The effect of different hemostatic agents on hemorrhage control, pain and quality of life after endodontic microsurgery

University of Turin, Department of Surgical Sciences, Dental School, Endodontics, Turin, Italy.

Running Title: Surgical glue in endodontic microsurgery

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STUDY PROTOCOL

Background

The endodontic microsurgery aims to achieve a complete cleansing and a three-dimensional obturation of the apical portion of the root canal system through a surgical approach [1]. The introduction of new technologies, instruments and materials simplified the treatment steps and elevated the success rate, allowing a greater management of the apical anatomy and a higher success rate [2]. The use of the cone beam-computed tomography (CBCT) increased the precise understanding of the root apical anatomy and of the lesion landmarks, which is critical for the clinical success [3, 4]. Moreover, the surgical microscope and the ultrasonic tips for apical preparation allowed a minimally invasive approach reducing the postoperative pain and leading to a faster wound healing [5, 6]. Nevertheless, the achievement of a correct hemostasis is fundamental during endodontic microsurgery and reduces the surgical time positively affecting the post-operative pain incidence [7-9]. Thus, the use of an appropriate hemostatic agent helps to control the bleeding inside the bone crypt and influences the post-operative prognosis [10, 11].

The ideal characteristics of the hemostatic agents are a rapid effect, easy handling, biocompatibility and lack of interference with bone and tissue healing [12]. The ferric sulfate is widely used during endodontic microsurgery due to its hemostatic properties on gingival and periapical tissues. The ferric ions released by the ferric sulfate induce blood clotting through the denaturation of plasma proteins and platelets that causes the formation of a physical barrier that stops bleeding [12]. Moreover, ferric sulfate has an astringent effect, stimulating soft tissue contraction and further hemostasis [12].

Recently, the use of medical glues for bleeding control has been proposed for general surgery [13, 14]. In particular, cyanoacrylate-based glues have been used in oral surgery as tissue adhesives to promote wound healing [15-17]. However, no data are available about the use of a surgical hemostatic glue for the management of the endodontic microsurgical field. Although these materials could perform well clinically, they may be harmful for periapical tissues and they may negatively influence the post operative outcomes [18, 19].

This study tested the clinical efficacy of a N-hexyl cyanoacrylate commonly proposed for medical applications. This material is widely used in digestive tract and visceral surgery such as laparoscopies, as well as in urogenital tract and breast surgery [13, 20]. The aim of this randomized clinical trial was to evaluate the influence of the hemostatic glue on the bleeding control, postoperative pain and quality of life compared to ferric sulfate during endodontic microsurgery.

Materials and Methods

Ethical considerations

This randomized controlled clinical trial was authorized by Local Ethics Committee and Review Board (approval code: 00272/2023, approval date: 3/2/2025, NCT number: NCT ID not yet assigned). All recruited subjects provided an informed written consent for participation in the study. The trial was written according to Preferred Reporting Items for Randomized Trials in Endodontics (PRIRATE) 2020 guidelines [21].

Eligibility criteria

Consecutive informed and consenting healthy subjects (ASA 1-2) of both genders with no medical history of systemic disease and presenting a diagnosis of symptomatic or asymptomatic apical periodontitis in correspondence of endodontically treated teeth with medium (2-5 mm^3) and large (≥5 mm^3) periapical lesions were enrolled. The diagnosis was performed clinically and radiographically through periapical radiographs and small field of view (FOV) Cone-Beam Computed Tomography (CBCT). The lesions volume and diameters were evaluated using the dedicated software Mimics 24.0 (Materialise, Belgium). Only periapical defects with one or two residual cortical walls were considered, while bone cavity designs with no cortical walls were excluded. The clinical indications for retrograde endodontic retreatment were reported for all cases: the teeth presented inadequate root canal treatment with periapical radiolucency and impossible access through orthograde retreatment due to the presence of prosthetic restorations, posts,

canal blocks and ledges. Moreover, the teeth presented an adequate coronal seal and absence of pathological periodontal records.

