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TITLE: A systematic review of outcome measures used in clinical trials of treatment interventions following traumatic dental injuries.

Running Title: A systematic review of outcome measures used in dental trauma trials

Key words: Randomized Controlled Trials, Controlled Clinical Trials, Research Design, Treatment Outcomes, Traumatic Dental Injuries, Outcome Measures

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ABSTRACT

Background:

Traumatic Dental Injuries (TDI) are common, appropriate treatment will maximise the chances of maintaining teeth in function while safeguarding their longevity and aesthetics. Subjectively it appears that outcome measures used in trials for TDI are numerous and diverse.

Objectives:

To identify by way of a systematic review the outcomes used in clinical trials of treatment interventions for TDI.

Data sources:

The following electronic databases were searched up to June 2014: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and EMBASE. Reference lists of eligible studies were cross-checked to identify additional studies and strategies to identify grey literature and on-going trials were employed.

Study selection:

Following predefined criteria, two review authors independently studies for inclusion and then undertook data extraction. The following study designs were included: systematic reviews with/without meta analyses, randomised controlled trials, pseudo randomised controlled trials and controlled clinical trials. There were no language restrictions.

Results:

Ten studies confined to two types of TDI: avulsion (5) and non-vital immature permanent incisor teeth (5) were eligible for inclusion. The outcomes reported predominantly concentrated on injury activity and the physical consequence of injury domains. There was little consistency between studies in terms of the length of

follow-up, the time points at which outcomes were evaluated or the methods used to measure them.

Conclusions:

There is currently significant heterogeneity in outcomes reported for TDI in the current literature. These findings preclude meaningful meta-analysis between studies. Future clinical studies need to consider collecting a wider range of outcomes, which should include one, or more from each of the following domains: health resources utilisation, adverse effects and quality of life and family outcome.

There is a clear need for the development of a Core Outcome Set TDI using robust and established methodology to be developed, thus optimising the value of future research.

Introduction

Traumatic Dental Injuries (TDI) are common, dentists endeavour to provide the most appropriate treatment following such injuries to maximise the chances of healing (teeth and the surrounding tissues) and thereby maintaining function and aesthetics of the dentition. Treatment may be undertaken at any point from shortly after the injury to several years later. With some injuries, superior outcomes are achieved when an observational approach is undertaken, while for others active treatment is essential. Identifying the most appropriate treatment for different TDI requires not only clinical experience but also evidence from high quality studies, preferably clinical trials. Clinical trials require defined primary and secondary outcomes to answer questions generated by research hypotheses. It is evident that TDI outcomes reported in such trials are numerous and diverse, furthermore, it is unclear how and at what time point these outcomes should be collected. This heterogeneity has been highlighted in recent systematic reviews that have looked at treatment interventions for various TDIs (1,2,3,4). Indeed concerns have been raised over the validity of a series of systematic reviews (5,6,7), which undertook meta-analyses of non-randomised studies where there was significant heterogeneity in the data being amalgamated (8)

Establishing a Core Outcome Set for different traumatic dental injuries, how these outcomes are measured and the timing of these measurements is essential to enable research findings to be reported in a transparent manner to a wider community including research, clinical and patient populations. The outcomes are not restricted to randomized controlled trials but can be used for clinical audit and other study designs. They allow results to be compared, contrasted or combined as appropriate. Once a Core Outcome Set has been established, journals such as Dental Traumatology may oblige authors to, as a minimum, report these outcomes. However, this does not prevent the researcher from collecting and reporting other outcomes. (9). In addition, for researcher and clinicians designing future clinical studies and trials, a Core Outcome Set provides clear guidance as to what minimum data should be collected, how these outcomes should be measured and the time points for data collection (10).

Where a Core Outcome Set does not exist, the following problems can occur:

Heterogeneity between trials: This leads to difficulty in the interpretation and comparison of findings across trials and this therefore hinders potential meta-analysis (8).

Outcome Reporting Bias: This occurs when results are selectively reported, an example of this is the tendency to report only outcomes that show positive findings (11).

A previous review (10) identified core outcome sets for trials of childhood conditions. No studies relating to dental trauma were retrieved. The authors did however identify 25 studies from the wider paediatric literature for inclusion in their review, including one from the dental literature (12). The information obtained from these 25 studies was then used to categorise the outcomes into six broad outcome domains: disease activity, physical consequence of disease, functional status, social outcome and quality of life, side effects of therapy and health resource utilisation (10). The first two domains for this review have been renamed to injury activity and physical consequence of injury.

