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DOI:

[10.1177/0022034518769255](https://doi.org/10.1177/0022034518769255)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Ali, A. H., Koller, G., Foschi, F., Andiappan, M., Bruce, K. D., Banerjee, A., & Mannocci, F. (2018). Self-Limiting versus Conventional Caries Removal: A Randomized Clinical Trial. *Journal of Dental Research*.
<https://doi.org/10.1177/0022034518769255>

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Self-limiting versus conventional carious tissue removal: a randomized clinical trial.

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Manuscript word counts:

Words count (without abstract, author contribution, acknowledgment, conflict of interest declaration): 3080 words

Total words count: 3659 words

Total number of tables/figures: 5

Number of references: 23

Appendix word counts:

Words count: 697 words

Total number of tables/figures: 5

Abstract

A single-blind randomized controlled clinical trial in patients with deep caries and symptoms of reversible pulpitis compared outcomes from a self-limiting excavation protocol using chemo-mechanical Carisolv™ gel / operating microscope (self-limiting) vs. selective removal to leathery dentin using rotary burs (control). This was followed by pulp protection with mineral trioxide aggregate (MTA), restoration with glass ionomer cement and resin composite, all in a single visit. The pulp sensibility and periapical health of teeth were assessed after 12 months, in addition to the differences in bacterial tissue concentration post-excavation. Apical radiolucencies were assessed using Cone beam computed tomography/periapical radiographs (CBCT/PA) taken at baseline 0 months (M0) and 12 months (M12). 101 restorations in 86 patients were placed and paired subsurface and deep (post-excavation) dentin samples were obtained. DNA was extracted and bacteria-specific 16S rRNA gene quantitative PCR was performed. No significant difference was found in bacterial copy numbers

normalised to mass of dentin ('load') between the self-limiting (96.3% reduction) and control protocols (97.1%, $p=0.33$). The probability of 12 month success was 4 times (OR=4.33 C.I. 1.2-15.6; $p=0.025$) higher in the self-limiting protocol compared to the control (conventional excavation technique), with pulp survival rates of 73.3% and 90% respectively ($p=0.049$). Molars had a 4 times higher probability of success compared to premolars (OR=4.17 C.I. 1.17-14.9; $p=0.028$) and symptom severity did not statistically predict outcome (OR=0.41, C.I. 0.12- 13.9, $p=0.153$). Teeth with severe pain symptoms failed at a higher rate in the control group. CBCT detected significantly more periapical (PA) lesions than PA radiographs at the baseline visit ($p<0.001$). In conclusion the self-limiting caries excavation protocol under magnification increased pulp survival rate compared to rotary bur excavation. (ClinicalTrials.gov NCT03071588).

Keywords: Pulpitis, Radiography, Bacteria, CBCT, qPCR, selective caries excavation, Carisolv

Introduction

Reviews of the clinical management of deep carious lesions in teeth with reversible pulpitis have concluded that selective carious tissue removal protocols reduce the risk of pulp exposure, post-operative symptoms and increase ultimate pulp survival (Schwendicke *et al.* 2013, Ricketts *et al.* 2013, Banerjee *et al.* 2017). However, there is little evidence currently available to identify the optimal operative method to excavate carious tissue (Schwendicke *et al.* 2015).

Cone Beam Computed Tomography (CBCT) has been found to be more effective than periapical radiographs (PA) in assessing the outcome of pulp protection procedures

(Hashem *et al.* 2015) and in radiographic/histologic studies on human cadavers, more effective in detecting the presence of apical periodontitis (Kanagasingam *et al.* 2017). Indirect pulp protection of teeth presenting with pulp inflammation and pre-operative periapical radiolucencies in CBCT had less successful outcomes than those with no radiolucencies (Hashem *et al.* 2015). In addition, a minimally invasive chemo-mechanical excavation method, Carisolv™ gel (Rubicon Lifesciences, Gothenburg, Sweden) has been shown to remove the more heavily contaminated carious dentin whilst retaining the demineralized, affected dentin (Banerjee *et al.* 2000). The use of an operating microscope, combined with chemo-mechanical Carisolv™ gel in deep carious tissue excavation procedures, has the potential to further minimize sound tooth structure loss.

