INTRODUCTION

Pain perception is a highly subjective and variable experience. It is influenced not only by the performed treatment but also by various physical and psychological factors (1). Conventional dental procedures are associated with pain postoperatively, but the incidence and severity are highest with root canal therapy (2). The main contributing factor for post-endodontic pain is the extrusion of canal contents, debris and microbes from root canal space to the periapical area, leading to intense inflammatory response and infection (3).

Previous systematic reviews have extensively explored the data on administering Non Steroidal Anti-inflammatory Drugs (NSAIDs) for effective postoperative pain control in patients undergoing root canal treatment (4-8). The mechanism of action is mainly by inhibiting prostaglandin synthesis at the sites of inflammation (9). Some studies conclude the beneficial effect in administering non-narcotic analgesics (4-8, 10, 11), others claim no efficient results (12-14). Various other drugs such as corticosteroids (15-18) and opioids are used alone or in a combination for treating endodontic pain (19-21).
NSAIDs provide excellent pain relief due to their anti-inflammatory and analgesic action. The most common NSAIDs used are aspirin and ibuprofen (22). Ibuprofen is a peripherally acting analgesic with a potent anti-inflammatory action that works through a reversible and balanced cyclooxygenase (COX1/COX2) inhibition (23). Ibuprofen has been extensively evaluated for controlling post-endodontic pain and literature supports its efficacy (4, 24). Basically ibuprofen exists as a racemic mixture of both R(-) and S(+) enantiomers. Its analgesic and anti-inflammatory effects are related to S(+) enantiomer (25-27). Ibuprofen is well absorbed orally and its peak concentrations in serum are attained 1-2 hours after the oral administration. Its serum half-life is around 1.8 to 2 hours with rapid biotransformation and eliminated through metabolism in 24 hours after the last dose (28).

Although, a systematic review revealed that the greater pain relief was observed with 600 mg of oral ibuprofen than placebo in patients undergoing root canal treatment (4), a recent review concluded an unclear role of oral ibuprofen in controlling postoperative pain (14). Literature on controlling acute postoperative pain in adults using single dose of oral ibuprofen showed favourable results towards prescribing 600 mg dosage of ibuprofen as compared to 200 and 400 mg respectively (29-31). As far as surgical extractions are concerned, 600 mg of ibuprofen preoperative dosage seemed more beneficial in reducing the postoperative pain and swelling after extractions of mandibular third molars, and dental implant surgeries (32, 33). As far as the postoperative ibuprofen dosage is concerned, only one study evaluated the analgesic effect of 200 mg of ibuprofen postoperatively in patients with symptomatic irreversible pulpitis and proved its beneficial effect (34).

The preemptive approach focuses on delivering the analgesic before the painful stimulus, to prevent or pre-empt the afferent input that amplifies the pain. Preemptive analgesic administration is an anti-nociceptive therapy, which decreases postoperative pain by preventing altered afferent input (35). As most of the patients present with pain preoperatively have higher levels of inflammatory mediators being released. Thus, pre-treatment analgesia decreases the establishment of central sensitization, a mechanism by which spinal neurons increase their response to the peripheral nociceptive impulse (35). Whereas, the preventive approach is not time-related and may or may not be initiated before the treatment and is defined by reduced postoperative pain or analgesic consumption, relative to the treatment.

Systematic review data revealed that the drugs prescribed preoperatively (4, 18, 36-38, 24) and postoperatively (10, 39) to reduce the endodontic pain showed conflicting results. Literature states higher postoperative pain levels in patients undergoing single visit root canal treatments (40, 41). But, studies concentrating on pharmacological pain management in single visit root canal treatment are scarce (18, 24, 39). Hence, our study design would give precise data on the effectiveness of therapeutic drug administrations in single visit endodontics. Although the gender-wise analysis on the postoperative pain levels is rather investigated by previous studies (42-46), the current study is unique in assessing the effect of different drug delivery protocols on postoperative pain levels in different genders. So considering all these factors, the current study is unique in the present norm, as it has considered the effect of genders, clinical condition, preoperative parameters to evaluate the effectiveness of preemptive versus preventive oral administration of ibuprofen in patients undergoing single visit root canal treatment.

The purpose of this randomized controlled trial was to compare and evaluate the postoperative pain levels and analgesic intake on preemptive versus preventive oral administration of NSAIDs in single visit root canal treatment. The null hypothesis tested was there was no statistically significant difference in the postoperative pain levels and analgesic intake on preemptive versus preventive oral administration of ibuprofen in single visit root canal treatment.