The aim of this systematic review was to identify the outcomes used in clinical trials of treatment interventions for TDI and to clarify when and how these outcomes were measured.

Methods

A systematic review of the literature was undertaken to identify outcomes reported in studies investigating different treatment interventions following TDI. The conduct of this review was detailed in an *a-priori* protocol.

Inclusion Criteria

Types of studies

- Systematic reviews with/without meta analyses of:
    - Randomised Controlled Trials (RCTs)
    - Pseudo randomised controlled trials
    - Controlled Clinical Trials (CCTs)
- RCTs and pseudo randomised controlled trials
- CCTs

Types of intervention

- Any intervention used to treat TDI

Types of participants

- Children and adults

Exclusion criteria

- Animal studies
- Studies investigating treatment interventions for primary tooth TDI
- Studies investigating educational interventions to increase the knowledge of health care professionals or lay public in how to manage TDI in the emergency setting
- Studies investigating methods to prevent TDI

Search methods for identification of studies

Electronic searches

A search strategy to identify studies for inclusion was designed for MEDLINE. This was adapted appropriately and applied to the Cochrane Central Register of Controlled

Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and EMBASE. Studies published up to June 2014 were identified.

The MEDLINE search strategy utilised was as follows:
(Tooth or Teeth or Incisor* or Dental or Root or Crown or Pulp or Dentin* or Nerve or Enamel or Cementum or Periodontal ligament or PDL or Alveolus or Alveolar process or Incisor* or Incisal* or Apical or Apex*) AND (Trauma* or Injur* or Fracture* or Avuls* or Concussion or Sublux* or Luxat* or Intrusi* or Extrusi* or Displac* or Dislodg* or Rupture* or Non-vital or Nonvital or Immature or Dead)
Limits: Humans, Reviews, meta analysis, RCTs and CCT.

Additional searches
To identify possible unpublished or on-going studies, the reference lists of all potential clinical trials were examined to help find additional studies missed by the electronic searches.

The World Health Organization's International Clinical Trials Registry Platform (http://who.int/ictrp/en/), the Current Clinical Trials Register (http://controlled-trials.com/mrct/) and the ClinicalTrials.gov (http://clinicaltrials.gov/) databases were searched to identify any on-going trials.

Hand Searches
No hand searching was undertaken.

Language
There was no language restriction on included studies. Arrangements were made to translate and assess studies that were not published in English (13). One of the authors (PD) has been involved with a number of Cochrane reviews and research papers translated for these reviews were also used where appropriate in this publication (1, 14).

Eligibility of studies
Two review authors [Mohammad O Sharif (MOS) and Peter Day (PD)] independently assessed the abstracts of studies resulting from the searches. Full text copies of studies

deemed relevant, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, were obtained.

The full text papers were assessed independently by MOS and Ambareen Tejani-Sharif (ATS), any disagreement on the eligibility of included studies were resolved through discussion. If a resolution was not possible, a third review author (PD) was consulted.

Data extraction

Data was extracted independently and in duplicate by MOS and ATS. MOS and ATS then reviewed the extracted data together with PD to arrive at a consensus.

The following data were extracted from each study:

- Study type
- Author details
- Year and journal of publication
- Intervention(s) under investigation
- Study population – nature of trauma
- Age and number of participants included

Data extracted in relation to reported outcomes:

- The outcomes measured including the method and unit of measurement
- The time points at which they were measured

Assessment of methodological quality

It was decided that a critique of the overall methodological quality of the studies was unnecessary (as there was no attempt to meta-analyse the results of the studies identified).

Results

Description of studies

After de-duplication, the search strategy identified 1001 potentially eligible studies. Following a screen of the titles and abstracts, 18 studies were potentially eligible. A screen of the reference lists of these 18 studies identified a further two studies which were potentially eligible for inclusion in our review. After assessing the full text of these 20 papers, ten studies were excluded. A flowchart of this process is shown in Figure 1. Through support from Cochrane Oral Health group, a further six potential studies where identified in the Chinese literature. Five studies were unretrievable. One study could not be included as critical information was not reported in their paper and no reply was received to our email requests for further information(15). A final study was excluded as the follow up time (up to six months) was insufficient to be eligible for this Cochrane review(16)

Excluded Studies

Four of the full text studies were excluded as they were systematic reviews (3,5,6,7). Two were excluded as they were undertaken on healthy participants with no injured teeth (17,18). A further two studies were excluded as they were published protocols (19,20). Finally one case report (21) and one a prospective cohort with no direct comparison group (22) were excluded. However, prior to exclusion they were screened to identify any additional studies.

