vs no inflammatory res s Pulpectomy >10 days n/N	2 0.5 1 2 5 14 days Favours > development of infl pulp extirpation after sorption OR (random) 95% Cl	10 •14 days ammatory res 10 days Weight %	orption OR (random) 95% Cl
nfluence of pulp of Review: Comparison: Outcome: Study or sub-category Andersson and Kinirons et al Chappius and vo	extirpation within 10 da Pulp extirpation time 02 Pulp extirpation 10 0 04 Inflammatory resorp Pulpectomy <10 days n/N Bodin 0/1 7/28 on Arx 1/27	$0.1 \ 0.2$ Favours < ays of replantation on the days or less compared with tion vs no inflammatory res a Pulpectomy >10 days n/N 6/17 14/47 1/10	2 0.5 1 2 5 14 days Favours > development of infl pulp extirpation after corption OR (random) 95% Cl	10 14 days ammatory reso 10 days Weight % → 8.13 80.88 10.99	OR (random) 95% Cl 0.59 [0.02, 16.68 0.79 [0.27, 2.27] 0.35 [0.02, 6.13]

Favours<10 days Favours>10 days

Fig. 4. (a) Influence of pulp extirpation within 14 days of replantation on the development of inflammatory resorption. (b) Influence of pulp extirpation within 10 days of replantation on the development of inflammatory resorption.

The non-significant overall effect (z = 0.73; P = 0.47), indicated a lack of effect for PE within 10 days on periodontal healing without inflammatory resorption. No between-study heterogeneity was found ($\chi^2 = 0.29$; P = 0.87; $I^2 = 0\%$).

Forest plot

In plotting the effect of PE within 10 days on development of inflammatory resorption, all lines cross the vertical line, indicating no statistically significant ORs (Fig. 4b). Diamond placement left and crossing the vertical line favours PE within 10 days of replantation, but without statistical significance.

Answer to the PICO question

Meta-analysis of the currently-available evidence on functional healing, acceptable healing, development of replacement resorption and development of inflammatory resorption indicates that: (P) for a replanted avulsed permanent tooth, (I) early PE within 10–14 days of replantation, (C) compared with delayed pulp extirpation, (O) is associated with an increased likelihood of successful periodontal healing after tooth replantation.

Discussion

Based on an evidence-based assessment of six papers written between 1974 and 2005, reporting clinical studies on a total of 236 replanted avulsed teeth (113 with PE within 10-14 days, 123 with PE delayed beyond 10-14 days), the present meta-analyses have provided evidence supporting the clinical guideline for the timing of PE. The likelihood of successful periodontal healing was improved by PE within 14 days of replantation because of decreased risk of developing inflammatory resorption. A statistically significant association was shown between extirpation within 14 days and an increased likelihood of successful periodontal healing. While no significant relationships were found for the periodontal healing outcomes of functional healing, acceptable healing or development of replacement resorption, there was a significant association between extirpation delayed beyond 14 days and development of inflammatory resorption. No significant association was observed between extirpation within 10 days and the four periodontal healing outcomes studied.

For development of inflammatory resorption, the statistically significant COR (0.37) meant the likelihood of developing inflammatory resorption as a healing complication is approximately one-third when PE is within 14 days of replantation. For the other periodontal healing outcomes considered, no significant associations were found, confirming the recommendation that the pulp should be extirpated early to help prevent development of inflammatory resorption (2). Extraoral time is a major determinant of functional healing, such that studying the effect of early PE would require a large sample of avulsed teeth replanted within 5 min. For development of replacement resorption, the COR (2.32) favoured delayed PE beyond 14 days after replantation, but the difference was not statistically significant. Confounding factors could have promoted periodontal ligament cell necrosis and replacement resorption.

For PE within 10 days, no significant association was found for any periodontal healing outcome assessed. The meta-analysis supports the clinical guideline for early PE, although the critical period may be 14 rather than 10 days (2, 3, 6–8). Although the guideline promotes early PE, no previous study has shown a need for extirpation within this time period. The critical time for PE to avoid inflammatory resorption has been reported as 20 days (17). Although suggesting that delaying PE for 2 weeks would advance periodontal healing (noting advanced inflammatory resorption at this stage), Andreasen has recommended initiating endodontic therapy 7–10 days after replantation (1). The present metaanalysis did not find a significant effect for PE within 10 days in avoiding inflammatory resorption.