The subjects affected by diabetes mellitus, hypertension and hepatic or renal diseases were excluded from the study. Similarly, exclusion criteria included bleeding disorders, pregnancy and antiplatelet or anticoagulant therapy. The teeth that were considered unrestorable and the elements affected by fractures or extensive periodontal defects were also dismissed. A written consensus reporting information about the surgical procedure and the clinical and radiographical follow-up was supplied.

Sample size calculation

The sample size calculation was estimated basing on clinical outcomes. In particular, basing on the VAS score reduction as primary endpoint, a study power of 80%, with a significance level of 5%, and a standard deviation of 6.24 was calculated and 10 subjects per set group were needed.

Randomization and allocation

The patients were blind about the randomization that was performed by assigning a code. Double blinding was not possible due to the use of different hemostatic agents during the surgical procedure.

Treatment procedure

The procedure was completed by one single experienced surgeon in a sterile environment using an operating microscope (OPMI Pro Ergo, Carl Zeiss, Germany). After the administration of local anesthesia with articaine 1:100,000 (Septodont, France) and 10 minutes later lidocaine 2% with epinephrine 1:50,000 (Dentsply Sirona, USA), a full thickness mucoperiosteal flap was elevated. The debridement of the periradicular lesion was obtained using surgical curettes (Hu-Friedy) and the bone crypt was completed with

a dedicated bur (#557 SL Lindemann; Brasseler USA, Savannah, GA). After curettage, the surgeon and two independent assistants evaluated the hemorrhage degree and the visibility of the surgical field [8]. Afterwards, in group 1 (n=15) the surgical glue (IfaBond, Dipromed, Italy) was applied for the hemorrhage control in the bone crypt with a needle 23G, while in group 2 (n=19) the ferric sulfate 15.5% (Astringedent) was positioned in the surgical site through compression with a cotton pellet. The qualitative analysis of bleeding score and the visibility of the surgical site after the use of the hemostatic agent was evaluated.

The apical resection of 2-3 mm with a 0º–10º bevel angle was achieved with a surgical bur (#557 SL Lindemann; Brasseler USA, Savannah, GA). Afterwards, a solution of 2% methylene blue was used to stain the apical portion of the root to visualize anatomies, isthmuses and fractures. In both groups the preparation of the apical 3 mm was achieved following the long axis of the root with a piezoelectric device (MiniPiezon Device, EMS, Switzerland) and dedicated tips (ProUltra Surgical Tips, Dentsply Sirona, USA). Root end filling was completed with superEBA sealer (SuperSeal, OGNA, Italy). After irrigation with saline solution and the removal of the hemostatic agent, the wound site was filled with blood clot, and the bleeding recovery was measured using the hemorrhage control score and comparing data with the previous records. Afterwards, the flap was sutured with a 5-0 resorbable suture (Vicryl suture, Ethicon, Switzerland). A post-surgical protocol was presented to the patients according to Bharathi et al [8]. The patients were advised to follow a specific diet, and to dismiss hard physical exercise and smoking. Mouth rinses with chlorexidine digluconate 0.2% mouthwash for seven days were prescribed. A pharmacological prescription including optional analgesics (ibuprofen 600 mg), and no antibiotics was given in any case. All patients were booked for suture removal after five days.

Outcomes

According to a previous study, the hemorrhage control and the surgical field view were evaluated assigning a dedicated score [8]. The hemorrhage control and the surgical field view evaluation was performed two times: after the curettage of the bone lesion before the

use of the hemostatic agents, and after the hemostasis. The bleeding recovery was evaluated after the removal of the hemostatic agent.

