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ORIGINAL ARTICLE

Spontaneous and Masticatory Post-endodontic Pain After Using Endomethasone N vs SP Root Canal Sealers: A Randomised Controlled Clinical Trial

Yves Boucher,[1,2,3] Hugo Abrgall,[4] Vincent Bar,[4] Françoise Baslé-Thébault,[4] Stéphane Cano,[4] Hughes Colombel,[4] Gwenvael Le Guicher,[5] Charlotte Cameli[5]

[1]Department of Odontology, Pitié Salpêtrière Hospital, Paris, France
[2]Department of Odontology, Paris Cité University, Paris, France
[3]Orofacial Neurobiology Laboratory, Paris Cité University, Paris, France
[4]Private Practice, Paris, France
[5]SLB Pharma, Rennes, France

ABSTRACT

Objective: Post-endodontic pain (PEP) after endodontic treatment (ET) might be reduced by adding cortisone to the composition of root canal sealer (RCS). This study aimed to test this hypothesis using grade A methodology.

Methods: A multicentric prospective randomised controlled clinical trial was performed in general practice. Adult patients with an indication of ET in a molar or premolar performed in one session were included between 2021 and 2022 in 15 centres. The main objective was to demonstrate the superiority of Endomethasone N RCS (EndoN), compared to its hydrocortisone-free equivalent Endomethasone SP RCS (EndoSP), regarding the reduction of the maximum spontaneous PEP pain during the 7 days following the ET, self-estimated on a 0–100 mm Visual Analogic Scale (VAS). The secondary objectives were to assess 1) spontaneous PEP, 2) provoked (masticatory) PEP, 3) intake of analgesics, 4) quality of life and anxiety before and after ET, and 5) safety.

Results: The final sample consisted of 286 patients with a mean age of 47.7 years, including 51% men and 49% women. Before ET, 49.7% of the teeth were asymptomatic; provoked pain occurred in 29.4% and spontaneous pain in 21.0%. The study evidenced a lower maximum spontaneous PEP intensity during the 7 days following ET in EndoN compared to the EndoSP group (13.5±17.9 vs 23.9±26.6, IC 95% 10.5 [5.2–15.8], p=0.0001 Wilcoxon test). Maximal masticatory PEP was also lower in the EndoN group (12.3±19.1 vs 24.0±27.8, IC 95% 11.7 [5.8–17.6], p<0.0001 Wilcoxon test). At every evaluation time, the masticatory PEP in the EndoSP group was higher than in the EndoN group. In addition, no serious adverse events occurred during the study.

Conclusion: This RCT demonstrated EndoN's superiority over EndoSP in reducing spontaneous and masticatory PEP during the 7 days following ET. This study was funded by the Septodont company (Saint Maur des Fossés, France) and registered at ClinicalTrials.gov # NCT04885686.

Keywords: Corticoids, endodontics, post-operative pain, RCT, root canal sealer

HIGHLIGHTS

- There was evidence of the superiority of hydrocortisone-containing cement in reducing spontaneous and masticatory pain.
- The maximal spontaneous and masticatory pain intensities were significantly and strongly reduced, approximately 50%, in the group treated with hydrocortisone-containing cement.

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Address for correspondence:
Yves Boucher
Department of Odontology, Pitié Salpêtrière Hospital, Paris, France; Department of Odontology, Paris Cité University, Paris, France; Orofacial Neurobiology Laboratory, Paris Cité University, Paris, France
E-mail: yves.boucher@aphp.fr

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INTRODUCTION

Pain is an unpleasant experience frequently associated with nonsurgical endodontic treatment (ET), impairing its therapeutic acceptance (1). Post-endodontic pain (PEP) contributes to this phenomenon. PEP, in which the incidence is

3–58% (2), depends on patient-related and procedural factors (3–9). Patient-related factors include pre-operative pain, tooth type, age, gender, pulp, and periapical condition. Procedural factors include the number of sessions, the instrumentation technique, irrigation, root canal sealing, occlusal factors, and medications. Corticosteroids, for example, have been used as systemic or topical (intracanal) treatment. Systematic reviews and meta-analyses suggest moderate evidence of the efficacy of corticosteroids for PEP associated with ET, whether used as an intracanal paste or by systemic administration (3, 10).

PEP data related to root canal sealers (RCS) are challenging to synthesise due to protocol differences. The most common RCS used in current practice is Zinc Oxide Eugenol (ZOE) cement, despite the development of new materials such as resin or silicate-based cements. Endomethasone N (EndoN) is a ZOE RCS developed by the Septodont company (Saint Maur des Fossés, France) to decrease PEP. Adding hydrocortisone acetate to the composition of ZOE RCS resulted in decreased intensity duration and incidence of PEP (11–13). However, high-grade scientific evidence does not support these preliminary observations, i.e., randomised Controlled Clinical Trials (RCT).

The study aimed to assess, in a population of patients treated by general practitioners, PEP after ET with EndoN, compared to Endomethasone SP (EndoSP), two close formulas differing mainly by the cortisone content. The primary outcome of this study focused on the maximum spontaneous PEP reported during the 7 days following the ET. Secondary objectives include assessing masticatory pain and the quality of life associated with ET.

MATERIALS AND METHODS

Ethics, Design, Primary and Secondary Outcomes, Randomization

This study complied with the PRIRATE 2020 guidelines (14), was approved by an ethics committee (IDRCB: 2021-A00065-36), registered at ClinicalTrials.gov (NCT04885686) and conducted in accordance with the World Medical Association Declaration of Helsinki. All patients gave informed written consent before enrollment. A complete description of the protocol is available upon request.

The study's primary objective was to demonstrate the superiority of EndoN, compared to EndoSP, regarding reducing the maximum spontaneous PEP during the 7 days following the ET. The secondary objectives, detailed in Table 1, were 1) to assess spontaneous and provoked masticatory PEP at specific time points during 7 days; 2) To assess PEP by monitoring intake of analgesics, 3) to assess quality of life after ET, 4) to evaluate the safety of ET.

Design: This pragmatic (15) prospective, multicenter, single-blind RCT compared two parallel groups (allocation ratio of 1:1). Group 1 received the test product EndoN, and Group 2 received the reference product EndoSP. The trial used a superiority hypothesis, with µ ENDON being the mean of the maximum spontaneous PEP in the EndoN group and µ ENDOSP being the mean of the maximum spontaneous PEP pain in the EndoSP group, H0 was the null hypothesis: µ ENDON =µ ENDOSP and H1 the alternative hypothesis: µ ENDON ≠ µ ENDOSP. Two conditions were required to claim the superiority: 1) a significant difference between the mean values of two groups, as assessed by a Wilcoxon's test and a 5% two-sided type I error probability; 2) the mean value of the maximum spontaneous PEP is lower in the EndoN group than in the EndoSP group.

Randomization used a centralized computer-generated block list stratified by pre-endodontic pain and centre. The pre-ET pain was categorized as follows: symptomatic tooth (spontaneous pain the day of the ET, before the ET); symptomatic tooth (provoked pain with thermal or percussion test the day of the ET, before the ET); asymptomatic tooth. Only one tooth per patient was included. The study was single-blinded. The investigator could not be blinded to the treatment used. The coordinator was blinded to treatment allocation during both the review of the data and radiographs.