MATERIALS AND METHODS

Study protocol
The present study is a prospective randomized, double-blinded pilot clinical trial. The study was conducted in the Department of Conservative Dentistry and Endodontics at a university-affiliated hospital. The present study’s approval was obtained from the Institutional Ethical Committee, and the study was registered in Clinical Trial Registry (CTRI/2019/03/018244).

Inclusion and exclusion criteria
One hundred participants met the inclusion criteria with symptomatic irreversible pulpitis involving mandibular molars without any associated periapical pathology, systemically healthy American Society of Anesthesiologists (ASA I) individuals under 18-55. Additionally, individuals were selected to have severe baseline preoperative pain scores (Heft-Parker 170 mm Scale) (47). Exclusion criteria included participants other than ASA I. Individuals with periapical and periodontal pathosis, with additional teeth presenting with pulpal and periapical pathosis, under any medication or analgesic intake for pain management, participants with multiple teeth requiring endodontic treatment were excluded from the study. Teeth with the apical periodontitis or extensive calcifications were also excluded from the present study. The root canal curvature of the mandibular molars was assessed using an intraoral periapical radiograph using Schneider’s classification and any curvature greater than 20° were excluded as it is difficult to perform root canal treatment in a single visit in teeth with severe curvatures and chances of procedural errors are higher in such teeth.

Preoperative assessment
A single operator (K.V.T) has performed the entire treatment procedure. Before the participant allocation to the operator (K.V.T), an examiner (K.J) who was not involved in the present study has assessed the preoperative condition of the tooth and the prior recording of the baseline pain score using the 170 mm heft-parker visual analogue scale (34). Each participant received a sheet containing the heft-parker scale with
graded markings. They were asked to mark the possible experienced pain on the scale provided. As mentioned previously, individuals were selected such that they had severe baseline pain scores. Severe pain included several gradations as strong, intense and maximum possible, which corresponded to 114 mm, 144 mm and 170 mm, respectively. So, patients with strong, intense and maximum possible scores were only selected for the study.

The pulpal status was assessed before allocation. Patients were confirmed with the diagnosis of symptomatic irreversible pulpitis using the American Association of Endodontists (AAE) criteria. Individuals presented with mandibular molars having severe spontaneous pain and elicited an abnormal response to cold (Green Endo Ice; Hygenic Corp, Akron, OH, USA) and electric pulp testing (Kerr Analytic Technology Corp, Redmond, WA, USA) were included for the present study. The patient’s pain often lasted for 30 seconds or more after the removal of the stimulus. Participants eliciting tenderness on vertical or lateral percussion and teeth with any periapical pathosis diagnosed on radiographic examination were excluded from the present study. All the past and present symptoms were taken into consideration before the inclusion of the participant in the current study. Any participant who reported recurrent pain episodes or has taken analgesics previously or is currently under any medication for the pain control was not considered.

Participants having preoperative endodontic pain for more than 1-2 weeks were not included in the study.

**Sample size determination**

The sample size for the current pilot study was assessed using a G power 3.1 version. The estimated power was adjusted to 95% with a 5% marginal error. The minimal sample size calculated was 41 per group. The sample size was increased to 50 per group, to compensate for the loss of follow-up.

**Subject allocation and randomization:**

A computer-generated random sequence allocation method was followed; for proper randomization, allocation concealment was carried out using an opaque sealed envelope method. Participants were asked randomly to pick up their envelope, which contained a group code. (group I- preemptive group), (group II- preventive group) (48). In both groups, 200 mg of ibuprofen tablets (Brufen; Abbott India Ltd) were administered postoperatively and asked to consume only when required. Only participants under group I were administered 600 mg of ibuprofen tablet (Brufen; Abbott India Ltd) one hour before the procedure.

The entire course of dispensing pills was done by a blinded investigator (K.J) who was not involved in the study.

The details of either the group or the tablet’s dispensing and dosage protocol were not revealed to the operator until the end of the study. The participant was also unaware of the protocol of tablets and the dosage of pills dispensed. Each participant was given a three sealed envelope containing a total of nine 200 mg tablets and asked to consume analgesics only when required, not more than 3 per day for three days (34). Participants under group I were dispensed preoperatively with an additional sealed envelope containing a single 600 mg of ibuprofen tablet. The postoperative analgesic intake and pain scores were recorded by a blinded assessor (K.J), who was not involved in the study.

