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REVIEW

Factors affecting irrigant extrusion during root canal irrigation: a systematic review

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Abstract

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The aim of the present study was to conduct a systematic review and critical analysis of published data on irrigant extrusion to identify factors causing, affecting or predisposing to irrigant extrusion during root canal irrigation of human mature permanent teeth. An electronic search was conducted in Cochrane Library, LILACS, PubMed, SciELO, Scopus and Web of Knowledge using a combination of the terms 'irrigant', 'rinse', 'extrusion', 'injection', 'complication', 'accident', 'iatrogenic', 'root canal', 'tooth' and 'endodontic'. Additional studies were identified by hand-searching of six endodontic journals and the relevant chapters of four endodontic textbooks, resulting in a total of 460 titles. No language restriction was imposed. After applying screening and strict eligibility criteria by two independent reviewers, 40 case reports and 10 *ex vivo* studies were included in the review. A lack of clinical studies focusing on irrigant extrusion during root canal irrigation was evident. The reviewed case reports focused mainly on the clinical manifestations and management of the accidents and did not provide adequate details on the possible factors that may influence irrigant extrusion. The data from the included *ex vivo* studies were inconclusive due to major methodological limitations, such as not simulating the presence of periapical tissues and not assessing the validity of irrigant detection methods. The extensive variability in the protocols employed hindered quantitative synthesis. The choice of factors investigated in *ex vivo* studies seems not to have been driven by the available clinical evidence. These issues need to be addressed in future studies.

Keywords: accident, apical extrusion, complication, endodontic treatment, irrigant, sodium hypochlorite.

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Introduction

Irrigation of root canals with antibacterial solutions is considered an integral part of chemo-mechanical preparation (Haapasalo *et al.* 2005). In view of the findings showing that a substantial part of the root canal wall is left untouched by contemporary instrumentation techniques (Peters *et al.* 2001, Paqué *et al.* 2010, 2011), irrigation may be considered as the primary method to clean and disinfect these parts of the root canal system (Gulabivala *et al.* 2005, Zehnder 2006, van der Sluis *et al.* 2007).

Specific objectives of irrigation can be categorized into mechanical effects, that is, detachment and removal of microbes or biofilms, pulp tissue remnants, dentine debris and instrumentation products from the root canal system and chemical effects, that is, dissolution of tissue

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remnants, dentine debris, smear layer, chemical disruption of biofilms, killing of microorganisms and inactivation of their by-products (Gulabivala *et al.* 2005, Haapasalo *et al.* 2005, Zehnder 2006, Schäfer 2007). Whilst mechanical effects are exerted by the flow of the irrigant and can be achieved even when inert irrigants are used (e.g. saline), chemical effects are only exerted by chemically active solutions. Currently, sodium hypochlorite is considered the primary irrigant of choice (Zehnder 2006, Dutner *et al.* 2012), mainly due to its unique tissue-dissolving capability (Moorer & Wesselink 1982, Zehnder *et al.* 2002, Naenni *et al.* 2004) and strong antimicrobial effects, especially against biofilms (Arias-Moliz *et al.* 2009, Bryce *et al.* 2009). However, it has been shown to be extremely caustic when in contact with vital tissue *in vitro* (Pashley *et al.* 1985), even at concentrations lower than 0.1% (Chang *et al.* 2001, Heling *et al.* 2001, Barnhart *et al.* 2005). Therefore, its use should be restricted within the confines of the root canal system.

Although inadvertent extrusion of irrigant during root canal irrigation has been regarded as a rare clinical incident (Spencer *et al.* 2007, Crincoli *et al.* 2008), it has been described in a large number of case reports documenting subsequent tissue damage and pronounced symptomatology (Hülsmann & Hahn 2000, Balto & Al-Nazhan 2002, Gernhardt *et al.* 2004, Bowden *et al.* 2006, Pelka & Petschelt 2008, Baldwin *et al.* 2009, Chaudhry *et al.* 2011, Behrents *et al.* 2012). The true frequency of such accidents is unknown, as many of them may not be reported, whilst minor extrusion incidents might even remain undetected due to absence of severe symptoms. A recent survey indicated that nearly half of the responding endodontists (42%) in the United States had experienced at least one NaOCl accident during their practice career (Kleier *et al.* 2008).

As a result, *in vivo* (Lamers *et al.* 1980, Watts & Paterson 1993) and *ex vivo* studies (Hauser *et al.* 2007, George & Walsh 2008, Desai & Himel 2009, Mitchell *et al.* 2011) have tried to elucidate the parameters influencing irrigant extrusion. Literature reviews on the subject have also been published (Hülsmann & Hahn 2000, Mehdipour *et al.* 2007, Spencer *et al.* 2007, Hülsmann *et al.* 2009). However, despite the large number of case reports and experimental studies and the clinical importance of the symptoms following irrigant extrusion, there is a surprising absence of critical appraisal of the published data and synthesis of the available evidence, which are currently substituted by speculation to a large extent.

The aim of the present study was to conduct a systematic review and critical analysis of published data on irrigant extrusion to identify factors causing, affecting or predisposing to irrigant extrusion during root canal irrigation of human mature permanent teeth.

Materials and methods

Review questions

The following questions were addressed:

Which are the variables/factors that cause, affect or predispose to extrusion of irrigant during irrigation of root canals when performing orthograde root canal treatment of mature permanent human teeth?

How can irrigant extrusion during irrigation of root canals be prevented when performing orthograde root canal treatment of mature permanent human teeth?

Literature search

A segregated approach was selected due to the heterogeneous composition of the literature on irrigant extrusion. Ten key articles (one clinical study, five case reports and four *ex vivo* studies) representative of the type of papers that the search was intended to target were initially selected. Appropriate keywords and phrases were extracted from these articles to be used in the electronic searches. Key terms and their combinations were enriched and modified in the course of the search, as additional terms came up and the electronic search was repeated each time. Twenty-five key terms were finally used, combined in four search strategies (Table 1).

Table 1 Example of the electronic search strategy (here in PubMed)

Number	Search strategy	Results
#1	(irrigant OR irrigation OR irrigate OR irrigated OR irrigating) OR (rinse OR rinsing OR rinsed)	60 625
#2	(extrude OR extruded OR extruding OR extrusion) OR (inject OR injected OR injecting OR injection) OR complication OR (accident OR accidental) OR iatrogenic	1 015 909
#3	(root AND canal) OR tooth OR teeth OR endodontic	176 881
#4	#1 AND #2 AND #3	134

The electronic search strategies were adapted and applied to six databases: Cochrane Library (1995-), LILACS (1982-), PubMed (1950-), SciELO (1997-), Scopus (1966-) and Web of Knowledge (1899-). Articles from inception of these databases up to and including January 2012 (1st week) were considered. Moreover, all issues of six endodontic journals were hand-searched: International Endodontic Journal (1980-), Journal of Endodontics (1975-), Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics (1948–2011), Dental Traumatology (and Endodontics; 1985-), Australian Endodontic Journal (1982-) and Endodontic Topics (2002-). A complementary search was made in May 2012 (2nd week).