The sample size was estimated as follows: Based on recent peer-reviewed studies (2, 9, 16–22), the maximal PEP score after ET on a 0–100 VAS is, on average, 22.3 with a SD of 20.5 (min: 7.6; max: 33.0). The SD was then set at 20.5. A difference of 7 (≈33%) between EndoN and EndoSP was considered clinically relevant (23, 24). For a superiority trial with a type I error probability set at 5% (two-sided), a power of 80%, a SD of 20.5, and a mean difference of 7, the number of subjects was defined at 136 per group. With a 10% increase in follow-up lost, the total number of subjects was set at 300 (150 subjects per group).

The primary outcome was the maximum spontaneous PEP intensity during the 7 days following ET, measured with a 100 mm Visual Analogic Scale (VAS) (23), self-evaluated at 0 h, 3 h, 6 h, 12 h, 24 h, Day 2 (D2), D3, D4, D5, D6, and D7 after ET. The secondary outcomes are given in Table 1. For the categorial pain outcome, the pain score was converted into 5 classes: no pain (0), mild pain (1–39), moderate pain (40–59), severe pain (60–79), and unbearable pain (80–100). A flare-up was defined as a minimum of 20 mm VAS increase between 2 consecutive measurements after D3 (25, 26). The Quality of life was assessed using the 17-item version of the Oral Health Impact Profile questionnaire (OHIP-17) (27). The anxiety was assessed with a VAS from 0 (no anxiety) to 100 (worst imaginable anxiety) at D0 before the ET. The self-declaration of intake of analgesics was recorded as concomitant treatments.

Patients

Inclusion criteria were: Adult male or female (age ≥18 years); requiring ET or retreatment; needing a single visit for the ET for a mature molar or premolar, with or without pre-ET pain; having given written consent after information; affiliated or beneficiary of a health insurance system. **Exclusion criteria** were: Pulpotomy or pulpectomy performed at a prior visit; tooth with apical calcifications or suspected root perforation; immature tooth; other ongoing dental treatment or scheduled within the study period; symptomatic tooth other than that included in the study; known hypersensitivity to corticosteroids, local anaesthetics or any component of the RCS; use of long term anti-inflammatory drugs; use of illicit substances during

TABLE 1. Secondary objectives and secondary outcomes

Secondary objectives	Secondary outcomes	Time of measurement
To assess spontaneous PEP in terms of intensity, prevalence, and duration	The spontaneous pain intensity; continuous outcome The occurrence of spontaneous pain flare-ups; binary outcome The gradation of spontaneous pain intensity; categorial outcome based on the pain intensity continuous outcome The time to reach the maximum spontaneous pain during the 7 days following the root canal treatment; continuous outcome The duration of spontaneous pain; continuous outcome	Patient self-evaluation at 0 h, 3 h, 6 h, 12 h, 24 h, D2, D3, D4, D5, D6, and D7 (before dinner) after the ET If a higher pain occurs between 2 pre-specified measure times, the patient will be asked to assess and record this pain as an additional point The data is recorded in the electronic patient diary
To assess spontaneous PEP in the subset of subjects with • A pre-ET symptomatic tooth (spontaneous pain) • A pre-ET symptomatic tooth (spontaneous or induced pain)	The spontaneous pain intensity; continuous outcome The occurrence of spontaneous pain flare-ups; binary outcome The gradation of spontaneous pain intensity; categorial outcome based on the pain intensity continuous outcome The time to reach the maximum spontaneous pain during the 7 days following the root canal treatment; continuous outcome The duration of spontaneous pain; continuous outcome	
To assess masticatory PEP in terms of intensity, prevalence, and duration	The masticatory pain intensity; continuous outcome The maximum masticatory pain intensity; continuous outcome The gradation of masticatory pain intensity; categorial outcome based on the pain intensity continuous outcome The duration of masticatory pain; continuous outcome	Patient self-evaluation twice a day from D0 to D3 (lunch and dinner) and once a day from D4 to D7 (dinner) The data is recorded in the electronic patient diary
To assess masticatory PEP on the subset of subjects with • A pre-ET symptomatic tooth (spontaneous pain) • A pre-ET symptomatic tooth (spontaneous or induced pain)	The maximum masticatory PEP, the masticatory pain intensity at 24 h, the gradation of masticatory pain intensity at 24 h, and the duration of masticatory pain are described for the total sample above.	
To assess PEP by monitoring the intake of drugs	Type of analgesics used Motive Time to rescue medication intake Occurrence and cumulative dose over 7 days The proportion of patients who took oral analgesics over 7 days	Patient self-report from 0 h to D7 after the ET The data is recorded in the electronic patient diary
To assess the quality of life after ET	The answers to the OHIP 17-item questionnaire; categorial outcome The score from the OHIP 17-item questionnaire: continuous outcome	One assessment at D0 before the ET data was recorded in the electronic patient diary. A second assessment at 48 h after the ET; data recorded in the electronic patient diary
To evaluate the safety of ET	The occurrence of unscheduled visits Number of adverse events during and after the ET Description of AE, severity, and causality assessment The proportion of patients with at least 1 AE Number of device deficiencies and description of the deficiency	Dentist evaluation between D0 and the end of the study visit (D7) The data is recorded in the electronic patient diary and the eCRF

Secondary analyses focused on: 1) The maximum masticatory pain intensity during the 7 days following the ET measured using a 100 mm VAS, analyzed like the primary criterion 2) The pain intensity (spontaneous and masticatory) at 0 h, 3 h, 6 h, 12 h, 24 h, Day 2, Day 3, Day 4, Day 5, Day 6, and Day 7 after the ET measured using a 100 mm VAS and the area under the curve (AUC) using every available measure. 3) The gradation of pain intensity (spontaneous and masticatory) at 0 h, 3 h, 6 h, 12 h, 24 h, Day 2, Day 3, Day 4, Day 5, Day 6, and Day 7 after ET. 4) The time to reach the maximum spontaneous pain during the 7 days following ET 5) The duration of pain (spontaneous and masticatory). 6) The occurrence of spontaneous pain flare-ups. 7) The intake of analgesics. 8)The score from the OHIP 17-item questionnaire (measured at D0 before and 48 h after the ET).

ET: Endodontic treatment, PEP: Post endodontic pain, Pre-ET: Pre endodontic treatment, h: hour; D1: Day1; D2-D7: Days 2 to day 7, OHIP: Oral Health Index Profile, AE: Adverse effect, eCRF: Electronic Case Report File

TABLE 2. Composition of the powders of the Root Canal Sealers (RCS)

RCS	EndoN	Endo SP
Composition of the powder	Zinc oxide 49% Barium sulfate 15% Magnesium stearate 10% Thymol iodide 25% Hydrocortisone acetate 1%	Zinc oxide 53.38% Barium sulfate 10% Magnesium stearate 10% Thymol iodide 25% Erythrosine lake 0.125% Riboflavine 1.5%

The main difference between the two RCS was that Endomethasone N (EndoN) contained 1% hydrocortisone acetate while Endomethasone SP (EndoSP) contained 1.5% riboflavin. Both RCS powders were mixed with the same quantity of eugenol (Endomethasone liquid).

the 48h before the first visit; uncontrolled systemic diseases; a subject who cannot be contacted in case of emergency; simultaneous participation in another clinical trial; vulnerable subjects defined according to art. 66 of the Regulation (EU) 2017/745 on medical devices.