For the teeth with open apices, PE may be delayed to assess pulpal healing, reported to occur in 34% of immature teeth (12). As the data were unavailable, the present meta-analyses did not separate immature teeth with open apices (and a chance of maintaining pulp vitality), from mature teeth with closed apices. If metaanalyses were performed on study samples limited to teeth with closed apices, a smaller OR may have been found for the effect of early extirpation on development of inflammatory resorption, indicating a greater risk of delaying PE beyond 14 days for teeth with closed apices. In this study, some immature teeth were included in the sample with delayed PE, perhaps improving the overall outcome.

The present study has several limitations. The few studies fulfilling the inclusion criteria and few teeth available for meta-analysis are constraints; many relevant studies were excluded on the basis that periodontal healing outcomes were not reported in relation to extirpation timing. Some papers also lacked details of case selection, initial sample size, withdrawals, evaluator blinding, and sizes of intervention and comparison groups. Details of emergency care in some studies complicated evaluation of cohorts, which could not be determined without reported criteria.

In combining data from studies using different intracanal medicaments, it was assumed that these have minimal effect on periodontal healing outcomes. In two studies, CH was placed consistent with the clinical guidelines (24, 26); another study placed Ledermix[®] for 2–3 weeks and then replaced this with CH (39); a further study placed either gutta percha or CH depending upon the stage of root development (50); and two studies did not report the intracanal medicament (17, 27). As the present study aimed to assess extirpation timing and not intracanal medicaments, these treatments were included (50).

Heterogeneity (10.7%) between studies was observed in meta-analyses for early PE within 14 days and the effect on functional healing, confirming the source by deleting one study in a sensitivity analysis. Of note, this study was used in other meta-analyses without affecting the heterogeneity and statistical significance of the findings. Given the small sample sizes in the studies, which were combined, the power to detect heterogeneity was reduced. Accumulating large samples of replanted avulsed teeth in an institution takes time. Generating larger samples of teeth for meta-analysis by combining results from many studies is therefore advantageous and may reveal significant relationships missing in individual studies because of small sample sizes (54), although dissimilar data collection methods can be limiting. Using published data, the present meta-analyses have demonstrated an important finding not observed previously, thereby providing evidence for the clinical guideline.

The present study used defined criteria along with data extraction and critical appraisal forms. Two or more assessors (the present study used one) are recommended to minimize bias in selecting articles and applying criteria. The lack of RCTs (gold standard for evidence-based research) limits the present meta-analyses. While prospective cohort studies could be deemed top level of evidence in assessing research on replanted avulsed teeth, such inclusions in meta-analyses have been debated (55, 56).

The technique of direct meta-analysis assumes that variables or confounders in the intervention and comparison groups in a given study are distributed equally, but may differ from those in other studies. Different timing of PE may reflect tooth- or patientrelated factors and may affect the outcomes. Random allocation of PE timing was not described in any paper reporting the effects of PE timing. With uncontrolled confounders, the random effects model estimates treatment effect conservatively (in contrast to assuming a common treatment effect in all studies in the fixed effects model), and was therefore appropriate in the present study (53).

The present study indicates that PE delayed beyond 14 days after tooth replantation is associated with an increased risk of developing inflammatory resorption. Therefore, the pulp should be removed from mature teeth within 14 days of replantation, and from immature teeth where maintenance of pulp vitality is unlikely, to prevent this outcome. Meta-analyses of data assembled from selected studies of replanted avulsed human teeth demonstrate that the evidence supports the current clinical guideline.

Conclusion

This evidence-based study of data from six papers and pooling 236 replanted avulsed permanent teeth concludes that the likelihood of successful periodontal healing was improved by PE within 14 days of replantation because of a decreased risk of developing inflammatory resorption, thereby providing evidence to support the current clinical guideline.

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