Following CONSORT guidelines, this randomized controlled clinical trial (RCT) investigated the one-year clinical outcomes of two excavation protocols in deep carious lesions in patients with signs and symptoms of reversible pulpitis. Radiographic (PA/CBCT) and microbiological findings, as well patient symptoms were correlated with pulp vitality. The control excavation protocol (conventional subjective removal to leathery dentin using rotary burs without magnification) was compared to a self-limiting (experimental) protocol including the use of an operating microscope and Carisolv™ gel for the chemo-mechanical removal of deep carious dentin with hand instrumentation. The primary RCT outcome was the preservation of pulp sensibility and periapical health using clinical and radiographic assessment after one year of treatment. The secondary outcomes were the enumeration of the bacterial load (gene copy numbers/mg) in samples of excavated carious tissue collected pre- and post-excitation in each protocol. The null hypothesis was that there is no difference clinically and radiographically between the two operative protocols in preserving pulp

vitality after 12-month follow-up (M12), with the experimental group reducing bacterial tissue concentration as effectively as the control group.

Materials and Methods

Study design, patient recruitment and randomization

This single-blind, two-arm, parallel group randomized controlled clinical trial (RCT), approved by the London-South East research ethics committee and registered with NHS England Research Authority (14/LO/0880, IRAS project ID 156456; ClinicalTrials.gov NCT03071588), was designed to have 80% power and a Type I error probability $\alpha = 0.05$ to detect a difference between the two arms. The difference in the percentage of failures between the two arms was assumed to be 20% at M12. A sample size of 88 restorations was calculated anticipating a 10% loss to follow-up. Patients were recruited from the emergency dental clinics of King's College London Dental Institute, London, UK. Patient information sheets were distributed and informed written consent obtained prior to study commencement. Block randomization was performed centrally by the Biostatistics Unit, Dental Institute, King's College London with the tooth as the unit of randomization. The samples were stratified according to cavity size (1,2 or >2 walls) as a prognostic factor to be balanced during concealed allocation of patients in to each study group. Stratified random sampling was adopted for group allocation (using a random number generator). Allocation concealment was performed using a central telephone system. The patients, clinical & radiographic examiners were blinded to the protocol used. Teeth were divided according to the presenting symptoms (mild and severe), as described by Hashem *et al* (2015). Inclusion and exclusion criteria are described in Table 1.

Clinical procedures

Operative procedures were undertaken by 30 endodontic residents, who received calibration training on carious extracted teeth using both protocols. Methods of pulp assessment included pulp sensibility, palpation and percussion tests, along with the presence of pain, abscess, sinus tract, and abnormal mobility. Sensibility tests undertaken at M0 and M12 included thermal (Endo-frost, Roeko Coltène/Whaledent, Germany) and electric pulp testing (Kerr Vitality Scanner 2006; SybronEndo, Orange, CA, USA). PA and CBCT were taken with standardized settings (Appendix section 1) and used to assess the periapical area health/pathosis radiographically at M0 / M12. Teeth with PA or CBCT radiolucencies exceeding twice the width of the periodontal ligament space at baseline were excluded from the study (Bornstein *et al.* 2011).

In the control group, access through cavitated enamel was gained using a high-speed TA-98 handpiece (W&H Dentalwerk GmbH, Bürmoos, Austria) with carbide and diamond burs and copious water spray, to the enamel-dentin junction (EDJ). Superficial carious dentin samples were collected with a single sterile spoon excavator (Ash G5; Claudius Ash Ltd., Potters Bar, UK) and weighed. The removal of bacterially contaminated (caries-infected) dentin continued using carbon-steel rose-head burs (Ash Instruments, Dentsply, Gloucester, UK) in a slow-speed WA56A handpiece (W&H Dentalwerk Bürmoos GmbH, Bürmoos, Austria). In this group, no operating microscope was used. The excavation endpoint was the detection of a leathery dentin using a sharp dental explorer (Schwendicke *et al.* 2016, Banerjee *et al.* 2017) after which a final dentin sample was obtained and weighed, prior to immediate storage at -80C.