The patients' quality of life (QoL) questionnaire Oral Health Impact Profile-14 (OHIP-14) assessed the impact of the surgical procedure on the signs and symptoms affecting the oral and general functions [8, 22]. The questionnaire evaluated different domains: functional limitations, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. A 5-point Likert-like scale (1 = never, 2 = hardly ever, 3 = occasionally, 4 = fairly often, 5 = very often) was introduced. Pain assessment was conducted using the Numerical Rating Scale (NRS). In this scale a 20-point difference between groups is considered clinically significant [23]. The subjects were asked to record the amount of pain they felt every day after the surgical procedure. Moreover, patients were asked to fill out the frequency of the analgesic intake from immediately after surgery up to 1 week. All subjects were requested to fill out the questionnaire and the NRS scale and to record possible symptoms during the first seven days after surgery. To ensure the correct recording of these forms, they were contacted two times in the first week to check on their status and to answer any possible dilemma regarding the filling of the documents.

Statistical analysis

A blinded statistical analysis was performed. A chi-square-test was used for the analysis of the hemorrhage control, while the Fisher t-test was utilized for the quality of life and analgesic intake. Inter-examiner reliability was assessed using Cohen's Kappa statistic. Moreover, the Mann-Whitney U test was used for pain assessment on postoperative days. The statistically significant level was settled with a P value < .05. The software SPSS Statistics v.23.0 (IBM Corp, Armonk, NY) was used for the analysis.

Keywords: endodontic microsurgery; surgical glue, ferric sulfate, cone-beam computed tomography, hemostatic agents.

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Committee of the University of Turin – Dental School (approval code: 00272/2023, approval date: 3/2/2025, NCT number: NCT ID not yet assigned). A written informed consent to participate was obtained from all of the participants in the study.

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INTRODUCTION

INFORMED CONSENT

The endodontic microsurgery aims to achieve a complete cleansing and three-dimensional obturation of the apical portion of the root canal system through a surgical approach. Endodontics has undergone a revolution thanks to the introduction of new technologies, instruments and materials that have simplified the treatment steps and elevated the success rate, allowing a greater understanding of the apical anatomy and a better patient response in the intra- and postoperative phases. The introduction of the operating microscope, micro-instruments including dedicated ultrasonic systems for apical preparation and new biocompatible apical filling materials has made micro-endodontic surgery a minimally invasive technique with reduced patient pain, faster wound healing, and higher success rates. In addition, the development of cone beam-computed tomography (CBCT) has allowed the operator to precisely locate the root apex and the lesion anatomical landmarks, which is critical for the clinical success. One of the major concerns during periapical microsurgery is the attainment of an adequate hemostasis

- What are the objectives of the trial?

The trial is being conducted to answer the following question: 'Is it possible to optimize hemostasis during endodontic microsurgery using a surgical glue? "The study will be coordinated by the Endodontic Department of the Dental School of the University of Turin.

- Is it my free choice whether or not to participate?

You are free to choose whether or not to participate in the trial. Even after agreeing to participate, you can change your mind at any time.

- If I decide not to give my consent to participate in the trial, what options do I have?

If you decide not to participate in the trial, you can still be followed by the clinical centre that is treating you and will be treated using the best approved (non-experimental) therapeutic methods for your disease.

- What are the risks and benefits of participating in the trial?

Participation in this trial may involve both risks and benefits. It is important to carefully evaluate these before deciding. The benefits are a reduction of the surgical time and an improvement of the postoperative quality of life. There are no potential risks related exclusively to the experiment.

- Is consent final? Can I decide to withdraw from the clinical trial (voluntary withdrawal)?

You can decide to withdraw from the trial at any time and for any reason, without having to justify your decision. If you decide to withdraw, please inform one of the trial doctors as soon as possible: it is important to discontinue treatment safely. The doctor may consider a final check-up/examination appropriate. The doctor will keep you informed of any changes in the trial that may affect your willingness to participate.

- What examinations, tests and procedures are planned if I participate in the trial?

Intraoral X-rays and clinical measurements with a periodontal probe will be performed at specific intervals. For each individual examination or invasive procedure planned as part of the trial, specific consent will be obtained at the time of the medical procedure.

- Will I incur any costs for participating in the trial? Will I be reimbursed for any expenses? Will I receive compensation?

There are no costs to you for participating in the trial, as these are fully covered by the University. There is also no financial compensation for participating in the trial.

- What happens if I suffer harm as a result of participating in the trial?