All examinations, occurrence of dental visits, and products used were those of standard practice. The instructions for use were the same for both EndoN and EndoSP. Each practitioner performed ET under French/European recommendations. Investigators were instructed on how to prepare the RCS according to fabricant instructions. The composition of the RCS powders is indicated in Table 2. They were mixed with the same quantity of eugenol (Endomethasone liquid).

The radiographs were centralized and reviewed by the coordinator of the study (YB), blind to the treatment allocation group, for assessing 1) the quality of ET according to established criteria (28) 2) the periapical status according to the PAI system (29).

A paper patient diary was used to collect spontaneous and masticatory pain, the intake of analgesics, the occurrence of adverse events, and the OHIP-17 questionnaire at D0 and 48 h after ET. Data were centralised in an electronic Case Report File (e-CRF). Data monitoring was carried out by a Clinical Research Associate following Good Clinical Practices.

Statistic Analysis

ENNOV Clinical version 8.1.0 (Paris, France) was used for the design and configuration of the eCRF, JMP® version 15.0.0 (SAS Institute Inc, Cary, NC), and R Core Team (2021) (R Foundation for Statistical Computing, Vienna, Austria) for data analysis. Descriptive statistics are presented according to the type of variable 1) Continuous variables: number of observations, number of missing data, mean, standard deviation, median, minimum, maximum. 2) Categorial variables: number of observations, number of missing data, absolute and relative frequencies by class. Tests of statistical significance were not performed for baseline characteristics (30). The primary outcome analysis used Wilcoxon's test, with a 5% two-sided type I error probability. Secondary outcomes analyses are given in Table 1.

Safety data was expressed in the number of adverse events (AE) and serious AE, defined according to the IMDRF terminologies for categorized Adverse Event Reporting (AER), and in the number of patients reporting at least one AE during the study, compared between the 2 groups.

The statistical analysis plan was designed before carrying out the statistical analyses. No intermediary analysis was planned. Patients were analysed according to the Intention to Treat (ITT) principle.

Subgroup analyses exploring the primary and some secondary outcomes were performed. Continuous outcomes were compared using the Welch's test or Wilcoxon rank sum test (if N< 30). Categorial outcomes were compared using Pearson's chi-square test or Fisher's exact test (if at least one expected value is <5). Exploratory analyses were performed, i.e. multiple linear regression on subjects allocated to the EndoN group to determine parameters associated with a significantly lower spontaneous PEP intensity in the EndoN group. The correlation between 1) Anxiety VAS score (pre-operative measure) and maximum spontaneous PEP and 2) Maximum masticatory VAS score and maximum spontaneous PEP was assessed by Pearson correlation coefficient (r).

RESULTS

Chartflow, Demographics, Characteristics of the Sample and Deviations from the Protocol

Patients were included between June 2021 and May 2022. Three inclusion centres were added to the 12 initial centres in October 2021, November 2021 and March 2022. Out of 300 patients assessed for eligibility, 293 patients received the treatment, 286 had a measure of the primary outcome, and 265 subjects followed up on the study according to protocol (Fig. 1). Two hundred eighty-six patients were finally analysed with an equal distribution. More information on inclusions, follow-up of subjects and protocol deviations is available on request).

The mean age of the sample was 47.7±16.2 y.o. [range 18.4–84.8] and the M/F ratio was 51/49%, with no significant difference between the groups. Of the patients in the FAS population, 16.8% had one or several medical conditions with a similar distribution in both groups. The characteristics of the included teeth are described in Table 3. Asymptomatic teeth represented 49.7% of the sample, provoked (29.4%) and spontaneous (21.0%) symptomatology; pulp diagnosis required only for initial ET is presented in Table 4. Pre-ET diagnoses were similar in both groups. In the sample, 86.7% of ET were initial ET, and 13.3% were retreatments.

The mean spontaneous pre-ET pain scores were low, 12.4±23.2 and 9.6±20.2 in the EndoSP and EndoN groups, respectively. The masticatory pain was slightly higher than the sponta-

