Faculty of Dentistry
Department of Pediatric Dentistry and Dental Public Health

Study Protocol and Statistical Analysis Plan
Masters Degree In Pediatric Dentistry
Academic Year 2020-2021
Dr. Farah Safwat Nemr

Title: EFFECTIVENESS OF PRE-EMPTIVE ANALGESICS ON POST-OPERATIVE PAIN AFTER STAINLESS STEEL CROWN PLACEMENT ON PRIMARY MOLARS: RANDOMISED CONTROLLED CLINICAL TRIAL

NCT Number: Not yet assigned
Document Date: 19-10-2022

Keywords: Pre-emptive analgesia, ibuprofen, paracetamol, post-operative pain, stainless steel crown, primary molars

Supervision Committee:

1. **Prof. Dr. Karin ML Dowidar**
Professor of Pediatric Dentistry.
Department of Pediatric Dentistry and Dental Public Health.
Faculty of Dentistry, Alexandria University.

2. **Dr. Reham Soliman**
Lecturer of Pediatric Dentistry.
Department of Pediatric Dentistry and Dental Public Health.
Faculty of Dentistry, Alexandria University.

OUTLINE

ABSTRACT

Background: Pre-emptive analgesia is a concept which aims to minimize post-operative pain and discomfort following painful dental procedures, thus, ensuring a comfortable dental experience.

Objective: The aim of this study is to evaluate the effectiveness of pre-emptive analgesia using ibuprofen and paracetamol on reducing post-operative pain following the placement of stainless steel crowns on primary molars compared to placebo.

Method: The study will be a parallel, placebo-controlled, triple-blinded, randomized clinical trial. A total of 66 healthy children aged 5-8 years requiring the placement of a stainless steel crown will be selected from Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University, Egypt. The children will be randomly allocated into three groups according to the type of pre-emptive solution used. Group I will receive ibuprofen, group II will receive paracetamol, while group III (control) will receive a placebo solution. Children will self-report their level of pain using a Visual analogue scale (VAS) and/or a Facial pain scale (FPS) after local anesthesia administration, immediately after the cementation of the stainless steel crown, and 2, 6 and 24 hours post-operatively. Children's baseline anxiety and parental anxiety will also be assessed.

Results: Data will be collected, tabulated and statistically analyzed to obtain the results and conclusions of this study.

Keywords: Pre-emptive analgesia, ibuprofen, paracetamol, post-operative pain, stainless steel crown, primary molars

INTRODUCTION

Successful pediatric dental treatment depends on several factors, including the alleviation of fear and anxiety, efficient pain control and the establishment of a trusting relationship with the pediatric patient.(1,2) Painful, traumatic or negative dental experiences, especially in childhood could have long lasting negative effects, such as avoidance of regular dental checkups, increased dental problems and symptomatic treatment needs.(3–6)

Pain is a highly individualized experience.(7) Even though pain control can be effectively achieved with the use of local anaesthetics and the majority of children receive dental care without experiencing postoperative discomfort, it has been reported that about a third of children undergoing routine dental treatments under local anesthesia still experience postoperative pain.(8,9)

Pre-emptive analgesia is a concept that aims to minimize post-operative pain and discomfort by preventing peripheral and central sensitization, thus diminishing or ideally preventing the post-operative amplification of pain sensation, improving recovery and reducing postoperative analgesic consumption.(10,11) The concept was first introduced by Crile(12), and is known as the "anoci-association" theory. Crile studied the effect of administration of multiple anesthetic agents and techniques, before, during and after surgery and postulated that postoperative morbidity could be decreased by blocking the transmission of pain prior to the surgical incision.

The concept of pre-emptive analgesia has been employed in several studies conducted on adult patients. In patients undergoing third molar extraction under local anesthesia, the use of pre-emptive analgesics resulted in a marked decrease in post-operative pain scores.(13–15) Additionally, studies conducted on patients undergoing endodontic procedures have also reported a decrease in postoperative pain when pre-emptive analgesics were used.(16,17) The concept has also been investigated in patients undergoing implant surgeries and a recent study reported that the use of ibuprofen as a pre-emptive analgesic 1 hour before the procedure, resulted in a reduction in post-operative pain and less need for a rescue analgesic as compared to placebo, thus supporting the use of pre-emptive analgesics.(18)

Ibuprofen, paracetamol, diclofenac and tramadol have been used in pediatric dentistry for pain management, however, paracetamol and ibuprofen are the most commonly prescribed analgesics for treatment of acute pain.(19,20) Paracetamol is an analgesic that acts peripherally; although its primary site of action is still debatable, it is thought to inhibit prostaglandins in the hypothalamus.(21) Effective dosages are between 15–20mg/kg/day to a maximum of 60 mg/kg/day and its peak of action is achieved within 1-2 hours of administration.(22) Ibuprofen is a non-steroidal anti-inflammatory drug which acts by reducing the production of cyclo-oxygenases (COX-1 and COX-2)- derived prostanoids in the blood. (23)It is effective in dosages ranging from 10 mg/kg/day to a maximum of 40 mg/kg/day, and it reaches its peak concentration in the plasma between 15-30 minutes following administration.(22) Both drugs are safe, but some reports show that ibuprofen is slightly more effective due to its anti-inflammatory action.(24)

Ibuprofen and paracetamol have been used in several studies to investigate their effect as pre-emptive analgesics on reducing post-operative pain following the extraction of primary molars, however, the results were contradictory.(22,25,26) One study revealed that the use of pre-emptive analgesics showed lower post-operative pain scores compared to the placebo following the extraction of primary molars, while another study concluded that pre-emptive administration of analgesics did not significantly reduce trans- and post-operative pain in children after primary molars extraction. In a study investigating the effectiveness of pre-treatment with ibuprofen on post-operative pain following pulpotomy of primary molars, children who received ibuprofen as a premedication, experienced less pain following the pulpotomy and stainless steel crown placement in comparison to children who received placebo, however, it cannot be determined whether the post-operative pain experienced in the placebo group was due to the pulpotomy procedure or the placement of the stainless steel crown.(20)

A recent systematic review stated that there was not enough evidence to determine whether pre-emptive analgesia is beneficial in the reduction of post-operative pain in the pediatric population or not, due to the low methodological quality of the available studies.(27)

The placement of a stainless steel crown is a common dental procedure that is performed on daily basis and is not limited to teeth undergoing endodontic treatment. According to an observational study that was conducted to measure the incidence of pain and analgesic use following restorative and surgical procedures in children and adolescents, patients who had received a primary stainless steel crown were significantly more likely to report postoperative discomfort as compared to those who had undergone other routine procedures including primary teeth extraction, and the majority were given over-the-counter analgesics.(28–30) Therefore, seeking methods to decrease pain and discomfort following the placement of stainless steel crowns is of utmost importance to ensure a comfortable dental experience.