Randomization of study subjects and allocation was previously mentioned. Once the study subjects were allocated to specific groups, based on random assignment, participants categorized under preemptive group were administered with 600 mg of ibuprofen single dose orally 1 hour before the procedure. Participants under the preventive group were not given any analgesic orally before the treatment procedure but were given a placebo capsule with no active ingredient. Once the subject allocation was carried out randomly, the entire treatment protocol was finished by a single operator (K.V.T) in the same visit.

**Treatment protocol**

Once the subject allocation was done, each subject was anesthetized by the standardized inferior alveolar nerve block, using 1.8ml of 2% lidocaine with 1:200.000 epinephrine (LOX 2%, NEON Lab Ltd, India) (49), and an additional second dose is administered if no profound anesthesia was obtained. Before injection, a sterile gauze was used to dry the site of injection. Topical anesthetic 20% benzocaine was applied using a sterile cotton applicator tip. Once the negative aspiration was performed, the solution was deposited at a rate of 1ml/min using a 27 gauge long needle (49). After 15 minutes waiting period, the participant was assessed for profound lip numbness. Once the lip numbness was confirmed, the rubber dam isolation was done, and treatment was initiated. Subjects, who experienced a failure of anesthesia, were administered with supplemental infiltrations and intraligamentary injections. Intrapulpal anesthesia was a final resort in individuals who experienced intolerable pain during pulp extirpation or instrumentation.

As mentioned, after the confirmation of profound anesthesia, the rubber dam isolation was carried out, and the standardized access cavity was prepared under the operating microscope (CARL ZEISS, OPMI pico, Germany). After achieving the apical patency, the working length was assessed using an apex locator (J Morita; Root ZX mini, USA). The working length radiograph was taken as a confirmative. After establishing the working length, the treatment protocol was initiated. Standardized instrumentation was carried out by hybrid technique using No. 10- hand K-files (Dentsply Mallifer, Ballaigues, Switzerland) and Protaper NEXT rotary files (Dentsply Mallifer, Ballaigues, Switzerland). Apical preparation was established to be at least three sizes greater than the initial apical binding file (48). During instrumentation, irrigation was carried out using 30 gauge side vented needles (Navitip, Ultradent, South Jordan, UT). Intermittent irrigation was done with 3% sodium hypochlorite (Parcan, India). 15 ml of irrigant was used for each canal approximately. Once the complete shaping and cleaning were performed, the canals were rinsed using 5 ml of distilled water, and a final rinse was carried out using 2 ml of 17% EDTA solution (MD Cleanser, MetaBiomed, India). Once the activation was carried out using Endoactivator, canals were dried using sterile paper points, and the canals were coated with AH-plus (Dentsply Mallifer, Ballaigues, Switzerland) using the lentulo spirals and root canal filling was done with gutta-
percha (Dentsply Mallfer, Ballaigues, Switzerland) using continuous-wave condensation technique (Eq-V System, META BIOMED INC. 3015 Advance Lane Colmar, PA. 18915, USA). Once the obturation was completed, the tooth was temporized using Cavit (3M ESPE, St Paul, MN), and the postoperative radiograph was taken, and the patient was relieved out of occlusion (48).

Once the entire treatment protocol was performed, participants were dispensed with three opaque sealed envelopes containing 200 mg of ibuprofen tablets, three in each (34). They were advised to consume pills orally, only when required, not more than three tablets a day. No rescue drug was prescribed, and the participants who required additional analgesics per day or had intolerable pain were asked to report immediately to the assessor (K.J). The participants with intolerable pain and required other pain management drugs during the postoperative period were excluded from the present study. Each participant was given a dairy containing three sheets, including a heft-parker scale in each sheet and a column for noting the analgesic intake. Each participant was instructed to mention the pain scores and the analgesic intake by the assessor who had initially diagnosed and recorded the preoperative pain scores (K.J). The operator (K.V.T) who performed the treatment was blinded of the followed pre or postoperative protocol.

**Postoperative assessment**
The postoperative assessment was carried out on pain scores and analgesic intake at 6, 24, 48 and 72 hours after the treatment’s commencement. A 12 hour time interval of assessment was not possible in the present study. Participants included in the present study were selected at different periods during the day. It is difficult to ask the patient to record the pain scores and analgesic intake at 12 hour time periods. Once the entire postoperative period was completed, they were asked to report to the operator with their dairy for clinical assessment and evaluation. Our study was mainly aimed at assessing the experimental protocol on postoperative pain levels and analgesic intake. So, no data was assessed on the failure of the anaesthesia in the groups evaluated.