In addition, the literature search was further enriched with references from the relevant chapters of four endodontic textbooks: 'Endodontics' (Baumgartner *et al.* 2002; Frank 2002), 'Pathways of the pulp' (Himel *et al.* 2006; Peters and Peters 2006), 'Problems in endodontics: etiology, diagnosis, and treatment' (Hülsmann & Rodig 2009) and 'Problem solving in endodontics' (Gutmann & Lovdahl, 2011). Moreover, the reference lists of all full-text articles selected after the screening and of three previously published literature reviews on irrigant extrusion (Mehdipour *et al.* 2007, Spencer *et al.* 2007, Hülsmann *et al.* 2009) were hand-searched for titles not identified by the previously mentioned methods. No specific language restriction was applied to any of the searches, although the electronic searches could only identify studies including at least a title in English.

Study selection

Abstracts were obtained for all the titles identified during the electronic and hand-searches. In cases where an abstract was not available electronically, full-text copies were obtained. Two reviewers (CB and ZP) screened independently titles and abstracts or full-text copies to eliminate articles that clearly failed to meet the screening criteria (Table 2). In cases of disagreement, the studies were included in the next step for eligibility assessment.

Full-text copies were obtained for all titles remaining after screening. Articles not in English were translated. The articles were divided into three categories: (A) clinical studies, (B) case reports and (C) *ex vivo* studies. The reviewers evaluated further the full-text articles to determine eligibility according to more strict criteria within each of the three categories (Table 3). Disagreements at this stage were resolved

Table 2 Screening criteria for the studies identified during the electronic and hand-search

Screening criteria	
Inclusion	**Exclusion**
• Studies concerning irrigant and/or debris extrusion • Clinical studies, case reports or *ex vivo* studies	• Completely off-topic articles • Review articles not reporting any cases, surveys, conference abstracts, comment letters • Articles on the extrusion of microbes/medicaments/root canal filling materials • *In vitro* studies (on artificial root canals) • Animal studies

Table 3 Eligibility criteria applied to full-text articles, for each category. Studies were excluded if they met any of these criteria

Eligibility criteria
A. Clinical studies
1. Not treating mature permanent teeth.
2. Use of obsolete/highly toxic irrigants (e.g. sulphuric acid).
3. Outcome measures also influenced by co-variables other than extruded irrigant (e.g. simultaneously extruded debris or microbes).
4. Outcome measures also influenced by co-variables other than irrigation procedure (e.g. irrigant extruded during instrumentation).
B. Case reports
1. Not reporting the treatment of mature permanent teeth.
2. Studies using obsolete/highly toxic irrigants (e.g. sulphuric acid).
3. Studies reporting direct injection of irrigant into soft tissues (e.g. in place of anaesthetic) rather than extrusion during root canal irrigation.
4. Studies reporting subcutaneous emphysema or similar conditions (e.g. pneumomediastinum) related to root canal irrigants or studies reporting drying of root canals using pressurized air.
5. Studies reporting inhalation/ingestion of irrigants or direct contact of the irrigant with oral mucosa due to leakage through the access opening or through the rubber dam or due to syringe/equipment failure.
C. *Ex vivo* studies
1. Not using mature permanent human teeth.
2. Use of obsolete/highly toxic irrigants (e.g. sulphuric acid).
3. Assessing only debris extrusion, calculation of extruded irrigant not possible from the available data.
4. Outcome measures also influenced by co-variables other than extruded irrigant (e.g. simultaneously extruded debris) without presenting separate data directly on/allowing calculation of the amount of extruded irrigant.
5. Outcome measures also influenced by co-variables other than irrigation procedure (e.g. irrigant extruded during instrumentation).

by joined discussion with an experienced referee (LVDS).

Critical appraisal

Eligible studies were critically analysed independently by two reviewers (CB and ZP), according to predetermined requirements (Table S1). These requirements were based on published guidelines for systematic reviews of clinical studies (Higgins & Green 2008) and on factors that could possibly affect irrigant extrusion as determined in previous studies, to assess the quality of the selected studies in relation to the current review questions. Disagreements were resolved by discussion with an experienced referee (LVDS). A narrative description of methodological limitations was employed.

Data extraction and presentation

Predetermined data for each category (Table S2) were extracted and arranged into data tables. To facilitate comparisons and synthesis of the evidence, the following calculations and conversions were performed:

- Tooth notation was converted to FDI style.
- In case reports, if the periapical status of the involved tooth was not stated clearly, other data such as pulp vitality, radiographic appearance or presence of a fistula were evaluated to determine the presence of a periapical lesion, when possible.
- Statements about the pressure or force applied during syringe irrigation were converted into flow rate statements, according to Boutsioukis *et al.* (2007).
- Reported flow rates were converted to mL s^{-1}. If not reported, average flow rates were calculated by dividing the volume of irrigant (in mL) by the period of time it was delivered in the root canal (in s), when this information was available.
- In case that the type and size of commercially available needles/instruments used were not reported in the study, this information was retrieved from the manufacturer or from other studies employing the same systems/equipment. Needle sizes were converted to the 'Gauge' system (ISO 9626 2001).
- In studies where the position of the needle in the root canal was reported as 'slightly coronal to the binding point' or 'to the point where resistance is encountered', the needle insertion depth was approximated by estimating the point where a needle of known external diameter (D_N) according to ISO specifications (ISO 9626 2001) would bind in an ideal root canal with known apical preparation size (A) and taper (T), according to the equation:

$$L = \frac{D_N - A}{T}$$

  where L is the distance from working length (WL) at which the needle would bind. All values were expressed in mm.
- Weight of extruded irrigant was converted to volume (in mL) in cases that the density of the irrigant was known or could be retrieved from the literature.
- Volumes of extruded irrigant reported as percentage of the total volume of irrigant delivered were converted to mL (when possible) by multiplying the total volume of irrigant by the percentage reported.

In case that any of the required data were not reported in the article or it was impossible to calculate or retrieve them from other sources, they were coded as 'not available' (NA). The data are presented separately for each study category, in a descriptive form.

Results

The combined electronic and hand-search resulted in 460 titles. Abstracts could not be retrieved electronically for 19 of these titles; therefore, full-text copies were obtained. Of these 19 articles, three articles did not have an abstract (Walker 1975, Hirschmann & Walker 1983, Grob 1984), so the screening criteria were applied to the full-text copies.

After the screening, 71 papers were selected by at least one reviewer for full-text evaluation in the next step. Another 39 titles were recovered from the reference lists of these articles, resulting in a total number of 110 articles assessed for eligibility. The publication dates ranged from 1938 to 2012. These articles were written in English (96), German (8), Spanish (2), Portuguese (2) and Japanese (2), and included three clinical studies, 59 case reports and 48 *ex vivo* studies. Following detailed evaluation of the full-text papers according to the eligibility criteria, three clinical studies, 18 case reports and 37 *ex vivo* studies were completely excluded. In addition, one case reported in Becking (1991) and two cases reported in Hülsmann & Hahn (2000) were also excluded based on the eligibility criteria (Table S3). Furthermore, two cases described in two case reports were excluded (Hülsmann & Hahn 2000, Witton *et al.* 2005) because they were also described in other articles (Hülsmann & Denden 1997, Witton & Brennan 2005), so only the most extensive descriptions were assessed. Therefore, the case report of Hülsmann & Hahn (2000) was completely excluded from the review. Similarly, one *ex vivo* study (Fukumoto 2005) was excluded because it described a part of the experiments described in another study (Fukumoto *et al.* 2006); therefore, only the study with the largest sample size was assessed. In addition, from another *ex vivo* study (Fukumoto *et al.* 2004), only the groups consisting of human teeth were included. The reviewers' agreement prior to discussion was 100%, 91.5% and 95.8% for the clinical studies, the case reports and the *ex vivo* studies, respectively.