Most studies in the literature have investigated the effect of pre-emptive analgesia on post-operative pain in children who have undergone primary molar extractions; only a few have evaluated the effect of pre-emptive analgesia on post-operative pain following the placement of stainless steel crowns. Therefore, this study attempts to evaluate the effectiveness of pre-emptive analgesic drugs in reducing post-operative pain following the placement of a stainless steel crown on non-pulpotomized maxillary primary molars compared to placebo, taking into consideration confounding factors, such as age, child's dental anxiety, parental dental anxiety and the child's behavior during the dental treatment.

The null hypothesis is that there will be no significant difference in the level of post-operative pain experienced after the placement of stainless steel crowns with the pre-emptive administration of ibuprofen and paracetamol analgesics compared to placebo.

AIM OF THE STUDY

Primary Aim:

- To evaluate and compare the effectiveness of premedication with ibuprofen and paracetamol on reducing post-operative pain following the placement of stainless steel crowns on primary molars compared to placebo

Secondary Aims:

- To evaluate and compare the effectiveness of premedication with ibuprofen and paracetamol on reducing trans-operative pain during local anesthesia administration
- To evaluate the effect of dental anxiety on children's perception of pain
- To evaluate the effect of parental anxiety on their children's anxiety and behavior during dental procedures

RESEARCH DESIGN

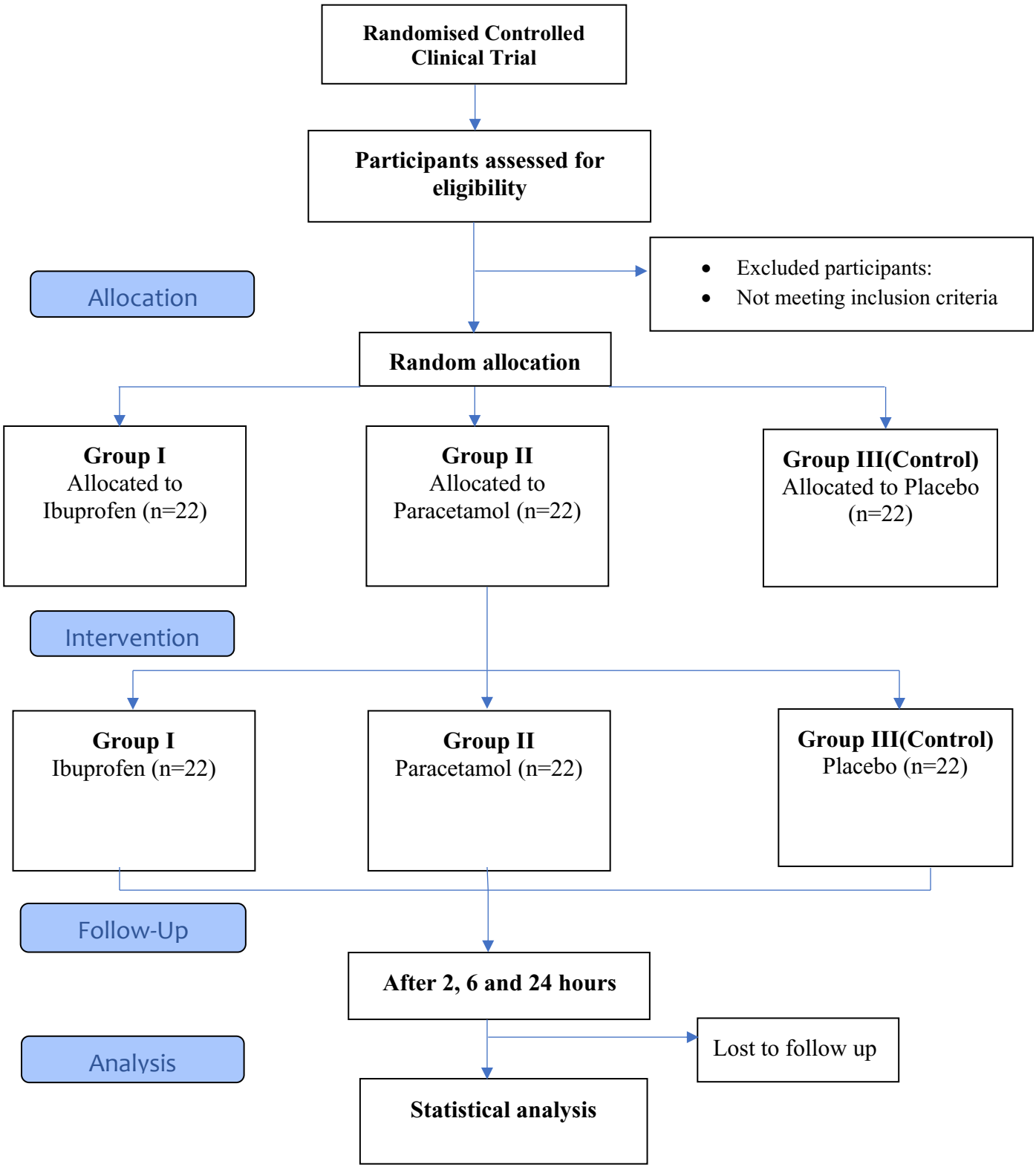


Figure (1): Flow Chart Study Design

PLAN OF THE STUDY

Study Design

This study will be a three arm, parallel group, triple blinded, placebo-controlled, randomized clinical trial. It will be set up and reported according to the CONSORT statement.(31)

The PICO question will be: Do pediatric patients aged 5-8 (P: population) receiving pre-emptive analgesics; ibuprofen and paracetamol (I: intervention) in comparison to placebo (C: control), experience less post-operative pain following the placement of stainless steel crowns (O: outcome)?

Study setting and location

Participants will be recruited from the outpatient clinic, Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University, Egypt.

Sample size estimation

Sample size was estimated assuming 5% alpha error and 80% study power. Viswanath et al.(32) reported mean ± SD pain score after 24 hours of using ibuprofen = 18.84 ± 14.32, and 36.5 ± 25.05 when acetaminophen (paracetamol) was used. Pre-emptive analgesics are assumed to have a similar effect in decreasing post-operative pain in children. (22) Based on comparison of means, sample size was calculated to be 20 per group, increased to 22 for procedural problems. The total required sample size= number of groups × number per group= 3 x 22 = 66.(33)

Eligibility Criteria:

Participant inclusion criteria:

- Age range 5 to 8 years old
- Children without any previous interventional dental experience
- Children free of any systemic disease or special health care needs (ASA 1)(34)
- Children free of any allergies or hypersensitivity reactions to local anesthetics or analgesic drugs
- Positive or definitely positive behaviour during preoperative assessments according to the Frankl Rating Scale (score 3 or 4) (Appendix I)(35)
- Parents/caregivers and children who are willing to participate in the study

Tooth inclusion criteria:

- Maxillary first or second primary molar teeth with extensive and/or multisurface caries where other restorations are likely to fail but without pulp exposure (29,30,36)
- Absence of clinical and radiographic signs or symptoms of irreversible pulpitis(37)
- Absence of fistula or abscess near the selected tooth clinically and radiographically(38)
- Absence of spontaneous pain(38)
- Absence of pulp exposure
- Absence of pathological mobility by placing the points of a pair of tweezers in an occlusal fossa, and gently rocking the tooth bucco-lingually(39)