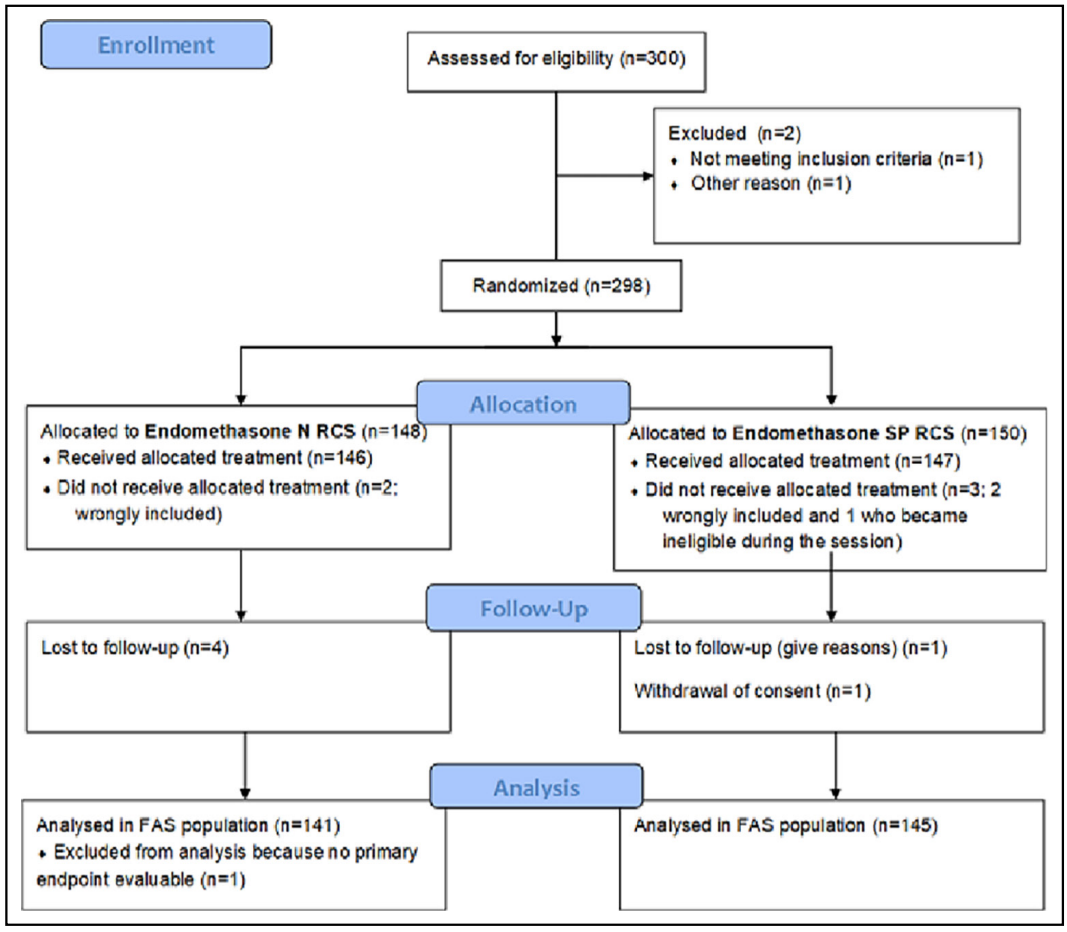

Figure 1. CONSORT flow diagram. 300 patients were assessed for eligibility and signed an informed consent. Among them, 2 were not included, resulting in a sample of 298 patients with a similar distribution between groups (EndoN=148, EndoSP=150), with no allocation error during the study. At the end of the study, 286 patients were analysed: 141 in the EndoN group and 145 in the EndoSP group

EndoN: Endomethasone N root canal sealer, EndoSP: Endomethasone SP root canal sealer

neous pain (14.6±26.3 vs 16.0±26.5 in EndoN and EndoSP). Anxiety before the ET was low (mean VAS=15.6±24.4). Information related to local anaesthesia, ET procedure, RCS preparation, complication during ET, coronal restoration, and clinical observations at the end of the study is available on request).

The PAI score was similar between the groups (mean score = 2.4±1.2 in the EndoN vs 2.5±1.2 in the EndoSP group). 26.4% of the patients had a PAI score of 1, i.e. no periapical lesion. The quality of the root canal filling was satisfying for 70.3% of the treated canals, and 55.9% of the patients had satisfying root canal filling for all the treated roots. The proportion of over or underfilled canals was similar in the EndoN and EndoSP groups.

Analysis of Primary and Secondary Outcomes

The maximum spontaneous PEP, described in Table 5 and presented in Figures 2 and 3, was significantly lower in the EndoN compared to the EndoSP group (10.5 VAS difference, 43.51% decrease, (IC 95% [5.2–15.8]), p=0.0001), rejecting the null hypothesis H0 and validating the H1 alternative hypothesis. EndoN was then superior to EndoSP in preventing spontaneous PEP. This superiority was confirmed when considering only the patients in pain (VAS ≥1), which represented 83.2% of the sample (8.8 VAS difference, p=0.0232, Wilcoxon test) (Table 5 and Fig. 2).

The detailed categorial spontaneous PEP outcome is available on request. In the EndoN group, the main class had "no pain" but "mild pain" in the EndoSP group. The time to reach maximum spontaneous PEP during the first 7 days (mean±SD) was 25.6±39.5 for the EndoN and 35.6±48.6 hours (h) for the EndoSP group (mean difference 10 h, p=0.0315). The mean (±SD) pain duration was 92.6±68.6 h in the EndoN and 97.6±65.8 h in the EndoSP group (not significant, p=0.3537). Seven patients presented a flare-up during the 7-day follow-up, 5 in the EndoSP group and 2 in the EndoN group (not significant; p=0.4631). The mean AUC of the EndoN group was significantly lower than EndoSP (597.2±1085.2 vs 1452.6±2249.6, p<0.0001).

The maximum masticatory PEP was mild, with 12.3±19.1 mean VAS scores in the EndoN group and 24.0±27.8 in the EndoSP group. Maximal masticatory PEP over the 7 days following the ET was significantly lower (decrease of 48.75%, p<0.0001) in the EndoN compared to the EndoSP group (Fig. 4). At every evaluation time, the masticatory PEP score in the EndoN group was lower in the EndoSP group. The mean AUC score was significantly lower in EndoN than in EndoSP (52.7±87.7 vs 128.4±196.8, p=0.0002).

TABLE 3. Characteristics of the teeth included in the sample (n=286); 41.3% (n=118) were mandibular, and 58.7% (n=198) were maxillary

FAS population	Endo N		Endo SP		Total	
	n	%	n	%	n	%
Tooth arch						
N	141		145		286	
Md	0		0		0	
Maxilla	88	62.4	80	55.2	168	58.7
Mandibular	53	37.6	65	44.8	118	41.3
Tooth type						
N	141		145		286	
Md	0		0		0	
Incisor	0		1	0.7	1	0.3
Canine	0		1	0.7	1	0.3
Premolar	68	48.2	59	40.7	127	44.4
Molar	73	51.8	84	57.9	157	54.9
Number of canals						
N	141		145		286	
Md	0		0		0	
1	37	26.2	41	28.3	78	27.3
2	37	26.2	30	20.7	67	23.4
3	63	44.7	66	45.5	129	45.1
4	4	2.8	8	5.5	12	4.2
Type of ET						
N	141		145		286	
Md	0		0		0	
Initial	120	85.1	128	88.3	248	86.7
Retreatment	21	14.9	17	11.7	38	13.3
Tooth symptomatology on the day of the ET, before the ET (randomisation variable)						
N	141		145		286	
Md	0		0		0	
Symptomatic tooth: spontaneous pain	26	18.4	28	19.3	54	18.9
Symptomatic tooth: pain caused by a thermal or percussion test	37	26.2	42	29.0	79	27.6
Asymptomatic tooth	78	55.3	75	51.7	153	53.5
Tooth symptomatology at inclusion						
N	141		145		286	
Md	0		0		0	
Symptomatic tooth: spontaneous pain	28	19.9	32	22.1	60	21.0
Symptomatic tooth: pain caused by a thermal or percussion test	42	29.8	42	29.0	84	29.4
Asymptomatic tooth	71	50.4	71	49.0	142	49.7

54.9% were molars and 44.4% premolar. One canine and one incisor were included despite the inclusion criterion #2. The proportion of molars and premolars was similar between the EndoN and EndoSP groups (51.8% vs 57.9% and 48.2% vs 0.7%). Additional descriptions can be obtained on request). FAS: FAS: Full analysis set, EndoN: Endomethasone N root canal sealer, EndoSP: Endomethasone SP root canal sealer, Md: Missing data, ET: Endodontic treatment

At every evaluation time, the distribution of patients among the pain categories showed a higher proportion of patients with no or mild masticatory pain when treated with EndoN compared to EndoSP. The distribution of patients among the classes became significantly different at D1 (p=0.0129) and remained significant until the end of the 7-day follow-up, except for the evening of D5 (p=0.1213) and evening of D7 (p=0.1020). The mean masticatory PEP duration was 106.8±65.9 h in the EndoN group vs 114.3±60.2 h in the EndoSP group (p=0.3175, NS).

Overall, 33.6% of the patients used analgesics or NSAIDs, with no significant difference between the two groups (p=0.1129). The EndoSP group took twice as many analgesics (all painkiller and NSAID drugs combined) than the EndoN group (n=51 vs n=99). Paracetamol was the most used, with a mean cumulative dose of 2300.0±1831.9 mg and 2500.0±2079.0 mg for the EndoN vs SP group.