Forty case reports and 10 *ex vivo* studies were finally included in the present review. Most of these articles were written in English, except for four articles in German, one in Japanese, one in Spanish and one in Portuguese. These studies were critically analysed to assess the quality of available evidence and extract the relevant data. A flow chart of the literature search and the selection process is depicted in Fig. 1.

Case reports

Critical appraisal

Of the 46 accidents described in 40 case reports, none fulfilled all the quality requirements set (Table S1) or provided all the information required for the data table (Table S2). To facilitate comprehension, all numbers within the case reports category from this point and on refer to patients/accidents reported rather than studies.

A description of the patient's profile and medical history was available in 19/46 cases. However, even though NaOCl is the main irrigant used in contemporary endodontic practice (Dutner *et al.* 2012) and a component of widely used household cleaning products, patients were not asked about possible hypersensitivity/allergy to this irrigant apart from three cases (Cymbler & Ardakani 1994, Crincoli *et al.* 2008, Behrents *et al.* 2012). A screening test for allergy was actually performed only in one case (Crincoli *et al.* 2008) to exclude the possibility of an allergic reaction to minor amounts of the irrigant, rather than massive irrigant extrusion. The need for such screening has been stressed by other authors (Kavanagh & Taylor 1998, Hales *et al.* 2001, Chaudhry *et al.* 2011) and

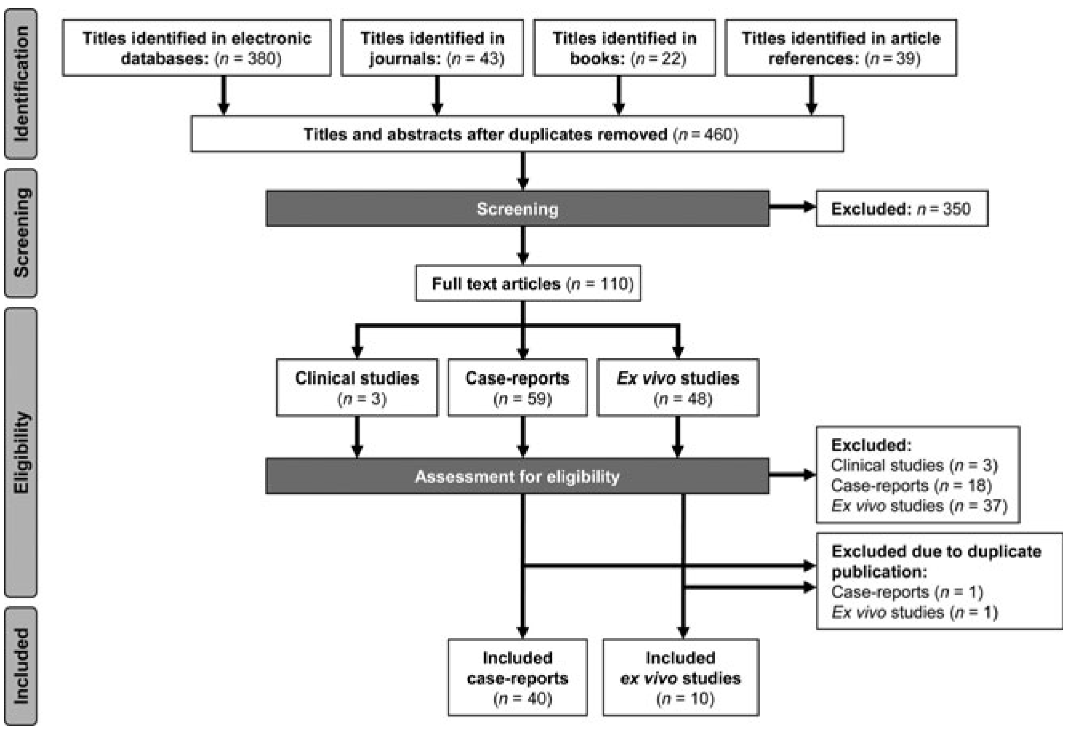

Figure 1 Flow chart of the literature search and the selection process.

by case reports documenting hypersensitivity to NaOCl (Dandakis *et al.* 2000).

All reports stated the involved tooth, but pulp vitality and periapical status prior to the accident were frequently omitted (16/46 and 17/46, respectively), although they may affect irrigant extrusion (Salzgeber & Brilliant 1977). In half of the cases (23/46), a periapical radiograph was not included, preventing a further overview of the root canal anatomy and condition of the periapical tissues. A cone beam computerized tomography (CBCT) scan, which could provide a more detailed three-dimensional view, was only available in one case (Behrents *et al.* 2012). Regarding the size of the root canal at the time of the accident, relevant information was provided only in seven cases, by mentioning the size of the last instrument used, but root canal taper was reported only in one case (Singh 2010).

Most descriptions focused specifically on the type and concentration of the irrigant, possibly due to their presumed relation to extrusion accidents. The type of the irrigant used was reported in all cases, but data on the concentration were not available in 17/46 cases. On the other hand, the volume of the irrigant used at the time of the accident was only available in eight cases, even though the amount of reactants is a critical parameter in chemical reactions.

A general statement on the irrigation method was available in all cases, but further details were very limited. The type of needle used during syringe irrigation, which may have an effect on the risk for irrigant extrusion, especially in case of needle wedging (Boutsioukis *et al.* 2010a, Shen *et al.* 2010, Verhaagen *et al.* 2012) was mentioned only in four accidents. An estimation of needle insertion depth at the time of the accident was reported only in two cases (Joffe 1991, Singh 2010), despite its significance for irrigation and irrigant extrusion (Sedgley *et al.* 2005, Fukumoto *et al.* 2006, Hsieh *et al.* 2007, Boutsioukis *et al.* 2010b). The maximum insertion depth could have been calculated approximately using the size of the needle and the size and taper of the root canal but needle size was reported only in nine accidents and information on the taper of the root canal was not provided in any of them. None of the studies reported quantitative data on the flow rate of the irrigant; instead, subjective estimations were reported in 16/46 cases, despite the fact that high flow rate was the most frequently cited cause of extrusion accidents. The capacity of the syringe used during syringe irrigation, which might also have affected irrigant flow rate (Boutsioukis *et al.* 2007), was mentioned only in 5/46 accidents.

In most of the cases (34/46), a statement was included to describe the time between last irrigation and initiation of signs/symptoms, which could provide an indication about their cause–effect relationship. Moreover, nearly all cases included a detailed description of the signs/symptoms developed (43/46) and the anatomical areas affected (43/46). With respect to the rationale of the accident, in the majority of the cases (28/46), one or more causes for the accident were mentioned. Data supporting the authors' conclusions on the causes of the accidents (e.g. radiographs) were presented only in 10/46 cases. Interestingly, in 39% of the accidents (18/46), the possible cause of extrusion was not discussed at all. In 28 of the 40 cases in which the endodontic treatment was eventually continued, no modifications of the irrigation protocol were reported to avoid repeating irrigant extrusion. Such data would have been extremely valuable for supporting the authors' conclusions regarding the cause of each accident.

Synthesis of evidence

A summary of the most important findings is presented in Table 4. The publication date ranged from 1974 to 2012. Most of the patients were women (39/46). Twenty-four anterior teeth, 15 premolars and seven molars were involved, predominantly in the maxilla (39/46). A vital pulp was reported in 8/46 cases and nonvital pulp combined with normal periapical tissues was reported in 4/46 cases, whilst in 13/46 cases it was associated with a periapical lesion. A horizontal root fracture leading to the necrosis of the pulp only in the coronal fragment was reported in one case.