Materials

- Periapical radiographs
- Ibuprofen 100 mg/5 ml*
- Paracetamol 250 mg/5 ml**
- Topical Anaesthesia – Benzocaine gel 20%. ***
- Short 30-gauge anaesthetic needles.
- Local anaesthetic carpules: Articaine hydrochloride 4% with adrenaline 1:100,000. ****
- Dental anaesthetic syringe (non-disposable breech loading, metallic cartridge type)
- Diagnostic sets
- Excavators
- Stainless steel crowns*****
- Glass ionomer cement ******

1

* BRUFEN®, Kahira Pharmaceuticals & Chemical Industries Co.[1]

** CETAL®, EGYPTIAN INT. PHARMACEUTICAL INDUSTRIES CO.
***Dharma Research, Inc. 5220 NW 72nd Ave Miami, FL 33166 USA..
**** ARTINIBSA, Inibsa Dental S.L.U, 08185 Lliçà de Vall, Barcelona, Spain
***** Stainless Steel Crowns, 3 M™ ESPE™, St.Paul, MN, USA
******Fuji IX capsules (GC Fuji IX GP,GC America)

Randomization

Participants complying with the inclusion criteria will be randomly assigned using a computer generated list of random numbers (40) to one of the three arms (Ibuprofen, paracetamol and placebo).

Allocation will be performed by a trial independent individual using permuted block technique, where the allocation ratio is intended to be equal to ensure that the study groups have equal number of children.

Allocation Concealment

The list of allocation will be generated prospectively using random allocation software where participants are allocated in blocks of six. Each child included in the study will be given a serial number that will be used in the allocation. These numbers will be written on identical sheets of paper with the group to which each child will be allocated. The papers will be placed in opaque envelopes carrying the respective sequence of the children.(41) A trial independent personnel will be assigned the role of keeping the envelopes and unfolding them only at the time of pre-emptive solution administration.

Grouping

The participants will be randomly divided into 3 groups according to the pre-emptive solution received:

Group I: (Study group I) will receive ibuprofen (N=22).

Group II: (Study group II) will receive paracetamol (N=22).

Group III: (Control) will receive placebo (N=22).

Blinding

The participant, operator and statistician will be blinded to the pre-emptive solution group. After data collection is completed, the randomization code will be broken to reveal the allocation group.

Intra examiner reliability

A theoretical training will be carried out by a gold standard researcher with the operator, assistant, and evaluator before the data collection, where all steps of the procedures will be discussed, and all the scales and questionnaires used in the research will be presented.

Thereafter, a pediatric dentistry specialist will calibrate the operator for the use of the Venham's behavior rating scale (VBRS) through the observation of videos of children undergoing dental procedures and the classification of the child's behavior after watching each video. After a 7-day interval, the exercise will be repeated, and the intra-examiner Kappa concordance coefficient will be calculated and score above 0.8 will be accepted (kappa >0.8).

Method

Preliminary screening visit

To ensure fulfillment of the inclusion criteria, a complete medical and dental history will be taken from the selected patients' parents/caregivers and only patients whose parents/caregivers will agree to give their consent to participate will be examined. Thorough clinical examination and an intraoral periapical radiograph of the tooth to be restored will be obtained for definitive diagnosis. Children fulfilling the selection criteria, whose parents/ caregivers consented participation will be scheduled for more visits.

Patient Preparation Visit(42)

This will be an introductory visit without any clinical intervention to acquaint the child with the dental atmosphere and help establish a good relationship between the child, and the dentist and the dental staff. 'Tell-Show-Do' technique will be used to introduce the dental instruments and materials to the child. Topical fluoride will be applied to the children's teeth and oral hygiene instructions will be given to both, the children and their parents.

Intervention Visit

Preparation of the pre-emptive solutions:

Both pre-emptive analgesics will be fruit-flavored, and the placebo solution will be freshly prepared by an assistant in a manner to match the color and odor of the analgesics. To ensure blinding, the three pre-emptive solutions will be placed in similar single-dose glass bottles. The bottles will be encoded and only the assistant who prepared the solutions will be aware of the content of each bottle.

Administration of the pre-emptive solution:

Children will be randomly assigned to one of three pre-emptive solutions:

- Group I: ibuprofen 100 mg/5 ml (BRUFEN®, Kahira Pharmaceuticals & Chemical Industries Co.)
- Group II: paracetamol 250 mg/5 ml (CETAL®, EGYPTIAN INT. PHARMACEUTICAL INDUSTRIES CO.)
- Group III: placebo solution (Control)

The assistant will weigh each child in the waiting area using a calibrated balance and each child will receive a weight-dosed volume of the assigned solution to maintain operator and evaluator blinding. The assistant will watch each child to make sure they drink the entire solution.

For standardization of the waiting period (ensuring participants' blinding) and for the drugs to reach their peak of action, the solutions will be administered 1 hour prior to the local anesthesia administration.(22) The time of the pre-emptive solution administration will be recorded on the data sheet.

Clinical Procedure

For standardization, all clinical procedures will be performed by a single trained and calibrated operator after undergoing a training period according to the criteria adopted.

Local Anesthesia administration:(43)

- Prior to the administration of local anesthesia, topical anesthetic gel will be applied for 1 minute to the area of injection after drying it with a piece of gauze to minimize the painful sensation of needle penetration into the soft tissues.
- The children will then receive buccal infiltrative anesthesia with Articaine to eliminate the need for a palatal injection. (44–46)
- Achievement of the anesthetic effect will be assessed by probing the soft tissues adjacent to the anesthetized tooth.
- After five minutes, when the anesthetic effect is observed, the operator will start removing the caries and preparing the tooth.

Caries removal and stainless steel crown preparation:(36)

- Using a high-speed handpiece and an excavator, all caries will be removed.
- The proximal surfaces of the teeth will then be reduced using Number 69L bur at high speed, taking care not to damage adjacent tooth surfaces.
- Slight separation between the teeth for better access could be achieved by tightly placing a wooden wedge between the surface being reduced and the adjacent surface.
- Near vertical reductions will be made on the proximal surfaces and carried gingivally until the contact with the adjacent tooth is broken.
- Using the same bur, the cusps and the occlusal portion of the tooth will be reduced, following the general contour of the occlusal surface until a clearance of approximately 1mm with the opposing teeth is achieved.
- All sharp line and point angles will be removed.