In the experimental group, access through cavitated enamel and microbiologic sampling was undertaken as above. Carisolv™ gel (Rubicon Lifesciences,

Gothenburg, Sweden) was used to excavate carious dentin using the hand instruments supplied, until no further carious tissue was removed. All procedures in this group were undertaken using an operating microscope (G6, Global surgical corporation, St. Louis, MO, U.S.A.), the magnification set at the operators' discretion. In both groups, MTA®caps (Acteon, Pierre Rolland, Merignac, France) were activated as per manufacturer instructions, a layer (~2 mm) applied on the pulp aspect of the prepared cavities and condensed gently and left for 5-6 minutes to allow initial setting before applying a layer of glass ionomer cement (GIC) (Fuji IX, GC Corporation, Japan). This was followed by etching with 37% orthophosphoric acid for 10-15 secs, rinsing with water then bonding with adhesive (Scotchbond Universal, 3M Oral Care, St. Paul, MN, USA) followed by the placement of an overlying restoration of resin composite (N'Durance; Septodont, Louisville, KY, USA). Standardized clinical / radiographic follow-up was carried out at 12 months (± 2 weeks) (M12). Examiners were blinded to the treatment groups.

Radiographic assessment

For each tooth, a periapical radiograph/CBCT scan that best confirmed the presence/absence of PA radiolucency was selected and assessed by a consensus panel comprising two experienced endodontists that were unaware of the objectives of the trial. A radiolucency was defined as one associated with the radiographic apex of the root, at least twice the width of the periodontal ligament space (Low et al. 2008, Bornstein et al. 2011). Details of the radiographic assessment are described in Appendix section 2 and an example of images is given in Appendix Figure 1.

DNA extraction and qPCR

DNA was isolated from the carious dentin samples using Sigma GenElute™ Bacterial Genomic DNA Kits (Sigma-Aldrich, Irvine, UK). An estimation of bacterial gene

numbers per mg weight was obtained by qPCR assays using a Rotor-Gene Sybr green PCR kit (Qiagen, UK). The detailed protocols are provided in the Appendix sections 3 and 4.

Statistical analysis

The primary outcome of the study was the success/failure of each tooth, expressed as a binary variable indicating whether the restored tooth maintained/did not maintain its vitality at M12. Success was evaluated by a positive response to thermal and/or electric pulp testing, the absence of spontaneous pain, no tenderness to percussion, the absence of sinus tracts, swelling and absence of PA radiolucency as determined by CBCT and PAs at M12. Two-tailed two samples z-tests was used to analyse the primary outcome, the association of the clinical variables and the primary outcome was assessed by means of a GEE (generalized estimation equations) multilevel logistic regression model. The degree of association was measured by means of odds ratio (OR) and 95% confidence interval, from the Wald's χ^2 statistic. The goodness of fit of different estimations (for different matrix correlations) was assessed by QIC statistics. Kappa was used to estimate radiographic examination agreements. For the secondary outcome analysis, paired sample t-test was used to compare bacterial tissue concentrations before and after excavation in each group an Independent samples t-test was used to compare reduction in bacterial tissue concentrations between groups. Mann-Whitney U test was used to compare between bacterial tissue concentrations of teeth with mild/severe symptoms, males/females, premolars/molars and failed/successful teeth.