The size of the root canal at the time of the accident ranged from 20 to 70, as reported in 7/46 accidents. Over-instrumentation leading to enlargement of the apical constriction was either reported ($n = 7$) or radiographically evident ($n = 1$) in 8/46 cases. Moreover, a pre-existing apicectomy without root end filling was reported in 1/46 case. Perforations of the root canal system were reported in 7/46 cases, and they were involved in the accident in all of these cases. Furthermore, a perforation could be suspected from the radiographic appearance in two additional cases, although not reported originally.

Regarding the irrigant used, in 42/46 accidents, NaOCl was used as the single irrigant, whilst in four accidents it was used in combination with hydrogen peroxide, saline or chlorhexidine. However, in these four cases, the accident was also related to sodium hypochlorite. A high concentration of NaOCl (5–5.5%) was used in 10/46 accidents, medium concentration (2–3%) was used in 12/46 accidents and low concentration ($\leq 1\%$) was used in 7/46 accidents. Volume of irrigant used at the time of the accident ranged from 0.5 to 30 mL, as reported in 8/46 cases.

Syringe irrigation was employed in all cases reviewed. An open-ended needle was used in 3/46 cases and a closed-ended needle in 1/46 cases. The size of the needles ranged from 23 to 28G, as reported in 9/46 accidents. The only available data on needle insertion depth referred to the coronal third in one case (Joffe 1991) and to 1 mm short of the apical foramen in another case (Singh 2010). The capacity of the syringe ranged from 3 to 10 mL, as reported in 5/46 cases. Only subjective qualitative estimations about the flow rate were available, stating high flow rate in 11/46 cases, medium flow rate in 1/46 case and low flow rate in 4/46 cases.

Initiation of signs/symptoms immediately after irrigation was reported in 34/46 cases. The signs/symptoms and the affected anatomical area were consistent with the hypothesis of irrigant extrusion related to the treatment of the involved tooth in all cases. According to the original authors' conclusions, the causes of irrigant extrusion were high flow rate (10/46), destruction of the apical constriction either due to over-instrumentation (7/46) or apicectomy (1/46), perforation of the root canal system, either iatrogenic (6/46) or due to root resorption (1/46), wedging of the needle in the root canal (5/46), presence of a periapical lesion (4/46), apical fenestration (1/46), horizontal root fracture (1/46), insertion of the needle beyond the apical foramen (1/46), volume and concentration of the irrigant (1/46) and intentional extrusion (1/46). More than one cause was mentioned in 11/46 accidents. Evidence of a pathway of reduced tissue resistance from the root canal towards soft tissues, oral cavity or maxillary sinus (e.g. fenestration or perforation of the cortical bone, active sinus tract, direct communication with the maxillary sinus and perforation of the root canal above the alveolar crest) was presented in 9/46 accidents.

In forty cases, the endodontic treatment was eventually continued, in the same ($n = 3$) or a subsequent session ($n = 37$), whilst the involved tooth was extracted in 6/46 cases. As a preventive measure, NaOCl was replaced by a different irrigant, either saline, chlorhexidine or hydrogen peroxide in 9/40 cases, the WL was re-established in 2/40 cases, a lower flow rate was employed in 1/40 case and surgical repair of a cervical perforation was conducted in 1/40 case. Reoccurrence of irrigant extrusion was not reported in any case.

Ex vivo studies

Critical appraisal

Amongst the 10 *ex vivo* studies included, none fulfilled all the quality requirements (Table S1) or provided all the information required for the data table (Table S2). Overall, a high variability was noted in the study protocols, even between studies evaluating the same irrigation methods. A specific research hypothesis or aim regarding irrigan extrusion was not defined in three studies (Lussi *et al.* 1999, Desai & Himel 2009, Parente *et al.* 2010). In addition, three studies did not include a group employing conventional syringe irrigation (Lussi *et al.* 1999, Tasdemir *et al.* 2008, Parente *et al.* 2010), precluding direct comparison of various irrigation systems to the current clinical standard (Dutner *et al.* 2012) and hindering comparison with other studies.

The number of specimens used per group ranged from 1 to 24, but none of the studies reported *a priori* sample size calculation, so the risk of inadequate power could not be excluded. Two studies employed unequal sample sizes in at least one of the comparisons described (Lussi *et al.* 1999, Mitchell *et al.* 2011). Initial standardization of the specimens was also inadequate in several studies. Only three studies mentioned selection of specimens with similar morphology but without further details (George & Walsh 2008, Tasdemir *et al.* 2008, Camoes *et al.* 2009). None of the studies evaluated the initial root canal taper of the specimens, seven studies did not assess the initial size of the root canals and nine studies did not take into account the initial cross-sectional shape of the root canals. Root canal curvature was not standardized in six studies, and in the other four studies, the method used to calculate the curvature was not mentioned.

Apical anatomy was also poorly standardized. No study reported verification of a single apical foramen, although in one study a single apical foramen was ensured by removing the apical 3 mm of each specimen (Fukumoto *et al.* 2006). Only three articles attempted to standardize the diameter of the apical constriction using endodontic files, even though in 2 of them it was uncertain whether the files were actu-

Table 4 Summary of the included case reports (NA: Not available)

Study	Tooth	Gender	Radio graph	Pulp status	Periapical lesion	Reduced resistance to extrusion (except periapical lesion)	Destruction of apical constriction
Becker *et al.* (1974)	13	F	✓	Vital			
Grob (1984)	22	F		Nonvital	NA		✓
Patterson & McLundie (1989)	14	F		Nonvital			
Reeh & Messer (1989)	11	F	✓	Nonvital	✓		
Sabala & Powell (1989)	25	M	✓	Nonvital	NA		
Neaverth & Swindle (1990)	22	F	✓	Vital			
Becking (1991)	27	F	✓	NA	NA	Maxillary sinus	
	35	M		NA	NA		
Gatot *et al.* (1991)	11	F		Nonvital	NA		
Joffe (1991)	23	F		NA	NA		
Ehrich *et al.* (1993)	16	M	✓	Nonvital		Maxillary sinus	✓
Cymbler & Ardakani (1994)	21	F		Nonvital	✓		
Tosti *et al.* (1996)	24	F		NA	NA		
	12	F		NA	NA		
Hülsmann & Denden (1997)	23	M	✓	Vital			✓
Kavanagh & Taylor (1998)	15	M	✓	Nonvital	✓	Maxillary sinus	
Juárez & Lucas (2001)	14	M		NA	NA		
Hales *et al.* (2001)	24	F		Vital			
Balto & Al-Nazhan (2002)	11	F	✓	Nonvital	✓		
Gernhardt *et al.* (2004)	34	F	✓	Vital		Cervical perforation	
Witton & Brennan (2005)	12	F	✓	Nonvital	✓	Fistula	
Witton *et al.* (2005)	15	F		Nonvital	✓		
Bowden *et al.* (2006)	37	M		Nonvital	✓		
Schwerin & Gerlach (2007)	11	F		NA	NA		
Thiessen *et al.* (2007)	16	F	✓	Nonvital	✓		
Crincoli *et al.* (2008)	13	F		NA			
Farren *et al.* (2008)	24	F		NA	NA		
Pelka & Petschelt (2008)	22	F	✓	Nonvital	✓		✓
Zairi & Lambrianidis (2008)	15	F	✓	Nonvital		Maxillary sinus	✓
Baldwin *et al.* (2009)	23	F	✓	Nonvital	✓		✓
Doherty *et al.* (2009)	31	F	✓	Nonvital	✓	Cervical perforation	
Markose *et al.* (2009)	16	F		NA	NA		
Sermeño *et al.* (2009)	13	F		NA			
Braitt *et al.* (2010)	21	F	✓	Coronal-nonvital, apical-vital			
Lam *et al.* (2010)	13	F		Vital			
Singh (2010)	15	F	✓	Nonvital	NA		
Wang *et al.* (2010)	23	F	✓	Nonvital			
	47	F	✓	Vital			
Chaudhry *et al.* (2011)	34	F		NA	NA		
	23	F		NA	NA		
	21	F		NA	NA		
	34	F		NA	NA		
Lee *et al.* (2011)	21	F	✓	Nonvital	✓	Cortical bone perforation	✓
Tegginmani *et al.* (2011)	21	F	✓	Nonvital	✓		✓
Behrents *et al.* (2012)	25	F	✓ + CBCT	NA		Apical fenestration	✓
Paschoalino *et al.* (2012)	28	F		Vital			