Quality of Life (QoL) was good before ET, with a mean OHIP-17 score of 14.7±12.3 and no significant difference between the two groups (p=0.9754). After ET, QoL was better with a mean OHIP-17 score of 8.4±10.1, but not significantly, in EndoN vs EndoSP groups (7.7±9.2 vs 9.1±10.9; p=0.3910). The treatment group had no impact on the evolution of the total OHIP-17 score (p=0.2855), but the timing of the completion of the OHIP-17 questionnaire (before or after the ET) did (p<0.0001). The QoL related to the dental condition improved significantly after ET, but there was no difference between the EndoN and EndoSP groups (p=0.2855).

Regarding safety, at least one adverse event (AE) occurred for 20.6% of the patients, with a similar distribution between groups (p=0.5220). The AE were mild (48.1%) or moderate (51.9%). None of these was serious, and 4.9% were possibly related to the RCS; thus, the products studied can be considered safe for use.

TABLE 4. Description of the pulpal and periapical diagnosis

FAS population	Endo N		Endo SP		Total	
	n	%	n	%	n	%
Pulp diagnosis						
N (initial ET)	120		128		248	
Md	0		0		0	
Irreversible pulpitis	37	30.8	41	32.0	78	31.5
Necrotic pulp	31	25.8	32	25.0	63	25.4
Vital pulp with ET indication	52	43.3	55	43.0	107	43.1
Pulp diagnosis among teeth with vital pulp						
N	52		55		107	
Md	0		0		0	
Unfavourable Prognosis for pulp vitality before restorative procedure	28	53.8	26	47.3	54	50.5
Probability of pulp exposure during coronal restoration	24	46.2	29	52.7	53	49.5
Root amputation or hemisection	0		0		0	
Gingival swelling around the treated tooth						
N	141		145		286	
Md	0		0		0	
Yes	6	4.3	5	3.4	11	3.8
No	135	95.7	140	96.6	275	96.2
Mobile tooth						
N	141		145		286	
Md	0		0		0	
Yes	7	5.0	4	2.8	11	3.8
No	134	95.0	141	97.2	275	96.2
Spontaneous pain						
N	141		145		286	
Md	0		0		0	
Yes	28	19.9	32	22.1	60	21.0
No	113	80.1	113	77.9	226	79.0
Painful during the cold test						
N	140		145		285	
Md	1		0		1	
Yes	38	27.1	35	24.1	73	25.6
No	58	41.4	57	39.3	115	40.4
Not performed	44	31.4	53	36.6	97	34.0
Painful during the heat test						
N	140		145		285	
Md	1		0		1	
Yes	9	6.4	8	5.5	17	6.0
No	45	32.1	43	29.7	88	30.9
Not performed	86	61.4	94	64.8	180	63.2
Painful during the percussion test						
N	140		145		285	
Md	1		0		1	
Yes	52	37.1	47	32.4	99	34.7
No	54	38.6	57	39.3	111	38.9
Not performed	34	24.3	41	28.3	75	26.3
Apical lesion						
N	141		145		286	
Md	0		0		0	
Yes	41	29.1	45	31.0	86	30.1
No	100	70.9	100	69.0	200	69.9

The cold, heat, and percussion test results were used for stratification. 25.6% of the teeth were painful in response to the cold test, 6.0% to the heat test, and 34.7% to the percussion test, with a similar distribution in both groups. However, these tests were not systematically performed by the dentist, hence the consequent proportion of missing data (63.2% for the heat test, 34.0% for the cold test, and 26.3% for the percussion test). PreET diagnoses were similar in both groups. FAS: Full analysis set, EndoN: Endomethasone N root canal sealer, EndoSP: Endomethasone SP root canal sealer, Md: Missing data, ET: Endodontic treatment

The main findings of the subgroup analysis are displayed in Table 6. Exploratory analysis revealed that after multiple linear regression, with the exclusion of variables with p>0.2, in the univariate model for multivariate analysis, and the backward method applied to selected variables, no variable was associated with a significant decrease in sponta-

TABLE 5. Description and comparison of the maximum spontaneous pain level 7 days after endodontic treatment (VAS 100mm). **(a)** In the full analysis set (FAS) population. **(b)** In the subset of patients with Post Endodontic Pain

a				**b**			
FAS population	**EndoN**	**EndoSP**	**Total**	**FAS population**	**EndoN**	**EndoSP**	**Total**
N	141	145	286	N	107	131	238
Md	0	0	0	Md	0	0	0
Mean	13.5	23.9	18.8	Mean	17.7	26.5	22.6
SD	17.9	26.6	23.3	SD	18.6	26.8	23.8
Median	7.0	12.0	9.0	Median	11.0	14.0	13.0
Q1	1.0	5.0	2.0	Q1	5.0	7.0	6.0
Q3	16.5	33.5	29.0	Q3	24.0	39.0	32.0
Minimum	0.0	0.0	0.0	Minimum	1.0	1.0	1.0
Maximum	92.0	94.0	94.0	Maximum	92.0	94.0	94.0
Difference of mean between two groups Δ SP – N [IC95%]	10.5 [5.2–15.8]			Difference of mean between two groups Δ SP – N [IC95%]	8.8 [2.9–14.6]		
Comparison *Wilcoxon test*	p=0.0001			Comparison *Wilcoxon test*	p=0.0232		

EndoN: Endomethasone N root canal sealer group, EndoSP: Endomethasone SP root canal sealer group, Md: Missing data, SD: Standard deviation, Q1: Lower quartile, Q3: Upper quartile

neous PEP intensity in the EndoN group. Maximum masticatory PEP and maximum spontaneous PEP were highly correlated (r=0.6922; p<0.0001). Pre-ET anxiety scores were weakly correlated with maximum spontaneous PEP scores (r=0.1994, p=0.0191).

DISCUSSION

This study was completed according to the protocol by general practitioners, reflecting common dental practice and not specialized settings such as university clinics or endodontist practices. The inclusion criteria were chosen to maximise evidence of an effect on PEP, targeting molar and premolars treated in a single visit (3, 6, 31).

Main Results

In this sample, preoperative pain was frequent and of moderate intensity. ET significantly improved pain scores in both groups. The Quality of life, evaluated with the OHIP-17 score, was also significantly improved by ET, but no significant difference was found between the EndoN and EndoSP groups. These results support previous data indicating a significant improvement in pain and QoL after ET (3, 7, 32).

