Efficacy of Piroxicam and Tramadol as a Pre-Emptive Analgesic Agent for Mandibular Third Molar Surgery

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: The purpose of this clinical trial is to examine the effectiveness of 20 mg piroxicam with 50 mg tramadol as a pre-emptive analgesic for mandibular third molar surgery.

Methods: In this prospective study, 30 patients were referred to the Department of Oral and Maxillofacial Surgery in Chennai for surgical removal of impacted mandibular third molars with similar difficulty indexes under local anesthetic. Patients were randomly distributed to one of two groups: Group A received 20 mg piroxicam intramuscularly (IM) 50 minutes before surgery, while Group B received 50 mg tramadol IM 50 minutes before surgery. The time to analgesic remedication, Pain intensity (VAS Scores) at 1st, 2nd, 12th, 24th hour, total analgesic consumption was evaluated.

Results: When compared to the group getting 50 mg of tramadol IM, the group receiving 20 mg of piroxicam IM demonstrated differences in pain intensity as measured by the visual analog scale and total analgesic consumption [lesser values], and the results were statistically significant (p<0.05). However, there were no statistically significant differences between the two groups in terms of time to first rescue analgesic medication, number of patients requiring the rescue analgesic procedure (10 mg of oral ketorolac), and number of patients without the need for
Conclusion: Within the limits of the study, patients who received 20 mg of piroxicam before surgery had less pain intensity and total analgesic consumption than those who received 50 mg of tramadol before surgery. In comparison to pre-emptively administered tramadol, piroxicam showed superior analgesic effects for intermediate surgical operations when given preoperatively.

Keywords: Third molar; pre-emptive analgesia; impacted, mandibular molar; postsurgical pain; piroxicam; tramadol.

1. INTRODUCTION

The extraction of impacted third molar teeth is one of the most common oral surgical procedures performed in dentistry, and it inevitably results in a number of postoperative complications, the most common of which is pain [1]. As the effects of the local anaesthetic drug wear off, pain normally sets in. Pre-emptive analgesia refers to the administration of an analgesic before the onset of a painful stimulus. It entails antinociceptive therapy to avoid central neural sensitization, which exacerbates postsurgical pain [2]. Analgesics given before to surgical trauma are thought to have a pre-emptive effect, indicating that analgesia will begin prior to the surgical stimulus, lowering CNS input and, thus, pain [2].

Tramadol is a low-addiction opioid analgesic that is clinically useful in treating moderate to moderately severe pain. It induces analgesia against a variety of pain situations in acute therapeutic use, including postsurgical pain, obstetric pain, terminal cancer pain, and pain of cardiac origin. By decreasing monoamine reuptake, the analgesic appears to affect the transmission of pain signals at opioid receptors [3]. After mandibular third molar surgery, several nonsteroidal anti-inflammatory medications (NSAIDs) have been used to manage pain, swelling, and trismus.[4]. These drugs work by inhibiting the enzyme cyclooxygenase (COX), which controls the inhibition of prostaglandin (PG) generation [5].

Piroxicam is an acidic enolic NSAID that inhibits the inducible Cox-2 enzyme preferentially and has a lower effect on the constitutive Cox-1 enzyme [6,7]. As a result, it is commonly used to treat acute and chronic pain, as well as inflammatory and degenerative diseases [7]. Intraperitoneal piroxicam and morphine have also been demonstrated to have antinociceptive synergism [8]. Nonsteroidal anti-inflammatory medicines have been shown to provide postoperative analgesia comparable to that of opioids (NSAIDS) [9,10]. NSAIDs have also been shown to have an opioid-sparing impact, as well as a reduction in opioid-induced nausea, vomiting, and respiratory depression. This decrease in opioid use and negative effects may benefit the patient by increasing postoperative analgesia and possibly shortening hospital stays [11].

Previously, our team has extensive expertise working on a variety of research projects in a variety of areas [12–26]. We decided to explore this project because of the growing trend in this field. We hope to examine the pre-emptive analgesic effectiveness of 20 mg piroxicam and 50 mg tramadol for mandibular third molar surgery based on this motivation.