		Proclaimed cause						
OCl %	Needle type– size	Needle wedging	High flow rate	Over-instrumentation	Perforation	Periapical lesion	Other	Reviewers' comments on the cause
5.25	25G	✓	✓					
3	NA			✓				
1	25G						NA	
1	NA				✓			
5.25	NA						NA	Suspected perforation (radiograph)
2.5	NA				✓			
NA	NA						NA	
NA	NA						NA	
5.25	NA						NA	
5.25	NA	✓						
5.25	Open-ended – 23G			✓				
2	NA						NA	
NA	NA						NA	
NA	NA						NA	
3	NA			✓				
NA	NA		✓				Volume, concentration of NaOCl	Suspected perforation (radiograph)
NA	NA						NA	
5.25	Open-ended – 23G	✓						
1	25G	✓	✓					
5.25	Open-ended – 28 G				✓			
NA	NA		✓			✓		
NA	NA		✓			✓		
NA	NA		✓			✓		
NA	NA				✓			
2.5	NA						NA	
NA	NA						NA	
NA	NA						NA	
3	NA		✓			✓	Apicoectomy	
2.5	Closed-ended		✓	✓				
1	27G			✓				
NA	NA				✓			
5.5	NA						NA	
5	NA		✓					
1	NA						Horizontal root fracture	
NA	NA						NA	
NA	NA						Intentional extrusion	
2.5	25G				✓			
2.5	25G						NA	
5.25	NA				✓			
2	NA						NA	
1	NA						NA	
NA	NA						NA	
NA	NA		✓					Suspected over-instrumentation (radiograph)
3	NA			✓			Root resorption	
3	NA			✓			Apical fenestration	
1	NA	✓					Needle beyond the apical foramen	

ally larger or at least equal to the initial constriction diameter (George & Walsh 2008, Tasdemir *et al.* 2008). Nonetheless, several case reports have linked extrusion to an enlarged apical constriction (Grob 1984, Hülsmann & Denden 1997, Gernhardt *et al.* 2004, Pelka & Petschelt 2008, Zairi & Lambrianidis 2008, Lee *et al.* 2011, Behrents *et al.* 2012).

Regarding the specimen assignment to experimental groups, three studies using different specimens in each group did not state if randomization or matching of the specimens between groups was achieved (Lussi *et al.* 1999, Fukumoto *et al.* 2004, 2006), which may have resulted in selection bias in favour of one of the experimental groups. Furthermore, one study assessed equality of baseline root canal volumes (Hauser *et al.* 2007), but total volume is an overall measure mostly affected by the volume of the coronal and middle third of the root canal; specimens with similar volumes may in fact have had very different canal anatomy, especially in the apical third.

All eight studies evaluating irrigant extrusion in prepared root canals standardized the apical preparation size and the root canal taper. However, three studies did not describe where the apical end-point of the preparation was defined (Fukumoto *et al.* 2004, Desai & Himel 2009, Parente *et al.* 2010). Moreover, in one study, the WL was established 'at the point where a size 15 file was visible at the root end under magnification' (Mitchell *et al.* 2011), which could have resulted in simultaneous enlargement of the apical constriction during root canal preparation, introducing a confounder. Although such modification of the apical constriction might be clinically realistic, it was not highlighted and may have rendered its results noncomparable to other studies.

Irrigants were well described in general. All 10 studies reported the type and concentration. Nevertheless, in two studies, a dye was added to a commonly used irrigant or was used as an irrigant, but no attempt was reported to ensure that the resulting solutions had physical properties (e.g. density, viscosity, surface tension) comparable to the ones of widely used irrigants. The total volume of irrigant used per specimen was not standardized in six studies, which could have a significant effect on both the frequency and the amount of extruded irrigant. Furthermore, in studies employing a negative pressure system with two pathways for irrigant evacuation (EndoVac, Discus Dental, Culver City, CA, USA), it was uncertain how much of the delivered irrigant actually reached the apical end of the preparation and was evacuated by the microcannula, rather than the evacuation tip at the pulp chamber.

The irrigation protocol, which described the main interventions of interest, was not standardized or reported adequately in most studies. Of nine articles describing use of a needle/file in the root canal, three studies did not clarify their type at least in one case (Hauser *et al.* 2007, Camoes *et al.* 2009, Parente *et al.* 2010). In view of the importance of needle type on irrigant flow (Boutsioukis *et al.* 2010a, Shen *et al.* 2010, Verhaagen *et al.* 2012), lack of this information hindered the interpretation of results. All studies mentioned the size of the needles/files/Gutta-percha points used, but in two studies the use of large needles (22–24 G) for irrigant aspiration necessitated excessive enlargement of the root canals far beyond common practice (size 50, .08–.10 taper). Insertion depth was not stated at all in one paper (Camoes *et al.* 2009), whilst in another two studies it was poorly standardized by linking the needle position to its binding point into the root canal (Hauser *et al.* 2007, Desai & Himel 2009), which was inherently affected by root canal geometry and preparation. Moreover, two studies employed a continuous longitudinal movement of the needle/file during irrigation (Desai & Himel 2009, Mitchell *et al.* 2011), which was difficult to standardize; thus, an additional confounding factor was introduced. It is also noteworthy that in 4 of 7 studies not investigating the effect of insertion depth, the position of needles/files was different amongst the compared groups. Such differences in the insertion depth may have introduced bias in the results in favour of certain irrigation systems, as insertion depth has been identified as a parameter affecting irrigant flow (Hsieh *et al.* 2007, Boutsioukis *et al.* 2010b, Malki *et al.* 2012). One study employing manual-dynamic activation (Parente *et al.* 2010) did not report the displacement of the Gutta-percha point during each stroke. In addition, in 2 of the 3 studies using irrigant activation, the power setting of the devices was not specified (Tasdemir *et al.* 2008, Desai & Himel 2009).