Stainless steel crown selection and cementation:(36)

- The smallest crown size that completely covers the preparation will be chosen, ensuring the establishment of the correct occlusogingival crown length.
- The crown should be shaped circumferentially to follow that natural contours of the tooth's marginal gingivae.
- If the crown is loosely fitting; Crown contouring pliers with a ball and socket design will be used at the cervical third of the buccal and lingual surfaces to help adapt the margins of the crown to the cervical portion of the tooth.
- After contouring the crown, the crown will be tried again to make sure it fits the preparation snugly and extends under the free margin of the gingival tissue.
- The crown will then be removed, cleaned and dried, and the tooth will be partially isolated using cotton rolls and a saliva ejector.
- The crown will be generously loaded with GIC (at least two thirds full) avoiding air bubbles and voids and will be placed over the tooth and seated into place by finger pressure or by asking the child to bite it into place.
- Excess GIC will be wiped away with a cotton wool roll or the gauze swab used to protect the airway.
- Removal of excess cement between the contacts will be achieved by flossing the contacts.

Post-operative instructions:

- Children will be instructed to avoid scratching, or injuring the lips, or the gingiva if numbness is felt
- Parents of children in the 3 groups will be given an elixir of either ibuprofen or paracetamol and will be instructed to use it only if necessary
- If the rescue medication is needed, the parents will be instructed to give the children only one dose every 6 hours and record the number of times the analgesic was used

Follow-up

Patients will be followed up via telephone at 2, 6 and 24 hours post-operatively

Study Outcomes

Primary outcome:

Post-operative pain evaluation: (0,2,6,24 hours post-operatively)

- The primary outcome to be evaluated is the post-operative pain experienced following the placement of a stainless steel crown.
- Pain will be measured via a visual analogue scale (VAS) based on a straight line of 100 mm where 0 mm indicates absence of pain and 100 mm indicates greatest pain felt, and a facial pain scale (FPS) (Fig.2).(47,48)
- Children will self-report their level of pain four times post-operatively; the first time will be immediately following the cementation of the stainless steel crown where the operator will explain the scales to the parent and the child, and the child will be asked to choose the face or score which best describes the level of pain that he/she feels.
- A copy of the VAS and FPS will then be given to the parents and they will be instructed to show it to their children at home to assess the level of pain at 2, 6 and 24 hours post-operatively and will report the score to the operator via telephone.

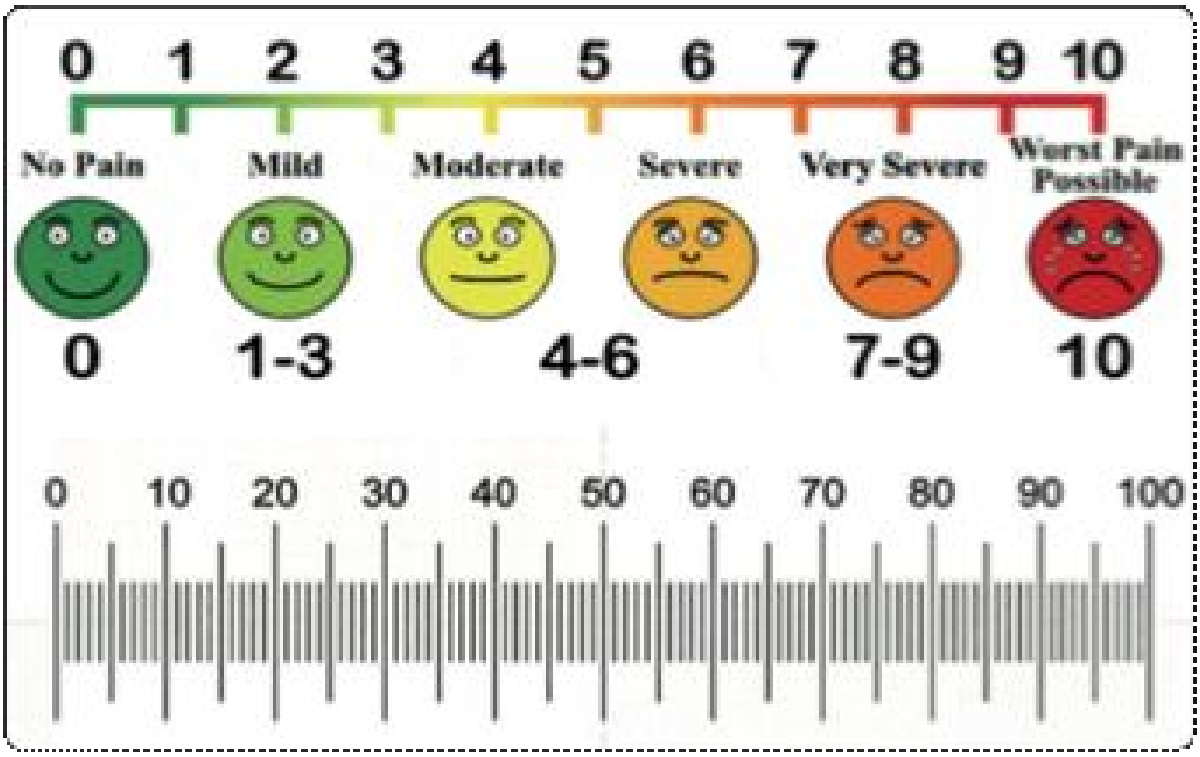


Figure (2) Visual Analogue Scale (VAS)and Facial Pain Scale (FPS)

Secondary outcomes:

1. **Trans-operative pain evaluation:**

   To assess the effectiveness of pre-emptive analgesics in reducing pain during local anesthesia administration, after local anesthesia administration, the child will be shown the VAS and FPS (Fig. 2) and he/she will be asked to choose the score or face which best describes the level he/she felt during administration of the anesthetic solution.