Included Studies

Characteristics

The characteristics of these studies are summarised in Table 1. Eligible studies were only identified for two types of TDI: avulsion (5) and non-vital immature permanent incisor teeth (5).

Outcomes reported

The outcomes reported and the methods used for their measurement are shown in table 2. The outcomes were then grouped under six outcome domains based on the review that identified core outcome sets for trials of childhood conditions (10). The allocation of outcomes identified to the different domains is summarised in Table 3.

Discussion

This review identified ten studies on TDI that were eligible for inclusion; these were limited to two types of TDI: avulsion (5) and non-vital immature permanent incisor teeth (5). The outcomes reported were almost exclusively concentrated on the 'injury activity' and 'the physical consequence of injury domains'. Patient related outcomes were particularly poorly represented with no outcomes reported for quality of life and family outcomes. In addition, there was only one outcome reported for the health resource utilisation and adverse effects domains. This systematic review has highlighted a paucity of reported outcomes in these domains and the lack of engagement with patients and their parents in designing appropriate research methodology.

There was little consistency between studies in terms of the time points at which outcomes were evaluated or the methods used to record them. For example, two of the four avulsion studies did not detail the criteria for how radiographs were assessed for root resorption and/or periodontal healing (13,23). The non-vital immature permanent incisor studies demonstrated more consistency in outcome reporting. The outcome "apical barrier formation" was reported in each of the five studies, however, three used a clinical method in addition to radiographs to detect this outcome while two studies relied on radiographs only.

The length of follow-up between studies of the same TDI was variable. For example, each of the avulsion studies reviewed patients at months 3, 6 and 12 post-injury. However, the maximum follow up period ranged from 12 to 48 months. This highlights the need for consensus on the minimum period of follow up for TDIs. The two Cochrane reviews in dental traumatology have identified that for periodontal healing this period should be a minimum of 12 months(1,14). This time period however, is too short to collect robust data for outcomes such as tooth loss (24). Collecting such information requires longer follow-up. This may necessitate researchers to consider more imaginative ways of collecting such outcomes as with time patient's enthusiasm to return for a clinical review is likely to wane. In this example, a telephone consultation or postal questionnaire may be an acceptable alternative. For included non-vital immature permanent incisors studies outcome data

was only collected until root end closure was achieved. No data was provided by any study on longer outcomes such as tooth loss or late stage crown root fracture.

In light of these findings, the ability to compare or summate the results from current studies relating to TDI is difficult and fraught with assumptions that compromise rigour especially when attempting to undertake a meta-analysis. This is therefore a clear indication for the development of a Core Outcome Set for TDI. More than 50 groups worldwide have been working to develop Core Outcome Set in specific areas of health care, including dentistry. A core outcome set for primary molar pulpotomy has recently been developed (25). The research team therefore plan to work with the International Association of Dental Traumatology to develop a Core Outcome Set for TDI using the established, transparent and robust methodological approaches that already exist (9).

Conclusion

There was significant heterogeneity in outcomes reported for TDI in clinical trials and outcomes reported in the current literature predominantly concentrate on the ‘injury activity’ and ‘the physical consequence of injury’ domains. Patient related outcomes were particularly poorly represented with no outcomes reported for quality of life and family outcomes. In addition there was variation in time points at which outcomes were evaluated and the methods used to classify them. These finding demonstrate a clear indication for the development of a Core Outcome Set for TDI.