Quantitative data on the irrigant flow rate were not available for at least one group in three studies (Lussi *et al.* 1999, Tasdemir *et al.* 2008, Camoes *et al.* 2009). In addition, in another three studies, a standardized flow rate was claimed by hand-control of a syringe (Hauser *et al.* 2007, Parente *et al.* 2010, Mitchell *et al.* 2011), which cannot be regarded as adequate standardization (Boutsioukis *et al.* 2007). More reliable approaches included a syringe pump (Fukumoto *et al.* 2004, 2006, Desai & Himel 2009), a regulated compressed air supply connected to the syringe plunger (George & Walsh 2008) or inherent control by the irrigation systems used (Lussi *et al.* 1999, Hauser *et al.* 2007, Desai & Himel 2009). In the case of negative pressure systems, flow rate is affected by the suction pressure applied. Nevertheless, 3 of 5 studies employing such systems did not report or standardize the suction pressure (Desai & Himel 2009, Parente *et al.* 2010, Mitchell *et al.* 2011). So, it appears that in 7 of 10 studies, the flow rate was either poorly controlled or not standardized at all at least in one experimental group, despite the fact that speculations on the correlation of high flow rate and irrigant extrusion were very common in the case reports reviewed, and a possible link has been shown in an *ex vivo* study (Fukumoto *et al.* 2004).

Surprisingly, the presence of periapical tissues was not simulated at all in four studies. In these studies, the apical foramen was surrounded by ambient air at atmospheric pressure. In one additional study, it was not stated clearly whether any material was used for this purpose. Three publications (Tasdemir *et al.* 2008, Desai & Himel 2009, Parente *et al.* 2010) employed approximately the same irrigant collection device originally proposed by Fairbourn *et al.* (1987) and later modified by Myers & Montgomery (1991). In that model, each root was attached to an empty collection vial (full of air), where extruded irrigant was collected. Atmospheric pressure in the vial was ensured by communication with the external environment (pressure equalization). One publication evaluated the amount of droplets ejected horizontally from the apical foramen during irrigation (George & Walsh 2008). The relevance of this method to *in vivo* conditions is also questionable. The choice of not simulating the periapical tissues constituted a fundamental methodological limitation, as emphasized also in 4 of 10 studies (George & Walsh 2008, Tasdemir *et al.* 2008, Camoes *et al.* 2009, Desai & Himel 2009), and it resulted most probably in a systematic bias of the amount of extruded irrigant towards overestimation, as periapical tissues may act as a natural barrier and inhibit apical extrusion *in vivo* (Salzgeber & Brilliant 1977). Five studies overcame this limitation by immersing the root ends into various solutions or gels, but four of them did not provide any justification for the selection of specific materials and their relevance to the *in vivo* conditions (Fukumoto *et al.* 2006, Hauser *et al.* 2007, Camoes *et al.* 2009, Mitchell *et al.* 2011).

Regarding the assessment of irrigant extrusion, three articles evaluated irrigant extrusion only as a binary variable (yes/no) and compared its frequency between different groups or the minimum flow rate causing extrusion. Nonetheless, binary evaluation assigned the same importance to minor and major extrusion and may have led to erroneous conclusions. Two papers additionally analysed the extent of the discoloured gel area to provide a quantitative measure of irrigant extrusion (Fukumoto *et al.* 2006, Mitchell *et al.* 2011). However, evaluation of a three-dimensional effect (volume of discoloured gel) based on a two-dimensional image mainly depicting the outer extents of the discoloured area may have discarded valuable data, as the discoloured volume may not have been uniform and isotropic. Furthermore, in one study (Fukumoto *et al.* 2006) both NaOCl and EDTA were used, without examining if extruded EDTA had any effect on the detection of NaOCl by the colour indicator. The exact quantification method of the extruded irrigant was not specified in one study (Parente *et al.* 2010). Blinded or automatic/computerized evaluation of the results was not mentioned in any of the studies.

None of the included studies reported any data on the validity of the method used to evaluate irrigant extrusion, such as accuracy, minimum amount of irrigant that could be detected (sensitivity) and possibility of false-positive results (specificity), whilst only two papers reported repeating the experiments under the same conditions and on the same specimens (Fukumoto *et al.* 2004, George & Walsh 2008), which could be used to assess the repeatability of the methods. In addition, in three studies expressing extruded irrigant into arbitrary units (Fukumoto *et al.* 2006, George & Walsh 2008, Mitchell *et al.* 2011), no attempt was made to correlate these results to actual volume of extruded irrigant, to provide clinically meaningful information and facilitate comparison with other studies. Furthermore, one study did not perform a statistical analysis of the results. Limitations of the evaluation methods were not discussed in any of the studies.

Synthesis of evidence

The publication date of the 10 *ex vivo* studies ranged from 1999 to 2011. The main independent variable under investigation (9/10) was the irrigant delivery or activation method. Other factors evaluated were

Table 5 Summary and main findings of the included *ex vivo* studies. All results refer to statistically significant differences, unless mentioned

Study	Teeth	Group size	Root canal shape	Periapical tissues	Irrigation method	Insertion depth (mm from WL)
Lussi *et al.* (1999)	Molars	14–24	Not instrumented	Zn-phosph. + blood-like solution	NIT device (previous version) NIT device (latest version)	Crown
Fukumoto *et al.* (2004)	Canines	1	40.06 or 50.08	NA	Syringe (27G open-ended needle) Syringe (27G open-ended needle) + aspiration (22G)	5[A] or 15[B] 5[C] or 15[D] (deliv) + 15[C] or 5[D] (asp)
Fukumoto *et al.* (2006)	Canines	7	50.10 - No constriction	Saline agar	Syringe (27G open-ended needle) + aspiration (24G)	12 (deliv) + 2[A] or 3[B] (asp) 2[C] or 3[D] (deliv) + 12 (asp)
Hauser *et al.* (2007)	Single-rooted <10°	15	30.02	Gelatin	A. Syringe (25G needle)[a] B. Syringe (25G needle) C. RinsEndo (26G open-ended needle)	Estimated ≥ 10 Estimated ≥ 7.5
George & Walsh (2008)	Single-rooted <10°	8	50.05 (F5), constriction 15 or 20	No	Syringe (25G open-ended or closed-ended needle) Syringe delivery[a] + Er, Cr:YSGG or Er:YAG laser, two types of tips	5 or 10
Tasdemir *et al.* (2008)	Incisors	20	30.09 (F3)	No	A. Syringe (30G closed-ended needle)[a] B. Syringe delivery[a] + PUI	1–2 1
Camoes *et al.* (2009)	Molars	17	A. no instrument B. size 15 C. size 20	Starch	Syringe (22G needle)	Canal entrance
Desai & Himel (2009)	Incisors	22	50.04	No	A. EndoVac microcannula (30G) B. EndoVac macrocannula (24G) C. Syringe delivery (pulp chamber) + EndoActivator (35 .04 tip) D. Syringe (30G closed-ended needle) E. Ultrasonically activated 25G open-ended needle F. RinsEndo (26G open-ended needle)	0 Estimated ≥ 1.3 2 – moving 2 – moving Estimated ≥ 1.3 – moving Coronal third – moving
Parente *et al.* (2010)	Single-rooted	10	40.06	No	A. EndoVac-full sequence B. Syringe delivery (4 mm from WL) + Manual-dynamic irrigation (40. 06 Gutta-percha cone)	0 0 – moving
Mitchell *et al.* (2011)	Single-rooted anterior <20°	10	35.06 or 50.06	Agarose gel	A. Syringe delivery[a] + EndoActivator (25 or 35 .04 tip) mode 3 B. Syringe delivery[a] + Rispi-Sonic file on MicroMega 1500 C. Syringe delivery[a] + PUI (size 15/25 mm file) at 36% power D. EndoVac microcannula (30G) E. Syringe (27G open-ended needle)	2 – moving 2 – moving 1 0 – moving ≥ 2 – moving

NA: Not available.
[a]Syringe irrigation was used to fill the root canal passively with a small volume of irrigant.