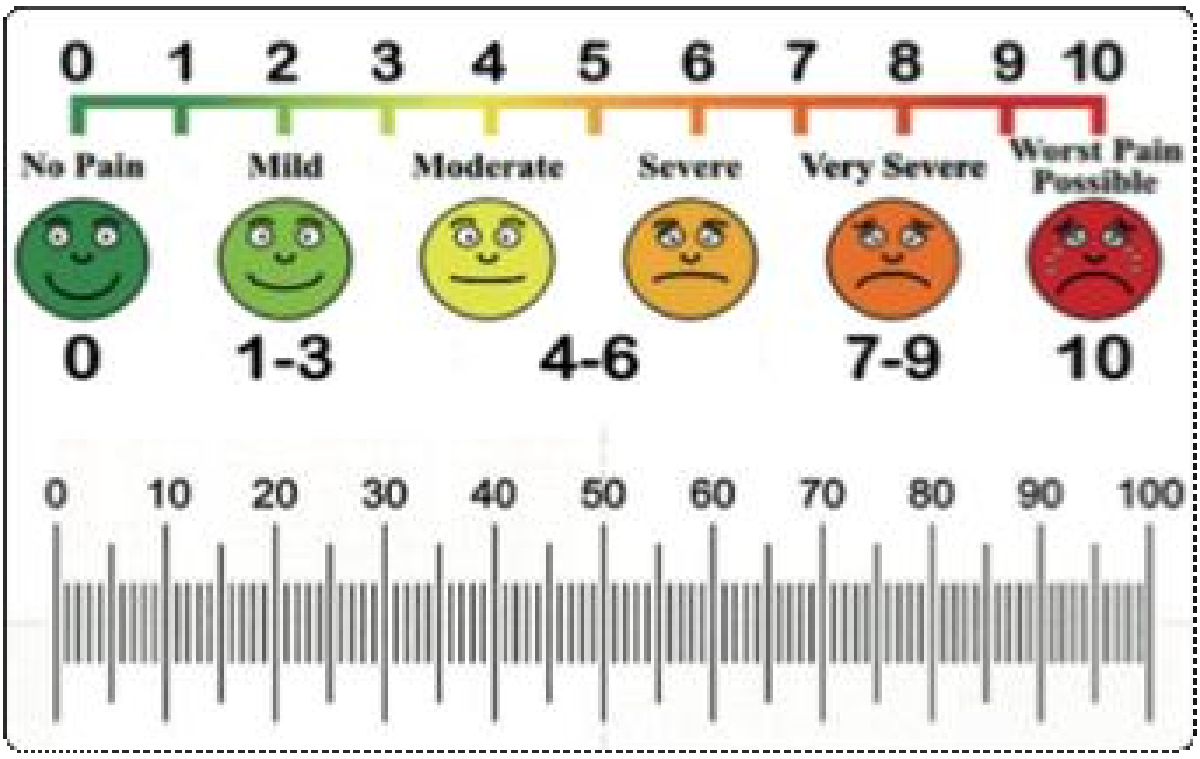


Figure (2) Visual Analogue Scale (VAS)and Facial Pain Scale (FPS)

2. Evaluation of the child's dental anxiety:

To assess the child's anxiety, the Arabic version of the faces version of Modified Child Dental Anxiety Scale ($MCDAS_f$) (Fig.3) will be used. The MCDAS consists of eight questions to assess dental anxiety about specific dental procedures. A five-point Likert scale is used to determine dental anxiety with scores ranging from 'relaxed/not worried' to 'very worried'.(49) The faces version of Modified Child Dental Anxiety Scale ($MCDAS_f$) has a faces analogue scale anchored above the original numeric form.(50) In the Arabic version of the $MCDAS_f$, the last question about conscious sedation was removed as per the experts' opinions because the children are unfamiliar with this practice.(51) In the waiting room, prior to the administration of the pre-emptive solution, the evaluator will explain the questions and the 5 faces to the child and the child will be asked to point to the face which best describes how he/she feels about the dental procedure explained.

How do you feel about …	**Relaxed/not worried** 	**Very slightly worried** 	**Fairly worried** 	**Worried a lot** 	**Very worried** 
..going to the dentist generally?	**1**	**2**	**3**	**4**	**5**
..having your teeth looked at?	**1**	**2**	**3**	**4**	**5**
..having your teeth scaled and polished?	**1**	**2**	**3**	**4**	**5**
..having an injection in the gum?	**1**	**2**	**3**	**4**	**5**
..having a filling?	**1**	**2**	**3**	**4**	**5**
..having a tooth taken out?	**1**	**2**	**3**	**4**	**5**
..being put to sleep to have treatment?	**1**	**2**	**3**	**4**	**5**
..having a mixture of 'gas and air' which will help you feel comfortable for treatment but cannot put you to sleep?	**1**	**2**	**3**	**4**	**5**

Figure (3) Faces version of Modified Child Dental Anxiety Scale ($MCDAS_f$)

3. **Evaluation of parental anxiety:**

Parental anxiety will be evaluated using the Arabic version of the Modified Dental Anxiety Scale (MDAS)(Fig. 4).(52) The questionnaire will be answered by parents in the waiting room before the intervention.

Can you tell us how anxious you get, if at all, with your dental visit?
Please indicate by inserting 'X' in the appropriate box

1. **If you went to your Dentist for TREATMENT TOMORROW, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

2. **If you were sitting in the WAITING ROOM (waiting for treatment), how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	Extremely *Anxious* ☐

3. **If you were about to have a TOOTH DRILLED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	Extremely *Anxious* ☐

4. **If you were about to have your TEETH SCALED AND POLISHED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	Extremely *Anxious* ☐

5. ***If you were about to have a LOCAL ANAESTHETIC INJECTION in your gum, above an upper back tooth, how would you feel?***

Not Anxious ☐	*Slightly* Anxious ☐	*Fairly* Anxious ☐	*Very* Anxious ☐	Extremely Anxious ☐

Instructions for scoring (remove this section below before copying for use with patients)
The Modified Dental Anxiety Scale. Each item scored as follows:

Not anxious	=	1
Slightly anxious	=	2
Fairly anxious	=	3
Very anxious	=	4
Extremely anxious	=	5

Total score is a sum of all five items, range 5 to 25: Cut off is 19 or above which indicates a highly dentally anxious patient, possibly dentally phobic

Figure (4) Modified Dental Anxiety Scale (MDAS)

4. Evaluation of the child's overall behavior during the dental treatment:

Venham's Behavior rating scale (VBRS) (Fig. 5) will be used to evaluate the overall child's behavior during dental treatment. VBRS classifies the child's behavior into 6 categories with scores ranging from 0 to 5. A score of 0 means total cooperation and a score of 5 refers to complete absence of compliance and cooperation and the requirement of physical restraint.(53) At the end of the dental visit, the operator will assign a score to each child based on the child's overall behavior during the dental visit.

Score	Behavior
0	Total cooperation, best possible working conditions, no crying or physical protest
1	Mild, soft verbal protest, or (quiet) crying as a signal of discomfort, but does not obstruct progress. Appropriate behavior for procedure, that is, slight start at injection, 'ow' during drilling if hurting**,** etc
2	Protest more prominent. Both crying and hand signals. May move head around making it hard to administer treatment. Protest more distracting and troublesome. However, child still complies with request to cooperate
3	Protest presents real problem to dentist. Complies with demands reluctantly, requiring extra effort by dentist, body movement
4	Protest disrupts procedure, requires that all of the dentist's attention be directed toward the child's behavior. Compliance eventually achieved after considerable effort by dentist, but without much actual physical restraint. (May require holding child's hands or the like to start). More prominent body movement
5	General protest, no compliance, or cooperation. Physical restraint is required

Figure (5) Venham's Behavior Rating Scale (VBRS)

STATISTICAL ANALYSIS

The results will be collected, tabulated, and statistically analyzed to fulfill the aim. Intention-to-treat analysis concept will be adopted throughout the analysis. Descriptive quantitative data will be analyzed using mean and standard deviation, while count and percent will be used for qualitative data. Comparison between normally distributed data will occur using Independent samples t- and Paired t-tests. For non-normally distributed data, Mann-Whitney U and Wilcoxon signed-rank tests will be used.

ETHICAL CONSIDERATIONS

The study will be conducted following the ethical principles for medical research involving human subjects in Declaration of Helsinki.(54) Ethical approval will be obtained from the Research Ethics Committee, Faculty of Dentistry, Alexandria University before starting the study.