This RCT evidenced a superiority of EndoN compared to EndoSP in decreasing spontaneous and masticatory PEP at every time point, the difference in pain scores becoming significant 12 hours after the ET. Both the maximum and total

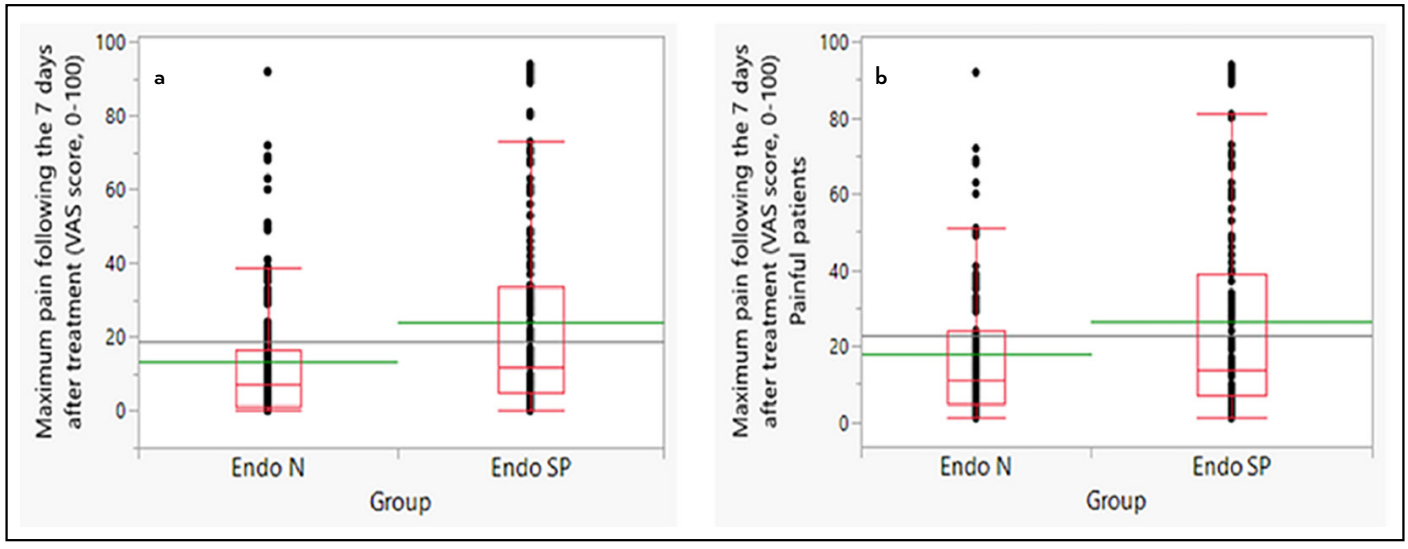

Figure 2. Boxplots of maximum spontaneous pain level following the 7 days after endodontic treatment (VAS 100mm). (a) In the whole sample, a 10.5 VAS significant difference was found between the EndoN and EndoSP groups (p=0.0001). (b) In the subset of patients with post-endodontic pain, an 8.8 significant VAS difference was found between the EndoN and EndoSP groups (p=0.0232). In red; Min: Minimum (lowest value excluding outliers), Q1: Lower Quartile (25th percentile), Med: Median value (50th percentile), Q3: Upper Quartile (75th percentile), Max: Maximum (highest value excluding outliers), mean by group (green lines), global mean (grey line) and observed values (black dots) of maximum spontaneous pain level following the 7 days after endodontic treatment (VAS 100mm)

EndoN: Endomethasone N root canal sealer, EndoSP: Endomethasone SP root canal sealer, VAS: Visual Analogic Scale

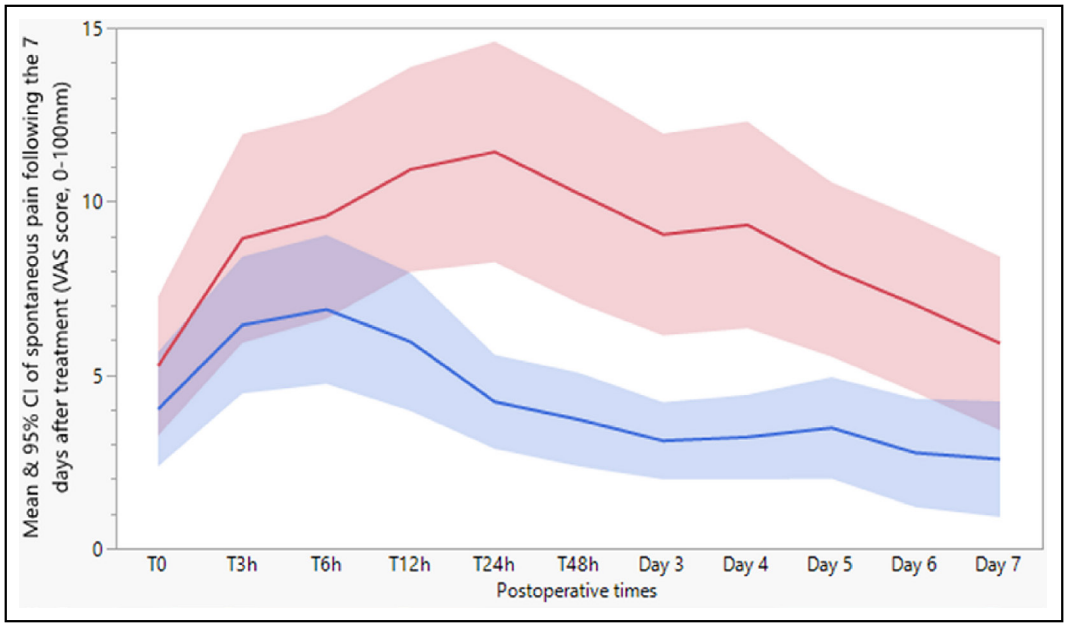

Figure 3. Mean and CI95% of VAS score (0-100) for spontaneous pain according to group in FAS population after endodontic treatment. At every evaluation time, the pain intensity reported by the patients was higher in the EndoSP group than in the EndoSP group. This difference in pain intensity was not significant at T0h (p=0.3442), at T3h (p=0.1111) and at T6h (p=0.1582) but became significant at T12h (p=0.0034) and stayed significant until the end of the 7 days follow-up period; at 24h (p=0.0009), 48h (p=0.0020), day 3 (p=0.0002), day 4 (p=0.0022), day 5 (p=0.0219), day 6 (p=0.0037) and day 7 (p=0.0033)

CI: Confidence interval, VAS: Visual Analogic Scale, FAS: Full analysis set, EndoSP: Endomethasone SP root canal sealer