Irrigant	Irrigant volume (mL)	Time (s)	Flow rate (mL s^{-1})	Results
NaOCl 1%, 2% or 3%	NA 70–105	600 or 900	NA 0.116	No extrusion
NaOCl 6% or EDTA 15%	NA	NA	Under evaluation (0.016–0.15)	Maximum flow rate without extrusion: A, B < C < D
NaOCl 6% + EDTA 14%	6 (NaOCl) + 9 (EDTA)	180 (EDTA) + 120 (NaOCl)	0.05	Amount of extruded irrigant: A, B, D < C
NaOCl 2% + fuchsin	Root canal NA	180 NA	NA 0.083 0.103	Frequency of extrusion: A, B < C
Toluidine blue	1	5	0.2	Amount of extruded irrigant: Laser, open-ended > closed-ended
	Root canal		NA	Constriction: size 20 > size 15 Needle depth: 5 mm > 10 mm
NaOCl 6%	Root canal	180	NA	Amount of extruded irrigant: A>B
NaOCl 5.25%	3	NA	NA	Frequency of extrusion: A < B < C No statistical analysis
Tap water	3.5	30	0.116	Amount of extruded irrigant: A, B, C < D, E, F
		34	0.103	
NaOCl 5.25% + EDTA 17%	15	180	0.083 0.083 (during delivery)	Amount of extruded irrigant: A < B
NaOCl 6%	Root canal	30	0.066 (during delivery)	Frequency of extrusion: Size: 35 .06 < 50 .06 In 35 .06 canals: A, C, D < B, E
	Root canal			Amount of extruded irrigant: In 35 .06 canals: B < C, E In 50 .06 canals: A, B, C, D < E
	Root canal			
	2 2		0.066 0.066	

needle insertion depth (3/10), apical preparation size (2/10), canal patency size (1/10), apical constriction size (1/10), needle type (1/10) and irrigant flow rate (1/10). Four studies assessed the influence of more than one factor. A summary of the methodology and the results of the included *ex vivo* studies are presented in Table 5, to limit data duplication in the text.

Due to the significant methodological limitations described above and the extensive variability in the protocols employed, the available data were not considered reliable or homogenous and detailed quantitative synthesis or meta-analysis was not attempted. Thus, only a qualitative description of the main findings was attempted to summarize possible trends and serve as a starting point for further research.

Syringe irrigation may result in more extrusion compared to negative pressure systems, sonic or ultrasonic activation (Tasdemir *et al.* 2008, Mitchell *et al.* 2011). However, it is uncertain whether there is a difference compared to a positive pressure system (RinsEndo; Hauser *et al.* 2007, Desai & Himel 2009). Open-ended needles seem to extrude more irrigant than closed-ended needles (George & Walsh 2008). Positioning the needle closer to WL and enlargement of the apical constriction may also lead to increased extrusion (Fukumoto *et al.* 2006, George & Walsh 2008). Negative pressure systems may be resulting in less extrusion than syringe irrigation, positive pressure systems or simultaneous delivery and ultrasonic activation systems (Fukumoto *et al.* 2004, 2006, Desai & Himel 2009), but it is unclear whether they may retain an advantage over sonic or ultrasonic activation systems (Desai & Himel 2009, Mitchell *et al.* 2011). It is also unclear if there is a difference between sonic and ultrasonic devices (Mitchell *et al.* 2011). Laser-activated irrigation may be comparable to syringe irrigation by open-ended needles in terms of irrigant extrusion, whilst closed-ended needles may extrude less irrigant (George & Walsh 2008). However, it must be emphasized that the available evidence was insufficient to allow more definite conclusions about these comparisons.

Discussion

Extrusion of irrigant in small quantities may be occurring during instrumentation of the root canal, regardless of the type of instruments and the preparation technique (Hülsmann *et al.* 2009). However, it has not been linked to the extreme sequelae described in case reports as irrigant extrusion accidents. Rather, in 34 of the 46 accidents included in the present review, it was clearly stated that acute symptoms developed immediately after irrigation. Thus, the present review focused specifically on the factors influencing irrigant extrusion during root canal irrigation and on preventive measures to avoid it. To fulfil these aims, strict criteria were implemented to exclude clinical and *ex vivo* studies evaluating outcomes such as postoperative pain (clinical) or the total amount of extruded material (irrigant and debris; *ex vivo*), which were influenced by confounding variables. In addition, studies evaluating irrigant extrusion during instrumentation or collectively during instrumentation and irrigation were also excluded to avoid confounding effects on the primary variable of interest, that is, the amount of irrigant extruded during irrigation.

Animal studies identified during the search (Lamers *et al.* 1980, Watts & Paterson 1993) were excluded from the present review due to anatomical differences between human and animal teeth (Holland 1992). Nevertheless, a sensitivity analysis showed that these studies would not have been eligible even without this restriction, because histological findings could not be attributed only to irrigant extrusion. Moreover, *in vitro* studies on artificial root canals (Lee *et al.* 1991) were also excluded due to the hydrophobic surface of the plastic compared to dentine, which could have an effect on irrigant penetration and extrusion, an assumption that has been verified experimentally (Fukumoto *et al.* 2004).

Despite the abundance in case reports and *ex vivo* publications, a lack of clinical studies concerning irrigant extrusion was evident. The adverse nature of irrigant extrusion and the related sequelae render prospective randomized controlled clinical studies unethical, unless chemically inert irrigants are employed. The relatively rare occurrence of such incidents also limits the use of observational prospective or retrospective designs. As a result, the available clinical evidence was limited to the uncontrolled descriptive data presented in case reports, which are ranked at the lowest level of evidence (Sutherland 2001). However, these publications were systematically reviewed to identify possible factors that may affect/predispose to irrigant extrusion and examine whether there is evidence supporting widely reported views on the causes of irrigant extrusion. Furthermore, identified possible factors could be used as input for future experimental studies.

Case reports describing the development of subcutaneous emphysema or related conditions (e.g. pneumomediastinum) were excluded from the present review even though they may have been caused by extrusion of H_2O_2. It is uncertain whether the gas responsible for the emphysema in these cases was produced outside the root canal following extrusion of the H_2O_2 or inside the root canal and later escaped through the apical foramen or a perforation. Due to the significantly lower density and viscosity, the flow of gases is markedly different from the flow of irrigants (Truskey *et al.* 2009); therefore, extrusion in these cases may not be comparable to the extrusion of NaOCl. Furthermore, the popularity of H_2O_2 as an irrigant has declined considerably (Dutner *et al.* 2012). Studies reporting drying of root canals using pressurized air were also excluded because air extrusion could have contributed to the accident.

A comprehensive description of the extrusion accidents was undertaken in only a small number of reports. The vast majority of the assessed publications provided minimum details and focused on the clinical manifestations, short- or long-term complications and the management of the injury, whilst little attention was put on the aetiology and prevention, mostly limited to authors' speculations. It is questionable whether such case reports can add to the current knowledge. Incomplete description of the accidents hindered the identification of potential factors influencing irrigant extrusion, and a direct cause–effect relation could not be documented for any of the factors reported. However, it is also possible that a more complicated combination of factors, both technique related and anatomy related, may be necessary to cause an extrusion accident. In the future, it would be helpful if extrusion accidents were registered in a standardized way in university clinics and private practices, to obtain more information on the prevalence and the conditions of the accidents.