The objectives, risks and benefits of the study will be explained to parents/ guardians and a signed informed consent will be obtained prior to treatment. (Appendix II). Verbal consent will be obtained from the children before the intervention. Data confidentiality will be ensured as well as interim analysis if needed.

Parents and children will be given age-appropriate dental health with proper oral hygiene instructions including proper teeth brushing twice a day especially before bedtime, as well as flossing if indicated. These measures will be demonstrated on a model. A fluoridated toothpaste and a brush will be provided to each participant on the day of the treatment.

All needed treatment will be provided to the child including any restorations, space maintainers and fluoride application. All the possible clinical and/or adverse outcomes will be explained to the parents and they will be asked to report immediately if any adverse outcome occurs.

PROBLEMS ANTICIPATED

1. Difficulty in finding patients who fulfill the inclusion criteria of the study

2. Lack of compliance from patients and/or their parents.

DURATION OF THE STUDY

Estimated time: 13 Months.

Tasks \ Months	1	2	3	4	5	6	7	8	9	10	11	12	13
Proposal writing	✓	✓											
Sample selection			✓	✓									
Dental procedure					✓	✓	✓	✓					
Data management and statistical analysis									✓	✓			
Writing thesis											✓	✓	
Thesis submission													✓

ESTIMATED BUDGET

Estimated total budget 22,000 LE

No	Materials	Total price (LE)
1	Materials	12,000
2	Statistical analysis	2,000
3	Computer services	2,000
4	Printing services	2,000
5	Publication cost	3,000
6	Others	1.000
Total		22,000

ROLE OF SUPERVISORS

1. **Prof. Karin ML Dowidar**

   Helping the student in interpreting the results and revising the thesis.

2. **Dr. Reham Soliman**

   Supervision of the blinding and the clinical work

APPENDICES

APPENDIX I

Rating	Behaviour	Mild discomfort
1	Definitely Negative	Refusing to play game, crying forcefully or fearfully, or any other overt evidence of extreme negativism
2	Negative	Reluctance to playing, uncooperative behaviour, and some evidence of negative attitude that is not pronounced
3	Positive	Acceptance of playing, willingness to comply with the dentist, cooperative behaviour
4	Definitely Positive	Good rapport with the dentist, interested in the environment, laughing, and enjoying the situation

Frankl Behaviour Rating Scale

REFERENCES

1. Goettems M, Zborowski EJ, Costa F, Costa VPP, Torriani DD. Nonpharmacologic intervention on the prevention of pain and anxiety during pediatric dental care: a systematic review. Acad Pediatr. 2017;17(2):110–9.
2. American Academy of Pediatric Dentistry. Behavior guidance for the pediatric dental patient. The Reference Manual of Pediatric Dentistry. Chicago, Ill. Am Acad Pediatr Dent. 2020;292–310.
3. Milgrom P, Mancl L, King B, Weinstein P. Origins of childhood dental fear. Behav Res Ther. 1995;33(3):313–319.
4. DS QT. Dental anxiety and regularity of dental attendance in younger adults. J Oral Rehabil. 29(6):604–608.
5. Armfield JM, Stewart JF, Spencer AJ. The vicious cycle of dental fear: Exploring the interplay between oral health, service utilization and dental fear. BMC Oral Health. 14(7).
6. Oliveira MA, Bendo CB, Ferreira MC, Paiva SM, Vale MP, Serra-Negra JM. Association between childhood dental experiences and dental fear among dental, psychology and mathematics undergraduates in Brazil. Int J Environ Res Public Health. 2012 Dec 17;9(12):4676–87.
7. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9).
8. Mittal M, Sharma S, Kumar A, Chopra R, Srivastava D. Comparison of anesthetic efficacy of articaine and lidocaine during primary maxillary molar extractions in children. Pediatr Dent. 2015;37(7):520–4.
9. Ashkenazi M, Blumer S, Eli I. Post-operative pain and use of analgesic agents in children following intrasulcular anaesthesia and various operative procedures. Br Dent J. 202(5):276–7.
10. Costa FWG, Esses DFS, de Barros Silva PG, Carvalho FSR, Sá CDL, Albuquerque AFM, et al. Does the Preemptive Use of Oral Nonsteroidal Anti-inflammatory Drugs Reduce Postoperative Pain in Surgical Removal of Third Molars? A Meta-analysis of Randomized Clinical Trials. Anesth Prog. 2015;62(2):57–63.

11. American Academy of Pediatric Dentistry. Pain management in infants, children, adolescents, and individuals with special health care Needs.The Reference Manual of Pediatric Dentistry. Chicago, Ill. Am Acad Pediatr Dent. 2020;362–70.
12. Crile GW. The Kinetic Theory of Shock and its Prevention Through Anoci-association. Lancet. 1913;182(4688):7–16.
13. Pozos-Guillen A, Martinez-Rider R, Aguirre-Banuelos P, Perez-Urizar J. Pre-emptive analgesic effect of tramadol after mandibular third molar extraction: a pilot study. J oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2007 Jul;65(7):1315–20.
14. Isiordia-Espinoza MA, Pozos-Guillén AJ, Martínez-Rider R, Herrera-Abarca JE, Pérez-Urizar J. Preemptive analgesic effectiveness of oral ketorolac plus local tramadol after impacted mandibular third molar surgery. Med Oral Patol Oral Cir Bucal. 2011 Sep;16(6):e776-80.
15. Isiordia-Espinoza MA, Sánchez-Prieto M, Tobías-Azúa F, Reyes-García JG, Granados-Soto V. Pre-emptive analgesia with the combination of tramadol plus meloxicam for third molar surgery: a pilot study. Br J Oral Maxillofac Surg. 2012 Oct;50(7):673–7.
16. Sethi P, Agarwal M, Chourasia HR, Singh MP. Effect of single dose pretreatment analgesia with three different analgesics on postoperative endodontic pain: A randomized clinical trial. J Conserv Dent. 2014 Nov;17(6):517–21.
17. Jorge-Araújo ACA, Bortoluzzi MC, Baratto-Filho F, Santos FA, Pochapski MT. Effect of Premedication with Anti-inflammatory Drugs on Post-Endodontic Pain: A Randomized Clinical Trial. Braz Dent J. 2018;29(3):254–60.
18. Pereira G-M, Cota L-O-M, Lima R-P-E, Costa F-O. Effect of preemptive analgesia with ibuprofen in the control of postoperative pain in dental implant surgeries: A randomized, triple-blind controlled clinical trial. J Clin Exp Dent. 2020 Jan 1;12(1):e71–8.
19. Hartling L, Ali S, Dryden DM, Chordiya P, Johnson DW, Plint AC, et al. How Safe Are Common Analgesics for the Treatment of Acute Pain for Children? A Systematic Review. Pain Res Manag. 2016/12/18. 2016;2016:5346819.
20. Shafie L, Esmaili S, Parirokh M, Pardakhti A, Nakhaee N, Abbott P V., et al. Efficacy of Pre-Medication with Ibuprofen on Post-Operative Pain after Pulpotomy in Primary Molars. Iran Endod J. 13(2):216–20.