2. MATERIALS AND METHODS

2.1 Study Setup

This randomised prospective controlled clinical study was done among patients who visited the oral surgery clinic's outpatient dental department between June 2020 and March 2021. The study comprised 30 adult patients who were randomly selected and allocated to the department of oral and maxillofacial surgery for surgical removal of an impacted mandibular molar using a simple lottery approach. The patients were separated into two groups, each with 15 patients, with Group A receiving 20 mg of piroxicam intramuscularly 50 minutes before surgery and Group B receiving 50 mg of tramadol intramuscularly 50 minutes before surgery.

2.2 Inclusion Criteria

- Patients between 18 years-50 years of age
- Both genders
- A partially bony impacted mandibular third molar based on clinical and radiographic diagnosis
- Up to the day of surgery, no pain associated with the subject third molar
2.3 Exclusion Criteria

- Patients with incomplete clinical and radiological records.
- Patients with severe systemic conditions like diabetes and hypertension.
- Analgesics usage 3 days prior to the procedure, previous history of seizure disorder, lactation or pregnancy, oral contraceptive usage, and known hypersensitivity to the study drugs.

2.4 Procedure

All surgical treatments were performed by the same surgeon at the Department of Oral and Maxillofacial Surgery, and evaluations were performed by a single independent investigator. Two 1.8-mL capsules of 2 percent lidocaine–containing 1:100,000 epinephrine were used to block the lingual, buccal, and inferior alveolar nerves, resulting in anaesthesia. Surgery began once anaesthetic was administered. An incision was made along the anterior border of the ascending ramus of the jaw, distal to the mandibular second molar, to prepare a mucoperiosteal flap. The surgical incision was closed using this flap. No. 3-0 silk was used for suturing. A partial bony impacted mandibular third molar was removed in each patient. The length of time between analgesic re-medication was recorded. The patients were given four 10-mg oral ketorolac pills and told to take one of them as a rescue drug at least six hours apart, depending on their needs. The patients returned the unused ketorolac at the end of the evaluation period (24 hours). The pills were counted to ascertain the quantity of pills ingested and the number of individuals in each group who didn't require any medication. The total amount of analgesics consumed was also calculated.

2.5 Diagnostic Criteria

2.5.1 Post Operative Pain Evaluation by Visual Analogue Scale

The pain was measured using a 100-mm visual analog scale (VAS). The VAS was a numerical scale ranging from 0 to 100, with 0 signifying no pain or discomfort and 100 representing the most severe pain or discomfort. The VAS report was completed at the 1st, 2nd, and 12-hour mark after the procedure, with the final evaluation taking place at 24 hours.

2.6 Study Parameters

For the purposes of the study, the following information was gathered:

- The patient's age
- The patient's gender
- Postoperative VAS pain Scores
- It's time to re-medicate with analgesics (ie, the time from the end of the surgery until the intake of the first rescue analgesic medication became necessary for the patient)
- The number of patients in each group who did not require any medication.
- The number of patients who require a rescue analgesic technique (10 mg of oral ketorolac)
- Total analgesic consumption

The study subjects were distributed into four age groups - Group 1 was 11-20 years old, Group 2 was 21-30 years old, Group 3 was 31-40 years old, and Group 4 was 41-50 years old.

2.7 Data Collection

Patients who reported to the Outpatient Department between June 2020 and March 2021 were used to collect data for the research parameters. A single examiner completed all of the assessments, and two investigators examined and recorded the results.

2.8 Statistical Analysis

IBM SPSS version 23.0 software was used to tabulate and analyze the data. Frequency and percentage were used to express descriptive statistics. The Student's t-test was used to compare variables between the Piroxicam and Tramadol groups (time to analgesic re-medication, number of patients in each group who did not need any pill, number of patients requiring the rescue analgesic process, total analgesic intake). The effects over time of the pre-emptive analgesics on pain intensity were evaluated by Mann-Whitney U-Test. The significance level was set at P<0.05 with a confidence interval of 95%.