Both teeth with vital and nonvital pulps with or without periapical lesions were involved in the extrusion accidents, which is in agreement to the findings of Kleier *et al.* (2008). Amongst the eight cases reported with a vital pulp, extrusion was linked either to needle wedging, perforation or over-instrumentation, except for two cases that did not discuss the cause of the accident. Needle wedging was a technique-related factor and has been shown to increase irrigant pressure at the apical foramen when open-ended needles are used (Boutsioukis *et al.* 2010c), whilst over-instrumentation and perforation were anatomy-related factors, leading to increased cross-sectional area of the pathways connecting the root canal to the surrounding tissues, so the resistance to irrigant extrusion was decreased. Based on the current evidence, there seems to be little justification for the assumption that irrigant extrusion may occur in vital cases, provided that the abovementioned errors are prevented.

Similar causes were also mentioned in the 21 cases of reported nonvital teeth. Needle wedging, perforation, over-instrumentation and apicoectomy were also linked to the accidents but only in half of the cases (10/21). The presence of a periapical lesion, which is an anatomy-related factor, was specifically reported as a cause in 4/21 cases, even though 13/21 teeth were associated with periapical lesions. As radiographic examination was primarily based on periapical radiographs, it is probable that the presence of periapical lesions was underestimated due to the low negative prognostic value of periapical radiographs (Wu *et al.* 2006), so approximately half of the 4/21 teeth reported with normal periapical tissues may have been associated with periapical lesions as well. A bone lesion could have contributed to the accident in these cases by reducing the periapical tissue resistance to extrusion, but long-standing periapical lesions have also been associated with an increased possibility of external apical root resorption (Vier & Figueiredo 2002), resulting in an effect similar to over-instrumentation. Hence, extrusion accidents may be more probable in teeth with nonvital pulps and periapical lesions, in accordance with Kleier *et al.* (2008), although the large number of case reports not providing data on pulpal and periapical conditions precluded more definite correlations.

Apart from the presence of a periapical lesion, a pathway of reduced tissue resistance towards soft tissues, oral cavity or maxillary sinus (e.g. cortical bone fenestration or perforation, sinus tract, direct communication with the maxillary sinus, perforation of the root canal above the alveolar crest) was documented in 9/46 cases and could be an additional factor leading to extrusion accidents, as hypothesized previously (Kleier *et al.* 2008). In addition, extrusion accidents were more frequently reported in women (85%) and in maxillary teeth (85%), in agreement to a recent survey (Kleier *et al.* 2008). These findings have been attributed to possible decreased bone thickness around the tooth apices, rather than imbalance between men and women or mandibular and maxillary teeth receiving endodontic treatment (Kleier *et al.* 2008), so reduced resistance to extrusion may also be expected in these cases. It has been shown that NaOCl may degrade cancellous bone but seems to be well contained by the cortical bone *ex vivo* (Kerbl *et al.*

2012). Therefore, it may be speculated that the severe symptomatology of extrusion accidents, which is mainly associated with soft tissues, may be more probable to develop when the integrity of the cortical bone is compromised. Application of cone beam computerized tomography in future accidents may provide the evidence to verify these hypotheses, as shown in a recent case report (Behrents *et al.* 2012).

Syringe irrigation was employed in all the reported accidents. However, this finding may be attributed to the wider use of this method compared to other irrigation methods and systems (Dutner *et al.* 2012). The same could apply to the open-ended needles that were used in 3/4 accidents reporting the needle type, although it has been shown that these needles result in the development of higher pressure at the apical foramen compared to closed-ended needles (Boutsioukis *et al.* 2010a, Verhaagen *et al.* 2012).

High irrigant flow rate was frequently reported as a cause of extrusion, and its avoidance was recommended to reduce the risk. Nevertheless, almost two-thirds of the descriptions did not include any data on the flow rate used, and the other one-third only provided qualitative data. The ability of clinicians to estimate irrigant flow rate inevitably relied on subjective estimation. There is no unanimous definition of 'low' or 'high' flow rate in endodontic irrigation. In addition, a wide variability in the flow rate during syringe irrigation has been reported amongst endodontists, despite the fact that all participants were aware of the possibility for irrigant extrusion and agreed that a low flow rate should be used in general (Boutsioukis *et al.* 2007). Therefore, qualitative data on irrigant flow rate presented in case reports should be evaluated with caution.

The main significant outcome of irrigant extrusion, especially in the case of NaOCl, is its caustic effect on vital tissues (Pashley *et al.* 1985). However, in *ex vivo* studies, the interest has been focused on the amount of irrigant leaking from the apical foramen, which is a surrogate outcome. The link among, the amount and concentration of the extruded irrigant, the effect on periapical tissues and the development of untoward signs and symptoms have not been established beyond doubt. No specific trend was identified in the reviewed case reports regarding either the volume or the concentration of the irrigant, and it should be noted that in many of the included cases a medium or low concentration was used. Nonetheless, it may be difficult to quantify the intensity of patient symptoms whilst controlling for individual differences; the clinically reported volume may also not be reliable because it is uncertain how much of the irrigant was actually extruded. Similarly, routine measurement of NaOCl concentration is uncommon amongst practitioners, so clinical reports on the concentration may be also inaccurate. Although there is no indication from the included case reports, it may still be reasonable to assume that, as tissue damage is the result of a chemical reaction, the amount (volume and concentration) of the reactant (irrigant) is related to the outcome, provided that the other reactant (tissue) is in excess.

It is noteworthy that possible anatomy-related factors that have been implicated in several case reports, such as perforation and presence of a periapical lesion, have not been evaluated *ex vivo*. Most of the reviewed *ex vivo* studies have focused on technique-related factors. Still, only one study investigated the effect of enlarging the apical constriction, which can be considered similar to mild over-instrumentation, and another one assessed the effect of irrigant flow rate, which was the most frequently reported technique-related factor in the case reports. Furthermore, no *ex vivo* data were found on the effect of needle wedging. To the contrary, published studies have mostly focused on the effect of irrigation methods and systems. Thus, it seems that the choice of factors investigated in *ex vivo* studies has not been driven by the available clinical evidence.

Currently employed irrigation methods can be divided into delivery and activation. Delivery methods, such as syringe irrigation or negative pressure irrigation, can be applied independently. Some irrigation systems, such as an ultrasonically activated needle (Desai & Himel 2009) or the Rins-Endo system (Air Techniques Inc, NY, USA), are capable of both delivery and activation of the irrigant, so they can also be applied independently. On the other hand, activation methods, such as sonic, ultrasonic or laser activation, normally require prior irrigant delivery, most frequently by syringe irrigation. Therefore, it is not reasonable to compare delivery methods to activation methods in terms of extrusion, unless the delivery prior to activation is also taken into account. In addition, irrigation techniques strive to maintain a critical balance between cleaning efficacy and patient safety, and these two parameters need to be evaluated always in combination (Haapasalo *et al.* 2010). Comparisons regarding irrigant extrusion are meaningful when conducted between methods or systems known to provide comparable cleaning effects.

Conclusions

There is a lack of clinical studies focusing on irrigant extrusion during root canal irrigation. Currently available case reports provide limited data on the possible factors that may influence irrigant extrusion. *Ex vivo* studies are inconclusive due to major methodological limitations and extensive variability in the protocols employed. The choice of factors investigated in *ex vivo* studies seems not to have been driven by the available clinical evidence. These issues need to be addressed in future studies.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Quality requirements during critical appraisal of eligible studies.

Table S2. Data extracted from included studies.

Table S3. Excluded studies.