21. Anderson BJ. Paracetamol (Acetaminophen): Mechanisms of action. In: A Practice of Anesthesia for Infants and Children. p. 915–21.
22. Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. Int J Paediatr Dent. 2011 Jul;21(4):306–13.
23. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009 Dec;17(6):275–342.
24. Goldman RD, Ko K, Linett LJ, Scolnik D. Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. Ann Pharmacother. 2004 Jan;38(1):146–50.
25. Kharouba J, Ratson T, Somri M, Blumer S. Preemptive Analgesia by Paracetamol, Ibuprofen or Placebo in Pediatric Dental Care: A Randomized Controlled Study. J Clin Pediatr Dent. 2019;43(1):51–5.
26. Santos PS, Massignan C, de Oliveira EV, Miranda Santana C, Bolan M, Cardoso M. Does the pre-emptive administration of paracetamol or ibuprofen reduce trans- and post-operative pain in primary molar extraction? A randomized placebo-controlled clinical trial. Int J Paediatr Dent. 2020;30(6):782–90.
27. Ashley PF, Parekh S, Moles DR, Anand P, Behbehani A. Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. Cochrane database Syst Rev. 2012 Sep;(9):CD008392.
28. Staman NM, Townsend JA, Hagan JL. Observational study: discomfort following dental procedures for children. Pediatr Dent. 2013;35(1):52–4.
29. Randall RC. Preformed metal crowns for primary and permanent molar teeth: review of the literature. Pediatr Dent. 2002;24(5):489–500.
30. American Academy of Pediatric Dentistry. Pediatric restorative dentistry. The Reference Manual of Pediatric Dentistry. Chicago, III. Am Acad Pediatr Dent. 2020;371–83.
31. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28–55.

32. Viswanath A, Oreadi D, Finkelman M, Klein G, Papageorge M. Does Pre-Emptive Administration of Intravenous Ibuprofen (Caldolor) or Intravenous Acetaminophen (Ofirmev) Reduce Postoperative Pain and Subsequent Narcotic Consumption After Third Molar Surgery? J oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2019 Feb;77(2):262–70.
33. Denyer M. Medical Statistics at a Glance. Vol. 216, Journal of Anatomy. 2010. p. 543.
34. Aronson WL, McAuliffe MS, Miller K. Variability in the American Society of Anesthesiologists Physical Status Classification Scale. AANA J. 2003 Aug;71(4):265–74.
35. Riba H, Al-Zahrani S, Al-Buqmi N, Al-Jundi A. A Review of Behavior Evaluation Scales in Pediatric Dentistry and Suggested Modification to the Frankl Scale. EC Dent Sci . 2017;16(6):269–75.
36. Dean J, Jones J, LaQuia WV. Restorative Dentistry. In: McDonald and Avery's Dentistry for the child and adolescent tenth edition. p. 185–205.
37. Kratunova E, Silva D. Pulp therapy for primary and immature permanent teeth: An overview. Gen Dent. 2018;66(6):30–8.
38. American Academy of Pediatric Dentistry. Pulp therapy for primary and immature permanent teeth. The Reference Manual of Pediatric Dentistry. Chicago, Ill. Am Acad Pediatr Dent. 2020;384–92.
39. Hariri M, Ramdi H, El Alloussi M, Chhoul H. The Hall Technique: A Non-conventional Method for Managing Carious Primary Molars. Dentistry. 2016;6(7):385.
40. Saghaei M. Random allocation software for parallel group randomized trials. BMC Med Res Methodol. 2004;4(1):26.
41. Kim J, Shin W. How to do random allocation (randomization). Clin Orthop Surg. 2014 Mar;6(1):103–9.
42. Wright GZ, Kupietzky A, Wright GZ. Behavior management in dentistry for children. 2nd ed. 2014.
43. Peedikayil FC, Vijayan A. An update on local anesthesia for pediatric dental patients. Anesth essays Res. 2013;7(1):4–9.
44. Leith R, Lynch K, O'Connell AC. Articaine use in children: a review. Eur Arch Paediatr Dent Off J Eur Acad Paediatr Dent. 2012 Dec;13(6):293–6.

45. Kolli NKR, Nirmala SVSG, Nuvvula S. The Effectiveness of Articaine and Lidocaine Single Buccal Infiltration versus Conventional Buccal and Palatal Injection Using Lidocaine during Primary Maxillary Molar Extraction: A Randomized Control Trial. Anesth essays Res. 2017;11(1):160–4.
46. Abu Sharkh M, Khalil A, Ong-Ly C, Wilson TD, Galil K. Buccal injection of articaine to anesthetize the palatal mucosa. Gen Dent. 2019;67(3):26–30.
47. von Baeyer CL. Children's self-reports of pain intensity: scale selection, limitations and interpretation. Pain Res Manag. 2006;11(3):157–62.
48. Shuman MA. Extraction of Maxillary Teeth Without a Palatal Injection: A Randomized Control Trial. Egypt Dent J. 2020;66(Issue 4-October (Oral Surgery)):2085–90.
49. Porritt J, Buchanan H, Hall M, Gilchrist F, Marshman Z. Assessing children's dental anxiety: a systematic review of current measures. Community Dent Oral Epidemiol. 2013 Apr;41(2):130–42.
50. Leko J, Škrinjarić T, Goršeta K. Reliability and Validity of Scales for Assessing Child Dental Fear and Anxiety. Acta Stomatol Croat. 2020 Mar;54(1):22–31.
51. Zeitoun S, Khalil A, Wahba N, Sayed M. The Use of a Respiratory Biofeedback Device to Reduce Dental Anxiety in Children: A Randomized Controlled Clinical Trial. Alexandria Dent J. 2021;0(0):0–0.
52. Abu-Ghazaleh SB, Rajab LD, Sonbol HN, Aljafari AK, Elkarmi RF, Humphris G. The Arabic version of the modified dental anxiety scale. Psychometrics and normative data for 15-16 year olds. Saudi Med J. 2011 Jul;32(7):725–9.
53. Venham LL, Gaulin-Kremer E, Munster E, Bengston-Audia D, Cohan J. Interval rating scales for children's dental anxiety and uncooperative behavior. Pediatr Dent. 2(3):195–202.
54. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov;310(20):2191–4.

Alexandria University
Faculty of Dentistry
Department of Pediatric Dentistry and
Dental Public Health

EFFECTIVENESS OF PRE-EMPTIVE ANALGESICS ON POST-OPERATIVE PAIN AFTER STAINLESS STEEL CROWN PLACEMENT ON PRIMARY MOLARS (RANDOMISED CONTROLLED CLINICAL TRIAL)

Name: Farah Ahmed Safwat Mohamed Amin Nemr

Summary Statement

Sample size was estimated assuming alpha error= 5% and study power= 80%. Viswanath et al.[1] reported mean ± SD pain score after 24 hours of using ibuprofen = 18.84 ± 14.32, and 36.5 ± 25.05 when acetaminophen (paracetamol) was used. Pre-emptive analgesics are assumed to have a similar effect in decreasing post-operative pain in children. [2] Based on comparison of means, sample size was calculated to be 20 per group, increased to 22 for any procedural problems. The total sample size required = number of groups × number per group= 3 x 22 = 66.[3]

Software

http://powerandsamplesize.com/Calculators/Compare-2-Means/2-Sample-Equality.