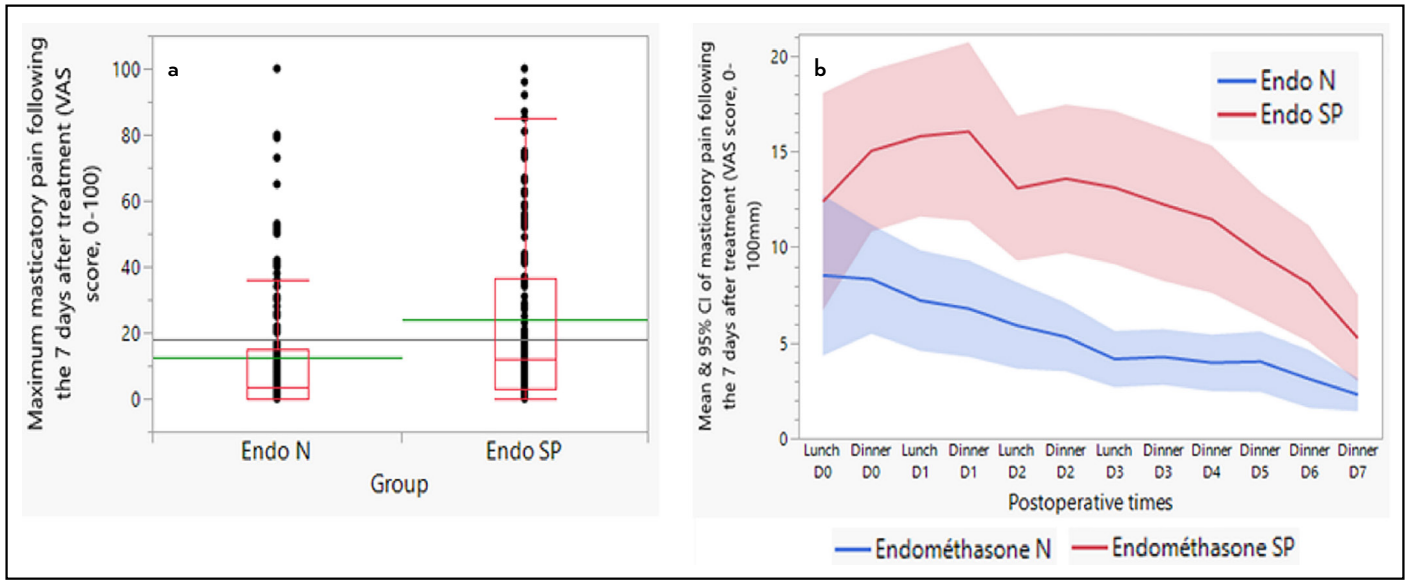

Figure 4. Maximum masticatory pain level in the 7 days after endodontic treatment self-estimated on a 0-100mmm visual analogic scale (VAS) in the FAS population. (a) Boxplot of maximum masticatory pain intensity. A significant difference was found between EndoN and EndoSP pain scores (p<0.0001). In red; Min: Minimum (lowest value excluding outliers), Q1: Lower Quartile (25th percentile), Med: Median value (50th percentile), Q3: Upper Quartile (75th percentile), Max: Maximum (highest value excluding outliers), mean by group (green lines), global mean (grey line) and observed values (black dots) of maximum spontaneous pain level following the 7 days after endodontic treatment (VAS 100mm). (b) Mean and CI95% of VAS score during the 7 days of the follow-up

EndoN: Endomethasone N root canal sealer, EndoSP: Endomethasone SP root canal sealer, FAS: Full analysis set, CI: Confidence interval

amount of PEP, reflected by the AUC score, were significantly lower in the EndoN group. Restricted analysis of the subset of painful patients confirmed the superiority of EndoN. Painful adverse events (flare-ups) were too rare to show a significant difference between the groups, even if the number of flare-ups was twice in the EndoSP group than in the EndoN group. A lower intake of analgesics in the EndoN group also evidences the overall pain reduction.

TABLE 6. Synthesis of subgroup analyses (superiority analysis)

Subgroup	Maximum spontaneous PEP	Maximum masticatory PEP	Time to reach maximum spontaneous PEP	Spontaneous PEP intensity at 24 h	Masticatory PEP intensity at 24 h	Gradation of spontaneous PEP intensity at 24 h	Gradation of masticatory PEP intensity at 24 h	Duration of spontaneous PEP	Duration of masticatory PEP	OHIP-17 score
FAS population	N>SP	N>SP	N>SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
spontaneous pain	N>SP	N=SP	N=SP	N>SP	N=SP	N>SP	N=SP	N=SP	N>SP	N=SP
Spontaneous pain or provoked pain	N>SP	N>SP	N=SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
Asymptomatic tooth	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP
Female	N>SP	N>SP	N>SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
Male	N>SP	N>SP	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Male vs female	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	difference	difference	difference
Premolar	N>SP	N>SP	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Molar	N=SP	N>SP	N=SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP
Molar Vs Premolar	difference	difference	difference	difference	difference	equivalent	difference	equivalent	equivalent	difference
Treatment Initial	N>SP	N>SP	N=SP	N>SP	N>SP	N=SP	N>SP	N=SP	N=SP	N=SP
Retreatment	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP
Initial Vs Retreatment	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent
Irreversible Pulpitis	N>SP	N>SP	N=SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Necrotic Pulp	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP
Vital pulp with ET indication	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP
Irreversible pulpitis vs Necrotic pulp vs Vital pulp with ET indication	difference	difference	equivalent	difference	difference	equivalent	equivalent	equivalent	difference	difference
Temporary coronal filling	N>SP	N>SP	N>SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
Permanent coronal filling:	Sample size insufficient									
Temporary vs permanent coronal filling	Sample size insufficient									
Prosthetic restoration performed: Yes vs no	Sample size insufficient									
Intake of analgesics: Yes	N>SP	N>SP	N=SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP
Intake of analgesics: No	N>SP	N=SP	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Intake of analgesics: Yes vs no	difference	difference	equivalent	difference	equivalent	difference	difference	equivalent	equivalent	difference
Antibiotics: Yes	Sample size insufficient									
Antibiotics: No	N>SP	N>SP	N=SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
Antibiotics: Yes vs no	Sample size insufficient									
Periapical lesion: al PAI≤1	N=SP	N=SP	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Periapical lesion: al PAI>1	N>SP	N>SP	N=SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Periapical lesion: PAI≤1 vs PAI>1	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent	equivalent
Root canal overfilled	N=SP	N>SP	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	N>SP	N=SP
Root canal underfilled	N>SP	N>SP	N=SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP
Root canal satisfying filling	N=SP	N=SP	N>SP	N>SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP
Root canal filling: Satisfying vs overfilled vs underfilled	equivalent	equivalent	equivalent	equivalent	different	equivalent	equivalent	equivalent	equivalent	equivalent
Cold lateral technique	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP	N=SP
Vertical warm technique	N=SP	N>SP	N=SP	N=SP	N>SP	N=SP	N=SP	N=SP	NA	N=SP
Spontaneous PEP: Yes	Focus on the OHIP-17 score									N=SP
Spontaneous PEP: No	Focus on the OHIP-17 score									N=SP
Spontaneous PEP: Yes* vs no	Focus on the OHIP-17 score									different
Swelling (D0): Yes	Sample size insufficient									
Swelling (D0): No	N>SP	N>SP	N=SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
Swelling (D0): Yes vs no	Sample size insufficient									
Swelling (D7): Yes	Sample size insufficient									
Swelling (D7): No	N>SP	N>SP	N=SP	N>SP	N>SP	N>SP	N>SP	N=SP	N=SP	N=SP
Swelling (D7): Yes vs no	Sample size insufficient									

TABLE 6. Cont.

*: At least one spontaneous pain measurement > 0 mm during the 7-day follow-up.