Table 1: Characteristics of included studies

Study	Study Type	Study setting, number of centres	Source of funding	Comparisons	Date of publication	Average length of follow up (months)	Age groups of children included (years)
Avulsion							
Chen 2000 (13)	Quasi RCT	Hospital, n=1	None stated	Use of hyperbaric oxygen vs standard protocol	2000	12	8-14
Loo 2008 (23)	Quasi RCT	Hospital, n = 1	None stated	Thymosin alpha 1 (Talpha1) vs standard protocol	Jun 2008	48	12-26
Giannetti 2005(26)	Quasi RCT	Hospital, n = 1	None stated	Extra-oral root canal treatment vs Replantation and root canal treatment at day 7	Sept 2006	12	Unclear
Day 2012 (27)	RCT	Hospital, n = 5	Department of Health grant and Henry Schein	Ledermix vs Ultracal XS	Feb 2012	12	7.7–17.6
Day 2011 (28)	RCT	Hospital, n = 5	Department of Health grant and Henry Schein	Ledermix vs Ultracal XS	Jun 2011	12	7.7–17.6
Non-vital immature permanent incisor teeth							
Roberts 1975 (3)	CCT	Hospital, n = 1	None stated	Tricalcium Phosphate vs CaOH	Aug 1975	12	8-23
Mackie 1994 (30)	RCT	Hospital, n = 1	None stated	Reogan Rapid vs Hypocal	Apr 1994	Unclear	6.5-13.7
Pradhan 2006 (31)	CCT	Hospital, n = 1	None stated	MTA vs CaOH	May – Aug 2006	4-11	8-15
Lee 2010 (32)	CCT	Hospital, n = 1	None stated	Ultrasonic vs Handfiling	Aug 2010	Unclear	7-10
Damle 2012 (33)	Quasi-RCT	Hospital, n = 1	None stated	MTA vs CaOH	Mar/Apr 2012	12	8-12

Table 2: Summary of outcomes reported in included studies and methods used for outcome measurement

	Outcome	Assessment	Units / Method Used to Measure	Intervals Measured At
Study				
Avulsion				
Chen 2000 (13)				
	Root resorption	Radiographically	Not reported	3, 6, 12 months
	Tooth mobility	Clinically	Not reported	3, 6, 12 months
	Tooth loss	Clinically	Not reported	3, 6, 12 months
	Compound outcome measure – including pulp vitality, periodontal healing, root resorption and mobility	Clinically and Radiographically	Not reported	3, 6, 12 months
	Pulp vitality	Clinically and Radiographically	Not reported	3, 6, 12 months
Giannetti 2005 (26)				
	Mobility	Clinically	Miller's Classification	1 week, 2 weeks, 1,3,6 and 12 months
	Root resorption	Radiographically	Parallelling technique - Light resorption: <1mm. Moderate: radicular point resorption >1mm. Severe resorption: radicular resorption in different locations	2 week, 1,3,6 and 12 months
Loo 2008 (23)				
	Pain	Clinically	Not reported	Days 1, 2, and 5.
	Infection	Temperature, Blood analysis (c-reactive protein, tumour necrosis factor alpha, interferon, interleukin 4&6 and white blood cell count)	Mediators of infection and inflammation	Days 1,2, and 5
	Ankylosis	Radiographically	Visually	Months 3, 6, 12, 18, 24, 30, 36, 42, and 48

	Tooth loss	Clinically	Not reported	Months 3, 6, 12, 18, 24, 30, 3 and 48
	Periodontal healing	Clinically & radiographically	Visually & 6 point periodontal probe at 0.5 mm	Months 3, 6, 12, 18, 24, 30, 3 and 48
Day 2011/2012 (27,28)				
	Discolouration Periodontal healing	Clinically & Radiographically	Patient Satisfaction & clinical photographs and quantification of colour change (CIELAB scoring) Colour, signs of infection, periodontal support, signs of infra- occlusion, percussion note and tooth mobility	3,6 and 12 months
Non-vital immature permanent incisor teeth				
Roberts 1975 (29)				
	Apical barrier formation	Radiographically & Clinically	Radiographically - paralleling technique Clinically - after 6 months a no. 25 file was used to feel for an apical stop	Every 12 weeks
	Root resorption	Radiographically	Visually	Every 12 weeks
Mackie 1994 (30)				
	Apical barrier formation	Clinically	Clinically - using paper points to check for absence of haemorrhage, exudate or sensitivity	At one month and then every thr months
	Number of visits	Clinically	Count variable	At one month and then every thr months
	Time taken for barrier formation	Clinically	Months	At one month and then every thr months
Pradhan 2006 (31)				
	Pain	Clinically	Not reported	Every 4 weeks until barrier had formed (4-11months)
	Apical barrier formation	Radiographically	Visually	Every 4 weeks until barrier had formed (4-11months)