3. RESULTS

This study enrolled a total of 30 patients, with a 100 percent participation rate.
3.1 Age Distribution
The patients who were the youngest and oldest were 18 and 50 years old, respectively. The age distribution of study participants revealed that the majority of patients were between the ages of 31 and 40 (67.50%).

3.2 Gender Distribution
Over the course of a ten-month period, the gender distribution of study subjects revealed that 20 patients (75%) were women and 10 patients (25%) were men.

3.3 Post Operative Pain Evaluation by Visual Analogue Scale
Pain score at 1st and 2nd hours after surgery were different between the two analgesic groups; the mean VAS scores recorded after injection of piroxicam at 1 and 2 hours respectively were significantly lower than after tramadol at 1st and 2 hours, respectively. The pain intensity was also highest at the end of 2nd hour for the tramadol group (Fig. 1). No significant differences in pain scores were observed between the two analgesics at 12 and 24 hours post-surgery (P>0.05) [Mann-Whitney U test].

3.3.1 Time to first rescue analgesic medication, number of patients requiring rescue analgesia, number of patients without the need of analgesia, total analgesic consumption
The parameters: There were no significant statistical differences (P > .05) in the time to first rescue analgesic medication, the number of patients requiring the rescue analgesic treatment (10 mg of oral ketorolac), or the number of patients without the need for analgesic during the evaluation period. However, there was a statistically significant difference in overall analgesic usage between the two groups (p=0.019) [Table 1].

There was no statistically significant difference on comparison of the parameters between the two groups, in time to usage of first rescue analgesic medication (p=0.42), the number of patients who require the rescue analgesic treatment (10 mg of oral ketorolac) (p=0.12), number of patients without the need for analgesic during the evaluation period (0.15). However, the difference between total analgesic consumption between the 2 groups was statistically significant (p=0.019).

4. DISCUSSION
"Pre-emptive analgesia" refers to the administration of analgesia before the onset of surgical stimulation. It prevents or lowers central hyperexcitability, resulting in better postoperative analgesia and a lower need for analgesics [27]. Pre-emptive analgesia is a contentious topic in oral surgery, with reports both in favor and against it [28]. As a result, several criteria and processes for evaluating the quality of randomised clinical trial reports in pain research have been developed. Blind assessments are said to yield much lower and more consistent scores than open assessments [29].

Fig. 1. Bar diagram depicting VAS scores of the piroxicam group (blue) and the tramadol group (orange) at the 1st, 2nd, 12th, and 24th-hour post-surgery. The X-Axis depicts the Post extraction hour and Y-Axis represents the VAS Scores
The VAS scores of the tramadol group were higher than the piroxicam group at the 2nd-hour post-surgery
Table 1. Depicts the distribution of variables (the time to first rescue analgesic medication, number of patients who require the rescue analgesic treatment (10 mg of oral ketorolac), number of patients who do not require the usage of analgesic during the evaluation period, and total analgesic consumption) between Piroxicam Group and Tramadol Group

| Parameters                                                                 | Piroxicam Group (Mean) | Tramadol Group (Mean) | Test Value | P-Value |
|---------------------------------------------------------------------------|-------------------------|-----------------------|------------|---------|
| Time to first rescue analgesic (hr)                                       | 1.05                    | 0.95                  | 1.23       | 0.42    |
| No. of patients (%) requiring rescue analgesic during the period of evaluation (24 hr) | 6                       | 3                     | 5          | 0.12    |
| No. of patients (%) who do not require analgesic during the evaluation period (24 hr) | 1                       | 6                     | -4         | 0.15    |
| Total analgesic usage (mg)                                                | 12.6                    | 24.2                  | -34.3      | 0.019*  |

*Statistically significant; Independent sample t-test

Ong et al. [30] conducted a meta-analysis to assess the ability of pre-emptive analgesia interventions to reduce postoperative analgesic requirements, prolong the time to first rescue analgesia, and attenuate and alleviate postoperative pain scores. They found an overall beneficial effect in selected analgesic regimens, which was most pronounced after epidural analgesia, local wound infiltrations, and systemic NSAID administration. Preoperative morphine lowered pain scores and postoperative analgesic doses in patients undergoing abdominal hysterectomy, according to recent research by Richmond et al. [31]. Another study found that giving 30 mg of ketorolac IV instead of 50 mg of tramadol IV preoperatively improves pre-emptive analgesic efficacy in third molar surgery [32].