**Statistical analysis**
The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. Unpaired sample t-test was used to find significance between the bivariate samples in independent groups. For the multivariate analysis in repeated measures, the repeated measure of ANOVA was used with Bonferroni correction to control the type I error on multiple comparisons. Significance in the categorical data was assessed using a chi-square test. Similarly, if the expected cell frequency is less than 5 in 2x2 tables, fisher’s exact was used.

**RESULTS**
Percentages cross-tabulation on gender and age of the subjects selected in different groups are presented in Tables 1 and 2. Gender and age-wise comparison revealed no statistically significant difference in different groups (P>0.05). Results on pain scores at different time intervals compared with baseline are presented in (Table 3). The results on tablet intake at base-line when compared at 6, 24, 48 and 72 hours are shown in Table 4. As a secondary objective of the study, a gender-wise comparison of pain scores at different time intervals was performed (Table 5).

The results on tablet intake showed a statistically significant decrease in tablet intake in group I (P<0.05) at 6, 24, 48 and 72 hours, compared to group II. Percentage cross-tabulation on the number of tablets in different groups is presented in table 4. Statistical comparison on baseline tablet intake is not applicable, as none of the individuals consumed any analgesics before subject allocation.

The results on pain scores in different groups showed a statistical decrease in pain scores at 6, 24, 48 and 72 hours in group I (P<0.05), as compared to group II (Table 3). When gender-wise
analysis on pain scores at different time intervals was analyzed, there was no statistically significant difference in both the groups compared (P>0.05), (Table 5).

**DISCUSSION**

The present study results proved that preemptive analgesic administration reduced the postoperative pain levels and tablet intake in the participants at all evaluated experimental time intervals. Previous literature on different modes of drug administration has demonstrated the superiority of preemptive analgesic administration in reducing the pain scores postoperatively (4, 18, 36-38, 24). Existing literature on the amount of tablet intake is not specific. However, 2 studies reported the reduced intake of medication by participants when administered preoperatively (4, 24).

The current study reported mild pain scores after a 24-hour time interval, which was in corroboration with the systematic reviews (4, 37, 39), which assessed the postoperative pain scores at 4 hours until 72 hours. The included studies reported moderate to severe scores at 6, 12 & 24 hours, after which the scores were barely noted. Previous literature focused on assessing the postoperative pain levels at 12 and 24 hours after root canal treatment (4, 50). Unfortunately, we could not include the 12 hours evaluation time in our study as the patients were recruited for the study at different time intervals. However, the first 24 hours after intervention are expected to be the most painful period after dental procedures with a high expectancy of moderate to severe pain. Our study results showed nil pain scores with 60% of participants who did not consume any analgesic at 24-hour time interval in group I. By this, it can be concluded that the actual beneficial effect of a single oral higher dose of ibuprofen as compared to prescribing it postoperatively.

When the time of preemptive drug administrations was evaluated, the literature showed administration periods ranging one day prior (24 hours), 12 hours, 6 hours, 1 hour and half an hour before the intervention (4, 24). Among the different
time intervals compared, administration of oral dosage one hour before the procedure was found to be effective (4). So, we administered the tablet preoperatively one hour before the intervention. Previous studies reported in systematic review assessed the ibuprofen oral tablets at 200, 400 and 600 mg dosages for preemptive administration and concluded 600 mg ibuprofen oral tablet to be safe and effective (4).

Hence, we considered choosing a preemptive oral dosage of 600 mg ibuprofen tablet in the present study. The dosage was standardized in the preventive group by prescribing 200 mg of ibuprofen tablets 8th hour, and participants were asked not to consume more than three pills a day.

The recent literature considers that 600 mg ibuprofen possesses both anti-inflammatory actions and analgesic actions, and such anti-inflammatory effects of 600 mg of ibuprofen, may occur up to 8-12 hours postoperatively, while ibuprofen at 200 mg has only an analgesic effect when used after dental/surgical procedures (29). Hence, in the current study, there was a valid preemptive analgesic effect, rather than the greater bioavailability in group I, in the first 24 hours. According to the experimental protocol of the current study, the patients were asked to consume analgesics only when they have uncontrolled or intolerable pain as unnecessary intake would alter the interpretation of both postoperative pain scores and analogical intake. The extra 200 mg prescribed postoperatively was not mandatory for the patient. Moreover, the study results showed that the analogical intake was more in group II than group I. So, the beneficial effect in the preemptive group was not because of greater bioavailability.