Results

Demographic characteristics of teeth at baseline (M0)

From July 2014 to June 2016, a total of 127 teeth in 111 patients were recruited. Following the exclusions described in Figure 1, 101 restorations (55 control, 46 experimental) were placed in 86 patients. Most of the restorations were placed in molars 74/101 (73.26%) compared to premolars 27/101 (16.74%). The demographic characteristics of the recruited patients are presented in Table 2.

Clinical and radiographic assessment

A flow diagram of recruitment and follow-up of participants is shown in Figure 1. At M12, 85 teeth (45/control and 40/experimental) in 73 patients attended for follow-up (84%). 16 teeth were lost to follow-up (10 and 6 in the control and experimental groups, respectively). Success rates were 73.3% and 90% ($z=1.962$, $p=0.049$) in the control and experimental groups respectively. Higher success rates were recorded if only PA radiographs were used to assess PA health/pathosis in the recalled cases at M12 (82.2%/92.5% (z score=-1.4, $p=0.16$) in the control/experimental groups respectively). Distribution of symptoms amongst failed teeth was as follows: 45.4% and 16.6% ($z=1.18$, $p=0.23$) of teeth with severe symptoms at M0 failed in the control and experimental groups respectively at M12. 20.5% and 8.8% ($z=1.36$, $p=0.17$) of teeth with mild symptoms failed in the control and experimental groups respectively at M12. In total, 35.2% of teeth with severe symptoms failed in comparison to 14.7% with mild symptoms at T12 ($z=1.94$, $p=0.052$; Appendix Table 1). 33.3% premolars compared to 14% molars failed with a significantly higher success rate in molars compared to premolars ($z=1.962$, $p=0.049$). The number of molars which failed in the experimental group was lower than that observed in the control group ($z=2.03$, $p=0.042$) as shown in Appendix Table 2.

According to GEE modelling, the outcome was associated significantly with tooth type and symptom severity ($p=0.009$ and 0.049 respectively). Excavation technique was significant at liberal 10% level ($p=0.07$, shown in Table 3). These variables were included in a multiple logistic regression model estimated by GEE modelling. The results showed that excavation protocols and tooth type were significant predictors of success. When compared to the control, a tooth treated with the experimental technique had 4 times higher probability of success (OR=4.33, C.I. 1.2-15.6; $p=0.025$). Similarly, molars had 4 times higher probability of success when compared to premolars (OR=4.17, C.I. 1.17-14.9; $p=0.028$). M0 symptoms severity influence was relaxed because of the presence of the previous key variables, remaining in the model as non-significant ($R=0.41$, C.I. 0.12-13.9, $p=0.153$) as shown in Table 4.

Ninety-six and 75 (M0+M12) paired CBCT scans and PA radiographs images were analyzed (10 teeth developed symptoms of irreversible pulpitis, underwent root canal treatment and had no M12 PA/CBCT radiographs and 11 teeth presenting with CBCT PA lesions at M0 were excluded from the study and had no CBCT at M12). At M12, 98.6% (74/75) and 92% (69/75) ($z=1.93$, $p=0.052$) of teeth were deemed healthy using PA/CBCT respectively. The T0 analysis, shows that 100% and 87% ($z=3.57$, $p<0.001$) of teeth deemed healthy using PA/CBCT, respectively. Intra-consensus agreement Kappa values were 1.00/0.65 for CBCT/PA radiographs and inter-examiner agreement was 0.64/0.46 for CBCT/PA radiographs respectively. Representative images of the radiographic outcomes are presented in the Appendix Figure 2.

Microbiological assessment

There was a mean reduction in the bacterial tissue concentration after excavation of $4.3 \times 10^6 \text{ mg}^{-1}$ with a reduction of 96.5% in total. A significant reduction in the bacterial

tissue concentration after excavation was found in both experimental and control groups, ($p < 0.001$ and $p = 0.001$ respectively). There was no significant difference between the two excavation techniques in reducing bacterial tissue concentration in deep carious lesions ($p > 0.05$) as shown in Appendix Table 3. Also, there was no significant difference in bacterial tissue concentration change between teeth with mild and severe symptoms ($p = 0.98$), males and females ($p = 0.72$), premolars and molars ($p = 0.065$) or between failed and successful teeth ($p > 0.05$).