Indications in the table must be interpreted as follows:

N>SP: Significant difference between the EndoN group (N) and EndoSP (SP) group, in favour of EndoN; N=SP: no significant difference between the EndoN and Endo SP groups;

N<SP: Significant difference between the EndoN and EndoSP groups, in favour of EndoSP. Difference: Difference in the results according to the subgroups. Equivalence: No difference in the results according to the subgroups.

Primary outcome: For each subgroup's analyses performed, the maximum spontaneous PEP level during 7 days was lower in the EndoN group. This reduction was significant for the following subgroups: symptomatic tooth with spontaneous pain, symptomatic tooth with spontaneous or masticatory PEP, asymptomatic tooth, Female and Male, Premolar, Initial treatment, Irreversible pulpitis, Necrotic pulp, Vital pulp with ET indication, Temporary coronal filling, Intake of painkiller or NSAID (yes and no), absence of antibiotic's intake, PAI score >1, Underfilled root canal and Absence of Swelling at D0 and the end of the follow-up (D7). Moreover, the maximum spontaneous PEP level was different according to the type of tooth, the pulp diagnosis, and the intake of analgesics but was equivalent according to the sex, the type of ET, the PAI score and ET quality.

Secondary outcomes: 1) The maximum masticatory PEP was lower in the EndoN group for each of the subgroup's analyses performed. This item was different according to the type of tooth, the pulp diagnosis, and the intake of analgesics but equivalent according to the sex, the type of ET, the PAI score, and the ET quality. 2) The time to reach maximum spontaneous PEP was different according to the type of tooth but equivalent according to the sex, the type of ET, the pulp diagnosis, the intake of painkillers/ NSAIDs, the PAI score, and the ET quality. 3) The Spontaneous pain intensity at 24 h was different according to the type of tooth, the pulp diagnosis, and the intake of analgesics but equivalent according to the sex, the type of ET, the PAI score, and the ET quality. 4) The Masticatory pain intensity at 24h was different according to the type of tooth, the pulp diagnosis, and the intake of analgesics but equivalent according to the sex, the type of ET, the PAI score, and the ET quality. 5) The gradation of spontaneous PEP intensity at 24 h was different according to the intake of analgesic but equivalent according to the sex, the type of tooth, the pulp diagnosis, the type of ET, the PAI score, and the ET quality. 6) The Gradation of masticatory pain intensity at 24 h was different according to the type of tooth and the intake of analgesics but equivalent according to the sex, the pulp diagnosis, the type of ET, the PAI score, and the ET quality. 8) The duration of spontaneous pain was different according to the type of tooth and the intake of analgesics, the pulp diagnosis, the type of ET, the PAI score, and the ET quality. 9) The duration of masticatory pain was different according to the sex and the pulp diagnosis but equivalent according to the type of tooth, the intake of analgesics, the type of treatment, the PAI score, and the ET quality. 10. OHIP-17 after ET was different according to the sex, the type of tooth and the pulp diagnosis, the intake of analgesics, and the spontaneous PEP but equivalent according to the type of ET, the PAI score, and the ET quality.

ET: Endodontic treatment, PEP: Post endodontic pain, NSAID: Non steroidal anti-inflammatory drugs, OHIP: Oral health impact profile, N: EndoN, SP: EndoSP, PAI: Peripacal ,ndex; D0: Day 0, D7: Day 7

Cortisone-related Effects

These results support previous data related to the diffusion of cortisone from intracanal dressing pastes (33, 34) and, more interestingly, from data from two preclinical studies performed *in vitro* and *in vivo* (35, 36) demonstrating that hydrocortisone acetate (HCA) from EndoN diffuses through the apex of the root canal to produce an anti-inflammatory effect. These studies evidenced 1) a decrease in the secretion of Interleukin-6 and Tumor Necrosing factor alpha (TNFα), a decrease of the adhesion and migration of inflammatory cells activating endothelial cells, 2) a peak of concentration of the HCA released from EndoN occurring 2 h after the ET in the periapical tissue 3) that the released HCA (about 10%) was mainly excreted within 48 h *in vivo* suggesting that HCA only remains in the periapical area for a few hours and do not accumulate in tissues or organs. The main analgesic effect of the RCS in this study is expected to be due to cortisone, which is not present in EndoSP. It should also be noted that in mice, riboflavin, present in EndoSP but not in EndoN, has shown anti-inflammatory and analgesic effects when administered at high doses (25–100 mg/kg) (37). Although not tested experimentally, this putative analgesic effect of riboflavin on PEP would have masked the effect of cortisone when comparing the two RCS. This suggests that a new formulation of RCS containing riboflavin and cortisone could be explored to reduce PEP since the association of these compounds might potentiate corticosteroid effects (38).

Subgroup and Explanatory Analyses

The subgroup analysis confirmed the superiority of EndoN vs SP observed in the FAS analysis for almost all the searched categories. Regarding the study's primary objective, the maximum spontaneous PEP level was different according to the type of tooth, the pulp diagnosis, and the intake of analgesics but was equivalent according to the sex, the type of ET, the PAI score and ET quality. Regarding the secondary objectives, the Maximum PEP masticatory pain was lower in the EndoN group for each subgroup's analyses. The explanatory analysis showed no variable was associated with a significant decrease in spontaneous PEP intensity in the EndoN group. Not surprisingly, since the study included patients with different diagnoses known to share common symptomatology, maximum masticatory PEP and maximum spontaneous PEP were highly correlated. Pre-ET Anxiety scores were weakly correlated with maximum spontaneous PEP scores, in accordance with previous studies indicating interrelations between anxiety and pain (39–41).

Safety

In the two groups, 20.6% of the sample experienced one mild or moderate adverse event (AE) with a similar distribution, in which 4.9% were possibly related to the RCS.

Strengths and Limits

Strengths

This RCT was performed by general practitioners, reflecting common practice among dentists with a high number of patients. The pain-related information was collected at early time points after ET, which is unfrequent in PEP studies, capturing

precisely the pain behaviour in patients. It measured spontaneous and provoked (masticatory) PEP, giving a more accurate picture of the consequences of pain on function and QoL.

Limits

The PEP was predominantly mild or moderate, with a limited impact on daily life. Evaluating the performance of the RCS by specialists and not general practitioners could have been more informative, although ET performed by endodontists in France, as in many other countries, is more expensive compared to GP, and this might induce a bias selection since the perception of pain is affected by socioeconomic status (42). Another limit is related to using the 2D PAI system for radiographic evaluation, instead of the 3D PAI (43), which is more accurate for detecting and quantifying periapical lesions. However, its use is uncommon in France for general practitioners as a routine tool and would have exposed patients to unnecessary radiation. Although trained in endodontic radiographic interpretation, the radiographic review performed by a single examiner is also a weakness. However, the PAI index and radiographic quality of ET were not items pertaining to the study's main objective.

CONCLUSION

This RCT demonstrates that the Endomethasone Root Canal Sealer reduced both the maximal intensity and total amount of spontaneous and masticatory PEP compared to its cortisone-free formulation, supporting preclinical data claiming a local anti-inflammatory effect via corticosteroids. Safety data indicate that the RCS can be used safely in general clinical practice.

Disclosures

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