Literature shows that single visit root canal treatments are associated with more postoperative pain than multiple visits (40, 41). But, studies mainly concentrating on the usage of drugs on pain management in single visit root canal treatment are scarce (18, 24, 39). Notably, there is no literature supporting adverse impact of the single oral higher dose of ibuprofen (4, 24). However, the efficacy of postoperative 200 mg ibuprofen in controlling the postoperative pain levels could not be concluded from the present study design.

When the side effects of the different dosages of NSAIDs used preemptive or postoperatively have to be assessed, only a few studies have addressed this point of interest (4, 24). Most of the studies stated that patients experienced gastrointestinal irritation when NSAIDs were used (4, 24). The results of this study revealed that preemptive drug administration, reduced the postoperative analgesic intake. In the present study, none of the individuals in both groups reported adverse effects. The reason may be the selection of systemically healthy ASA I patients.

Most of the literature shows evidence that females have more pain compared to males due to various reasons (42-44). Literature also shows that females elicit more pain compared to males (45, 46). But the current study results showed no gender-wise difference in elicited pain scores postoperatively. A systematic review analyzed ten years of research on sex/gender and experimental pain perception and stated a valid point that no consistent conclusion can be drawn in this specific field of research (51). So, from a clinical standpoint, in patients with symptomatic endodontic pain, the severity of pain might vary from individual to individual. Although females are more sensitive to pain, it might not always be accurate in endodontic scenarios.

The teeth selection and the specific preoperative condition were similar for all the patients included in the study. The reason for choosing mandibular molars and higher baseline pain scores for the present study was mainly because the literature shows that the reported postoperative pain was severe in these teeth (46). When selecting the participants, it is appropriate to choose the subjects with higher baseline pain scores, as there is increased activation of nociceptive impulse, leading to higher chances of postoperative pain in such cases (46, 50, 52). To exclude other possible reasons that might interfere with the inference of study measures, participants who did not consume any prior analgesic before the intervention were included in this study. Subjects with additional teeth presenting with pulpal and periradicular pathosis, under any medication or analgesic intake for pain management or any other medical condition, participants with multiple teeth requiring endodontic treatment were excluded. Only participants categorized under ASA-I were only selected for the present study. The present study is double-blinded, where the operator and the participant were blinded. So, the possible operator or participant related bias was eliminated in the present study.

The entire treatment protocol was standardized and performed by a single operator. In the current study, we used EDTA as a final rinse, as previous study reports reveal the highest bond strengths of AH plus sealer with root canal dentine when EDTA was used as a final rinse (53-55). Previous literature claims irrigant activation as a mandatory protocol because they improve the intracanal cleanliness by removing the smear layer and debris from the root canal (56). Hence, we preferred Endoactivator (Dentsply, USA) for the final irrigant activation. Although, studies state the minimal extrusion of debris and irrigant on
using different irrigant activation systems (57-59), the recent studies revealed the least extrusion (60, 61) with lesser postoperative pain on using sonic activation (62) and another study revealed the safer use when they were using within 1mm of working length (63). As far as systematic review data obtained from clinical studies revealed that mechanical active irrigation devices are beneficial in reducing postoperative pain and improving the canal and isthmus cleanliness (64, 65). Hence, the postoperative pain following irrigant activation might not be a significant factor of assessment in the present study, as the protocol was similar in both the assessed groups.

Discussion on the previous literature is not possible as none of the studies up to date compared the preemptive versus preventive analgesic administration superiority in single-visit root canal treatment. The literature on both the single visit root canal treatment strategies is scarce, and previous literature on the specific topic is ambiguous. Few studies reported preemptive strategies (4, 24) to be beneficial in reducing the postoperative pain levels, while others on postoperative NSAID administration (10, 39), especially in single visit root canal treatment. So, a clear cut distinction on the superiority of the treatment strategies is still inconclusive.

Future trials have to concentrate on increased sample sizes. The research has focused on using oral tablets, but when other NSAIDs are analyzed, fast releasing capsules are more beneficial than pills (66). Hence, future trials have to concentrate on analyzing this aspect.

CONCLUSION
Preemptive analgesic administration seemed beneficial compared to the preventive regimen in reducing the postoperative pain levels and analgesic intake in participants undergoing single visit root canal treatment.

Disclosures
Conflict of interest: The authors deny any conflict of interest.
Ethics Committee Approval: This study was approved by The Institutional Human Ethics Committee of Saveetha Dental College & Hospitals, (Date: 27/03/2018, Number: SRB/SDMDS03/18/ODS/10).
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