Discussion

This RCT compared the outcome of one-visit deep carious tissue excavation of teeth following a self-limiting (experimental) vs. conventional (control) carious tissue excavation protocols. Considering that the severity of pre-operative symptoms might affect the outcome of pulp protection procedures, only teeth with signs and symptoms of reversible pulpitis were included in this RCT.

A dual layer of MTA/GIC was used because direct placement of RC over partially set MTA could result in a weak mechanical/chemical bond between them in single-visit restoration of teeth capped with MTA (Ali *et al.* 2016).

In this trial, multiple logistic regression models were used, in order to obtain adjusted odds ratios and to control intra-subject dependence of the observations. Due to the relatively short follow-up time, binary success/failure was considered as the primary outcome. The experimental protocol had a significantly higher clinical/radiographic success rate. The difference could have been more significant if pulp exposure cases which were greater in the control group, had been classified as failures, rather than being excluded. The improved response of pulps in teeth treated using the experimental protocol could be associated with the reduced amount of mechanical

and thermal irritation caused to the pulp during carious tissue removal (Yip and Samaranayake 1998, Banerjee *et al.* 2000). Previous studies have shown the selective and self-limiting behavior of Carisolv™ gel in carious tissue excavation (Banerjee *et al.* 2000, Splieth *et al.* 2001).

The findings of a two-visit study (Hashem *et al.* 2015) which utilized Carisolv™ gel for excavation of carious dentin without magnification, showed that only 65.4% of teeth were deemed healthy using CBCT at M12. This finding is similar to the current control group (73.3%) but lower than the success rate in the experimental group (90%) in which operative microscopy was used, suggesting that the use of the operating microscope, increasing the visual capacity of the operator, may contribute to avoiding unnecessary tissue damage (Sitbon *et al.* 2014). Therefore, at this stage of intervention, there remains scope for the operator to optimise a tissue environment conducive to pulp repair and healing. Hashem *et al.* (2015) reported that cases with pre-operative CBCT radiolucencies had a higher failure rate, as they were associated with more severe features of pulp inflammation. Therefore, these were excluded from the present study. These two factors, together with the reduced chances of re-infection associated with the one-visit procedure, might have helped increase the success rate of pulp protection in the present study.

CBCT detected significantly more PA radiolucencies in teeth diagnosed with reversible pulpitis compared to PA radiographs, which led to a significant difference detected between the two protocols. This finding would not have been detected using periapical radiographs alone (Hashem *et al.* 2015). The use of CBCT for detection of a PA lesion in a trial setting can provide a more accurate assessment of treatment outcomes (Patel *et al.* 2012). The pre-operative use of CBCT in the clinical treatment of molar teeth with

borderline symptoms of reversible/irreversible pulpitis may help the clinician in informing the patient about the chances of success of such minimally invasive pulp protection procedures.

There was no significant association between symptom intensity at M0 and pulp vitality maintenance at M12 (Table 4). Several studies have shown little correlation between the histopathologic status of the pulp and the clinical diagnostic findings (Dummer *et al.* 1980, Langeland 1981). However, some levels of agreement between clinical and histologic classifications of pulp status have been reported (Ricucci *et al.* 2014). This supports the accurate diagnosis of the cases with reversible pulpitis in this study, which found ultimately a non-significant role of symptom severity of teeth diagnosed with reversible pulpitis in predicting treatment failure.

Tooth type was a significant predictor of treatment outcome success. Molars had a higher probability of success compared to premolars, possibly due to the mesio-distal dimensions of the cervical region of the crown which is important in the management of proximal cavities. The pulp size in molars usually is larger with a more abundant collateral vascular supply to inflamed areas of the pulp compared to premolar teeth (Hörsted *et al.* 1985).

