**Official title:**

The Effect of Trypsin-Chymotrypsin On Postoperative Pain After Single Visit Endodontic Treatment

A Randomized Controlled Trial

**NCT number: NCT05479747**

**Date: 9 September, 2022**

## Ethical considerations

This study approved by the institutional review of board (IRB) of the ethics committee at the Faculty of Dentistry, Ain Shams University, Cairo, Egypt. This trial was registered under approval number FDASU-Rec IM012110.

## Trial design

This study design was a prospective, parallel, triple blind phase IV randomized clinical trial. It was followed the consolidation standards of The Preferred Reporting Items for Randomized Trials in Endodontics (PRIRATE) 2020 guidelines

## Sample size calculation

A pilot study was performed on five patients in each group and its results were used for sample size calculation. Based upon the results of the pilot study; the minimum estimated sample size was a total of 52 patients. Sample size was increased to 60 for compensation of the drop-out. Sample size calculation was performed by using G*Power Version 3.1.9.2.

## Eligibility criteria

Patients were allocated from the outpatients' emergency clinic of the Endodontic Department, Faculty of Dentistry, Ain Shams University in Cairo, Egypt during six-month period between 1 June and 31 December 2021. All included patient signed an informed consent prior to start of the study.

## Inclusion criteria

- Egyptian healthy symptomatic both gender patients
- aged (18- 40) years old
- with no physical disability, facial paresthesia or psychological problems
- had mandibular first molars with symptomatic irreversible pulpitis and with normal appearance radiographically.

## Exclusion criteria

- The vulnerable group
- participants who unabled to read and fill the questionnaire,
- those who took preoperative analgesics 24 h prior to treatment
- those with known sensitivity to the drugs used in this study

## Randomization and blinding

60 patients who had the eligibility criteria were allocated randomly according to the ratio of 1:1 to each group. Randomization was performed by using computer software (www.randome.org).

Allocation concealment mechanism: Random sequence generations, allocation concealment and interventions preparation were occurred before starting by the help of one independent person who concealed the allocation sequence from the investigators in opaque and tightly sealed envelope. Before

study implementation, this person also divided the medicaments into 60 tightly sealed opaque envelopes contained a treatment specification with the prescriptive dose and labeled by one-digit alphabetical symbol (X, Y, Z, R).

Study implementation: After root canal treatment, post-operative medicaments were assigned by telephone verification. This independent person informed the operator which drug should be prescribed in the form of X, Y, Z or R to maintain operator blinding. The investigators used the computerized generated randomization protocol for each eligible patient. So, patients were enrolled into each of the groups and prescribed with different post-operative intervention. All pain assessment forms and data were monitored by a trained clinician. He was not a part of the study team. The statistician also was blinded.

**Intervention**

Patient history revealed diffuse lingering pulpal pain. Cold sensibility testing with Endo-Ice (1,1,1,2 Tetrafluoroethane; Hygenic Corp) indicated a moderate to severe response. Vitality was matched with the contra lateral as control. The vitality was established clinically by blood in the canal. Teeth had no sensitivity to percussion or palpation. Radiographically, normal periapical condition. Endodontic treatment procedures were done by the same operator in the post-graduate clinic of the Endodontic Department of the Faculty of Dentistry, Ain Shams University, Egypt. Patients were assessed by a trained clinician who was not a part of the study team.

85 patients were assessed for the eligibility criteria. 25 individuals were excluded due to different reasons. 60 participants were included. They were randomized into four groups ($n$ = 15).

**Group I: (Brufen)**

Participants were handed Brufen (Ibuprofen) (Abbott chemical laboratories, Advil, USA) 600 mg 3 times daily for 3 days after meals in tightly sealed envelope with an included written paper contained the instruction for dose administration.

**Group II: (Ambezim G)**

Participants were handed Ambezim G (Trypsin 5 mg Chymotrypsin 5 mg) (Global Napi Pharmaceutical Company, Giza, Egypt) 3 times daily for 3 days one hour before meals in tightly sealed envelope with an included written paper contained the instruction for dose administration.

**Group III: (Brufen + Ambezim G)**

Participants were handed Brufen (Ibuprofen) (Abbott chemical laboratories, Advil, USA) 600 mg 3 times daily for 3 days after meals and Ambezim G (Trypsin 5 mg Chymotrypsin 5 mg) (Global Napi Pharmaceutical Company, Giza, Egypt) 3 times daily for 3 days one hour before meals in tightly sealed envelope with an included written paper contained the instruction for dose administration.

**Group IV: (sugar pills)**

Participants were handed postoperatively sugar pills (Placebo pills) (Department of pharmaceutics & industrial pharmacy at Faculty of pharmacy Ain Shams University, Cairo, Egypt) 3 times daily for 3 days in tightly sealed envelope with an included written paper contained the instruction for dose administration.

**Outcome assessment**

Efficiency of the interventions was assessed by using a Numeric Rating Scale (NRS) from 6 hours following drug intake after obturation to 72 hours (start with 6 hours first interval then at 12 hours intervals).