References

1. Viswanath A, Oreadi D, Finkelman M, Klein G, Papageorge M. Does pre-emptive administration of intravenous ibuprofen (Caldolor) or intravenous acetaminophen (Ofirmev) reduce postoperative pain and subsequent narcotic consumption after third molar surgery? J Oral Maxillofac Surg. 2019;77(2):262-70.
2. Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. Int J Paediatr Dent. 2011;21(4):306-13.
3. Petrie A, Sabin C. Medical statistics at a glance.3rd ed. John Wiley & Sons, West Sussex, UK; 2009.

Maha El Tantawi; B.D.S, M.Sc, Ph.D

Maha Tanta.

Professor of Dental Public Health
Alexandria University
Saturday, March 20, 2021

Ethical Guidelines for Conduct of Research on Human Subject

- **Name of the Researcher:** Farah Ahmed Safwat Mohamed Amin Nemr
- **Name of the Department:** Pediatric Dentistry and Dental Public Health Department
- **Title of the Research:** Effectiveness Of Pre-emptive Analgesics On Post-operative Pain After Stainless Steel Crown Placement On Primary Molars: Randomised Controlled Clinical Trial

	ETHICAL CONSIDERATIONS	Yes	No
1	A clear scientific purpose is described	✓	
2	The research is for the good of the community	✓	
3	The study design is included	✓	
4	The estimated sample size document is attached	✓	
5	Informed consent of the human subject is signed by the Researcher	✓	
6	The research is based on previous animal studies or laboratory researches	✓	
7	The research will not lead to physical or mental suffering	✓	
8	There is no risk of disability, mortality or morbidity	✓	
9	Detailed invasive procedure (if present) with acceptable reasoning and related references are included	✓	
10	Safety of proposed intervention (if present) with related references are mentioned	✓	
11	Medical management for potential risk is involved	✓	
12	The risks are minimal in relation to benefit	✓	
13	Facilities for research are available	✓	
14	The investigator is scientifically qualified for this research & under supervision	✓	
15	Clinical termination when risk is expected is stated	✓	
16	The participants of research could quit the research if he/she suffers any complaints	✓	
17	Privacy & confidentiality of participants is assured	✓	
18	If any harm will occur he/she will be compensated	✓	

Recommendations of the Committee

• **Protocol is accepted from the ethics committee**	
• **Protocol is not accepted**	
• **Protocol should be revised for corrections**	

COMMENTS

.....

.....

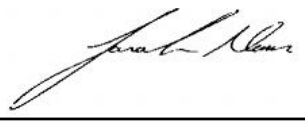
.....

Researcher Informed Consent for Ethics Committee

- **Name of the Researcher:** Farah Ahmed Safwat Mohamed Amin Nemr
- **Name of the Department:** Pediatric Dentistry and Dental Public Health Department
- **Title of the Research:** Effectiveness Of Pre-emptive Analgesics On Post-operative Pain After Stainless Steel Crown Placement On Primary Molars: Randomised Controlled Clinical Trial
- **Name of the Patient:** .....
- **ID number of the Patient:** .....

	ETHICAL CONSIDERATIONS	Yes	No
1	Statement to the participant that it is a research	✓	
2	Explanation is given to the participant of the research in clear understandable words about the procedure & its duration	✓	
3	The benefit of the research to the participant & others is described	✓	
4	The participant is informed about liable reasonable risk or discomfort	✓	
5	The participant is informed about any alteration in procedure if needed	✓	
6	Confidentiality is assured	✓	
7	The participant can quit at any time without any penalty	✓	

Signatures

• **Signature of the Participant:**	
• **Signature of the Researcher:**	
• **Date:**	04/04/2021

Researcher Pledge

The researcher is responsible to fulfill this attached consent form that involving the ethical considerations for each Participant during the period of the study.

Signature of the Researcher

---------- 

Researcher Application Form

1. **Name of the Researcher:** Farah Ahmed Safwat Mohamed Amin Nemr
2. **Title of the Researcher:** Instructor, Pediatric Dentistry and Dental Public Health Department, Faculty of Dentistry, Alexandria University
3. **Address of the Researcher:**
   - E-mail: farah.nemr@alexu.edu.eg
   - Phone Number 00201002153085
   - Fax Number .....
4. **Name of the Department:** Pediatric Dentistry and Dental Public Health Department
5. **Degree of the Protocol:**

	MD		PhD		MS		Research work	
Domestic					✓			
Multicenter within Egypt								
International								

6. **Title of the Research:**

Effectiveness Of Pre-emptive Analgesics On Post-operative Pain After Stainless Steel Crown Placement On Primary Molars: Randomised Controlled Clinical Trial

7. Type of the Research:

Clinical Trial	✓
Experimental Animal Study	
In vitro Biological Study (Studies of Biological Samples as; Cells, Fluids, Tissues, Extracted teeth etc. .....)	
In vitro Laboratory Study	
Cross Sectional Study (Survey, Case Control, Cohort etc. .....)	
Others ❖ *Please Mention The Research Type:*	

8. Subjects of Research:

Human	Adult Male	
	Adult Female	
	Child Male	✓
	Child Female	✓
Biological Samples as; Cells, Fluids, Tissues, Bone, Extracted teeth, Biopsy etc. ..... ❖ *Please Mention the Selected Subject:* …….....……		
Animal Species		
Others ❖ *Please Mention The Research Subject:*		

9. Study Phase

Study Phase	Phase I [Laboratory]	Phase II [Cell, Fluid, Tissue]	Phase III [Experimental Animal]	Phase IV [Clinical Trial]
				✓

Study Design of Clinical Trials	
Randomization	✓
Placebo – Positive Control – Negative Control	Placebo
Split Mouth	
Cross-Over	
Others ❖ *Please Mention The Study Design:*	

10. The Estimated Sample Size Document is attached:

Yes	✓	No	

11. The research provides potential benefits for the community:

Yes	✓	No	

12. Facilities for the research are available:

Yes	✓	No	

13. List the risks of the study:

Occurrence of complications or any adverse events.

Allergic reaction to analgesic drug or local anaesthetic drug.

Panic attacks or lack of cooperation of the children during the treatment.

14. List the potential benefits of the study: Decreasing/eliminating post-operative pain following the placement of stainless steel crowns on primary molars

15. The risks are reasonable to the potential direct benefits to the subjects, if any, or to the knowledge to be gained:

Yes	✓	No	

16. The researcher signed consent form is attached:

Names	***Signature***
The Researcher Farah Ahmed Safwat Mohamed Amin Nemr	
The Main Supervisor Prof. Karin ML Dowidar	
Date 04/04/2021	