Limitations of this trial include the relatively small sample size which might have affected the statistical significance of the results and the relatively low inter-examiner agreement achieved in the radiographic analysis (0.64/0.46 for CBCT/PA radiographs respectively). However, these findings were similar to other published studies examining pulp protection procedures (Hashem *et al.* 2015). This can be attributed to the difficulty of detecting smaller periapical radiolucencies developing in teeth with failing pulp protection procedures, compared to those observed in studies assessing the outcome of root canal treatment (Patel *et al.* 2012; Davies *et al.* 2015). Also, the

present study, unlike most of the other radiographic studies on outcomes of root canal treatment, involves only posterior teeth where greater levels of anatomical noise affect adversely the detection of apical radiolucencies in periapical radiographs.

Both tested excavation protocols reduced bacterial tissue concentrations to similar levels, suggesting the transition from infected to affected/healthy dentin being similar in both protocols (Banerjee *et al.* 2000). Although there might have been an expectation that the self-limiting protocol would result in a relatively reduced bacterial tissue concentration compared to the conventional control, present results agree with previous reports which found equal efficiency of both techniques in reducing bacterial tissue concentration (Lager *et al.* 2003, Ammari *et al.* 2014). The use of a dental bur may be expected to remove more carious dentin and thus more bacteria. However, CarisolvTM gel can reduce bacterial viability because of its antimicrobial properties and high pH (Azrak *et al.*, 2004). The levels of contamination determined in this study do not take into account cell viability, as quantitative PCR cannot discriminate between living and dead bacteria, but indicate the total amount of bacteria that had been present within a given mass. This study is the first however to use a self-limiting excavation protocol in teeth with deep, heavily bacterially contaminated lesions. Future exploration of this association in terms of biomarkers detection may have the potential to predict treatment outcome *in situ*.

Conclusions

The one-year success of the experimental self-limiting, minimally invasive protocol in preserving pulp sensibility and periapical health of teeth with deep carious lesions presenting with symptoms of reversible pulpitis was higher than that of the control

protocol. Therefore, the first null hypothesis has been rejected. The second hypothesis was supported because there was no significant difference between the two excavation techniques in reducing bacterial tissue concentration. Overall, this RCT supports the introduction of a self-limiting protocol including the use of Carisolv™ gel and operating microscope for pulp vitality preservation in teeth presenting with symptoms of reversible pulpitis.

Author Contributions

A. Ali, G. Koller, A. Banerjee and F. Mannocci contributed to conception, design, data acquisition, analysis, and interpretation drafted and critically revised the manuscript; Dr Ali and Dr Koller contributed equally to this manuscript. F. Foschi and K.D. Bruce contributed to data analysis, and interpretation, critically revised the manuscript; A. Manoharan, contributed to data analysis, critically revised the manuscript; all authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

This RCT was supported by the Centre of Excellence in Medical Engineering funded by the Wellcome Trust and by the Department of Health via the National Institute for Health Research Comprehensive Biomedical Research Centre award to Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. The authors also acknowledge the Iraqi Cultural Attaché in London for sponsoring and supporting the work. We gratefully acknowledge StHalley S.A. (XXX) for the independent statistical analysis. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Text-only Figure and Tables Legends:

Table 1: Inclusion and exclusion criteria for patients in the trial.

Table 2: Distribution of numbers of restorations according to various categories at baseline.

Table 3: Association between outcome and independent variables: results from GEE simple logistic regression models, odds ratio(OR) and 95%CI. Probability of success is the dependent variable in the model.

Table 4: : Association between outcome and relevant independent variables: results from GEE multiple logistic regression model, adjusted odds ratio(OR) and 95%CI. Probability of success is the dependent variable in the model.

Figure 1: Flow diagram showing patient recruitment and follow-up. Adapted from the CONSORT flow diagram. *Failed teeth are ones which underwent root canal treatments or gave a negative response to sensibility tests or had periapical radiolucency in 12-month CBCT scans.