Participation in a clinical trial may involve inconveniences and risks that cannot be determined in advance. For this reason, clinical trials provide insurance coverage to protect your participation. In compliance with current legislation, insurance is provided to cover any damage suffered as a result of participating in the trial, for the entire duration of the trial, covering the civil liability of the investigator and the sponsor.

- **How will my health data, including identifying information, be handled and who will have access to it during the trial?**

Your data, in particular personal data and health data, and only to the extent that it is essential in relation to the objective of the trial and for pharmacovigilance purposes, will be processed in compliance with EU Regulation 2016/679, known as the GDPR (General Data Protection Regulation), and Legislative Decree No. 101 of 10 August 2018. In practical terms, documents relating to participants will be kept in a secure location and will not bear their names in plain text, known only to researchers, but rather an identification code. The anonymized data may be subject to scrutiny by regulatory bodies and used for scientific publications (journals, conferences). Your clinical data collected for the purposes of the trial, as well as the results of the tests carried out, will be kept for the time required by the regulations and then destroyed. They will not be destroyed only if a) it is no longer possible to trace them back to your identity because they have been anonymized during the trial itself; b) you have given your specific informed consent. If personal data is transferred to a third country or an international organization, all the safeguards provided for in Article 46 of GDPR 679/2016 relating to the transfer will be adopted. Further information is included in the attached data processing authorization form.

Has the trial been approved by the Ethics Committee?

The trial protocol proposed to you has been reviewed and approved by the Local Ethics Committee of the A.O.U. Città della Salute e della Scienza di Torino (Turin City of Health and Science University Hospital) prior to the start of the study. The Ethics Committee verified that the trial complies with Good Clinical Practice standards and the ethical principles expressed in the Declaration of Helsinki, and that your safety, rights and well-being are protected.

Who can I contact for more information about the clinical trial I have been invited to participate in? If I decide to participate in the trial, who can I contact if I need help?

For any questions or unforeseen events during the trial (questions regarding the treatment, side effects, decision to withdraw from the trial, etc.), please contact:

- Prof. D. Pasqualini (damiano.pasqualini@unito.it)

- Prof. M. Alovisi (mario.alovisi@unito.it)

CONSENT FORM

I, the undersigned, _____

born in _____ on ____/_____/ _____

I DECLARE

☐ that I have received exhaustive explanations regarding the request to participate in the research in question, as reported in the information section, which is part of this consent form.

☐ that the nature, purpose, procedures, expected benefits, possible risks and drawbacks, and alternative treatment options to the proposed clinical trial have been clearly explained to me and I have understood them.

☐ that I have had the opportunity to ask the study investigator any questions and have received satisfactory answers.

☐ I have had sufficient time to think about the information received.

☐ I have had sufficient time to discuss it with third parties.

☐ I have been informed that the trial protocol and all the forms used have been approved by the relevant Ethics Committee.

☐ I am aware that the research may be interrupted at any time, at the discretion of the research manager.

☐ that I have been informed that I will be made aware of any new information that could compromise the safety of the research and that, for any problems or further questions, I can contact the doctors who are treating me.

☐ that for the best protection of my health, I am aware of the importance (and my responsibility) of informing my general practitioner about the trial in which I agree to participate. I am aware of the importance of providing all information (medications, side effects, etc.) concerning me to the investigator.

☐ that I have been informed that the results of the trial will be disclosed to the scientific community, while protecting my identity in accordance with current privacy legislation.

☐ that I am aware that any choice expressed in this consent form may be revoked at any time and without justification.

☐ that I have received a copy of this consent form.

I therefore DECLARE that

☐ I wish to participate in the trial

☐ I wish to ☐ I do NOT wish to be informed of any unexpected news regarding my present or future health that may incidentally emerge from the investigations.

☐ I wish to ☐ NOT wish to be informed of unexpected findings relating to my present or future health only when this may be useful for my healthcare.

☐ wish ☐ NOT wish to be contacted after the end of the trial to provide information about my health

Name	Date	time	signature
_____	_____		_____