The minimum score value is zero. The maximum score value is ten. Maximum scores indicate the worst possible outcome.

Passive surveillance of harm to detect clinical safety during the full follow up period. It depends on adverse effects reported by the participants.

**Statistical analysis**

Statistical analysis was undertaken with IBM SPSS Statistics. Age difference was analyzed using one-way ANOVA test. For Pain records, Kruskal-Wallis test for comparison among the four groups, Friedman's test for changes by time intervals in each group and Dunn's test for pair-wise comparisons when Kruskal-Wallis or Friedman's test was significant. Chi-square test was used for qualitative data. The significance level was set at $P \leq 0.05$

**Results**

There was no significant difference between mean age values or gender distribution or pre-operative pain scores in the four groups.

About the effect of type of medication, after six, 12, 24, 48 as well as 72 hours, Pair-wise comparisons between groups discovered that Placebo showed the statistically significantly difference. There was no significant difference between Ibuprofen, Trypsin-Chymotrypsin and combination of both Ibuprofen and Trypsin-Chymotrypsin groups'. Table:(1)

About the conclusion of time lapsed on post-operative pain, comparison in each group per time lapsed revealed significant change by time. Figure:(1)

Table (1): Descriptive statistics and results of Kruskal-Wallis test for comparison between pain scores in the four groups Time

| Time | Ibuprofen (n = 15) | Trypsin-Chymotrypsin (n = 15) | Ibuprofen + Trypsin-Chymotrypsin (n = 15) | Placebo (n = 15) | *P*-value | *Effect size (Eta Squared)* |
|---|---|---|---|---|---|---|
| Pre-operative | | | | | | |
| Median (Range) | 8 (7-9) | 8 (7-10) | 7 (7-10) | 9 (8-10) | 0.426 | 0.019 |
| Mean (SD) | 8.4 (0.63) | 8.53 (1.13) | 8.13 (1.36) | 8.73 (0.8) | | |
| 6 hours | | | | | | |
| Median (Range) | 3 (1-6) $^{B}$ | 3 (1-5) $^{B}$ | 3 (0-4) $^{B}$ | 6 (5-7) $^{A}$ | <0.001* | 0.515 |
| Mean (SD) | 3.47 (1.55) | 3.53 (1.46) | 2.93 (1.33) | 6.13 (0.64) | | |
| 12 hours | | | | | | |
| Median (Range) | 2 (0-4) $^{B}$ | 2 (0-4) $^{B}$ | 2 (0-3) $^{B}$ | 5 (3-5) $^{A}$ | <0.001* | 0.495 |
| Mean (SD) | 2 (1.41) | 1.87 (1.51) | 1.4 (0.91) | 4.47 (0.64) | | |
| 24 hours | | | | | | |
| Median (Range) | 0 (0-3) $^{B}$ | 0 (0-3) $^{B}$ | 0 (0-1) $^{B}$ | 4 (2-4) $^{A}$ | <0.001* | 0.583 |
| Mean (SD) | 0.87 (1.06) | 0.8 (1.08) | 0.2 (0.41) | 3.4 (0.74) | | |
| 48 hours | | | | | | |
| Median (Range) | 0 (0-0) $^{B}$ | 0 (0-2) $^{B}$ | 0 (0-0) $^{B}$ | 3 (1-3) $^{A}$ | <0.001* | 0.911 |
| Mean (SD) | 0 (0) | 0.13 (0.52) | 0 (0) | 2.47 (0.64) | | |
| 72 hours | | | | | | |
| Median (Range) | 0 (0-0) $^{B}$ | 0 (0-2) $^{B}$ | 0 (0-0) $^{B}$ | 1 (0-2) $^{A}$ | <0.001* | 0.63 |
| Mean (SD) | 0 (0) | 0.13 (0.52) | 0 (0) | 1.2 (0.77) | | |

**: Significant at P ≤ 0.05, Different superscripts in the same row indicate statistically significant difference between groups*

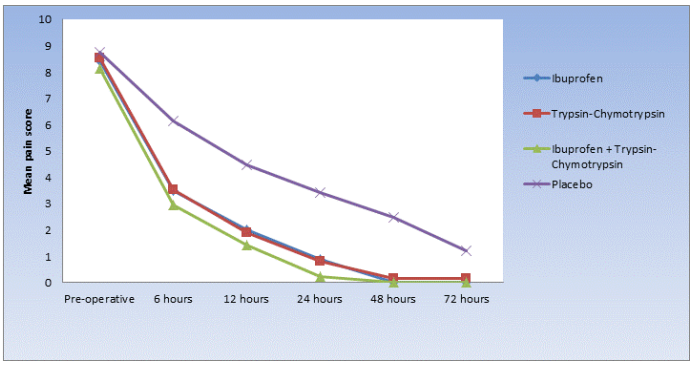


Figure (1): line chart of effect of drug per time intervals in the same group