	Periodontal Healing (TTP, mobility, swelling/sinus)	Clinically	Not reported	Every 4 weeks until barrier had formed (4-11months)
	Time taken for barrier formation	Clinically	Months	Every 4 weeks until barrier had formed (4-11months)
Lee 2010 (32)				
	Apical barrier formation	Radiographically & Clinically	Clinically - using a thin explorer probe to check for a hard apical barrier	3,6,9 weekly, then once a week
	Late stage crown/root Crown Fracture	Not reported	Presence or absence at follow up reviews	3,6,9 weekly, then once a week
Damle 2012 (33)				
	Apical barrier formation	Radiographically	Visually	1, 3, 6, 9, 12 months.
	Time taken for barrier formation	Radiographically	Months	1, 3, 6, 9, 12 months.
	Pain	Clinically	Not reported	1, 3, 6, 9, 12 months.
	Periodontal Healing (TTP, mobility, swelling/sinus)	Clinically	Not reported	1, 3, 6, 9, 12 months.

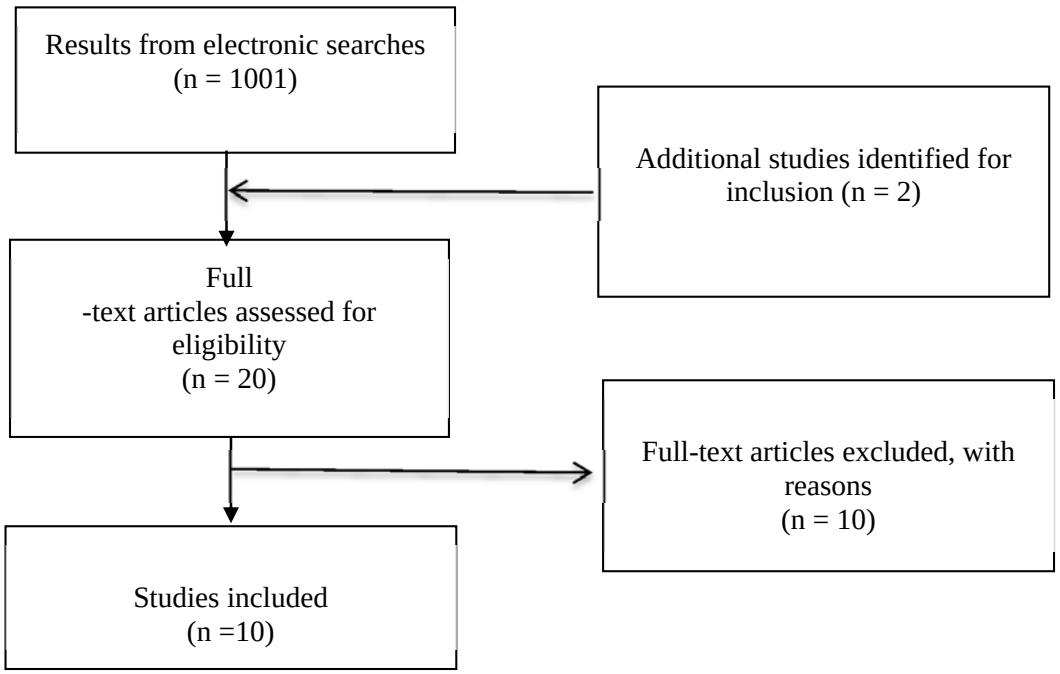
Table 3: Outcomes identified organised according to domains

N.B for the purpose of data reporting Day 2011 and Day 2012 have been combined due to the use of the same cohort of patients

Domain	Outcome	No. of Avulsion Studies Using Outcome	No. of non-vital immature permanent incisor teeth Studies Using Outcome	Total No. of Studies Using this Outcome
Injury Activity				
	Root resorption	2/4	1/5	3/9
	Apical barrier formation	N/A	5/5	5/5
	Time taken for barrier formation	N/A	3/5	3/5
	Periodontal Healing (TTP, swelling/sinus)	4/4	2/5	6/9
	Root & Crown Fracture	N/A	1/5	1/5
	Stage of apical development	1/4	0/5	0/9
	Ankylosis	1/4	0/5	1/9
	Mobility	2/4	0/5	2/9
Physical Consequences of Injury and Functional Status				
	Pain	2/4	2/5	4/9
	Infection	1/4	0/5	1/9
	Loss of vitality	1/4	N/A	1/4
	Tooth loss	2/4	0/5	2/9
Health Resource Utilisation				
	Number of visits	0/4	1/5	1/9
Quality of Life/Family				

Outcomes				
	None reported	0/4	0/5	0/9
Adverse Effects				
	Discolouration	2/4	0/5	2/9

Figure 1: Flow diagram of eligible studies



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