Isiordia et al. [28] performed a study which showed that patients receiving 15 mg of preoperative meloxicam had less pain intensity and total analgesic consumption than those receiving 50 mg of preoperative tramadol. All of these results were in accordance with the results of our study. However, a study by Nekoofar et al. [7] found no significant differences in the analgesic efficacy of meloxicam, piroxicam, or placebo, but did find that the time factor had a significant influence on lowering postoperative pain after endodontic treatment.

The dose of 50 mg tramadol employed in this study was chosen since it has been found to be effective and safe in the management of postoperative pain after third molar surgery.

According to [32–34], Tramadol is a safe and effective postoperative analgesic that lasts much longer than morphine. Tramadol's extensive use is hampered by the drug's significant side effects of nausea and vomiting [35]. Because this was a single-dose research, the major side effects were not visible.

Piroxicam's principal mode of action is the inhibition of COX, which determines PG inhibition. The PGs are released from injured tissues and directly sensitise peripheral nociceptors. They also play a role in primary and secondary hyperalgesia, both of which are crucial in pain regulation [36]. In comparison to other NSAIDs, piroxicam's suppression of the peroxidase enzyme gives a superior gastrointestinal tolerance. Furthermore, because of its long half-life, piroxicam may have a longer clinically significant effect when administered preoperatively [37].

This is the first study to compare piroxicam to an opioid analgesic as pre-emptive analgesics for pain control after third molar surgery, and few studies have compared its analgesic performance to other NSAIDs in this acute pain clinical paradigm [38–40]. These trials have demonstrated that piroxicam can be an effective pain reliever following the extraction of a mandibular third molar. In comparison to meloxicam, greater doses of tramadol (100 or 200 mg) might have a better analgesic effect.

However, adverse symptoms, particularly nausea and vomiting, are likely to be common. Dental pain is primarily inflammatory, and evidence-based medicine has determined that nonsteroidal anti-inflammatory drugs (NSAIDs) are the best analgesic for dental pain [41,42]. Our university is dedicated to high-quality evidence-based research and has achieved success in a number of areas [16,43–62].
5. CONCLUSION
Within the confines of this study, it may be inferred that patients who received 20 mg of piroxicam preoperatively had reduced pain intensity and total analgesic intake than those who received 50 mg of tramadol preoperatively. Therefore, piroxicam given preoperatively showed superior analgesic properties for intermediate surgical procedures in comparison to pre-emptively administered tramadol.

6. LIMITATIONS
As the VAS Scores were based on patients' perception, a subjective opinion regarding the results was obtained, hence it would be a limitation of our study. Also, the pain threshold for different patients would not be similar.

7. FUTURE SCOPE
Although the literature provides a number of studies on the pre-emptive analgesic efficacy of piroxicam and tramadol, there are limited studies related to comparing piroxicam with an opioid analgesic both as pre-emptive analgesics for pain relief following third molar surgery.

DISCLAIMER
The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

CONSENT
All of the participants were informed about the potential hazards of oral surgery and experimental therapies, and they signed a written consent form that had been approved by the institution.

ETHICAL APPROVAL
The Institutional Ethical Committee mentioned their approval to the project (SDC/SIHEC/2020/DIASDATA/0619-0320).

COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES
1. Seymour RA, Meechan JG, Blair GS. An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg. 1985;23:410–418.
2. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesthesia & Analgesia. 1993;77(2):362-79.
3. Scott LJ, Perry CM. Tramadol. Drugs. 2000;60:139–176.
4. Barden J, Edwards JE, McQuay HJ, et al. Relative efficacy of oral analgesics after third molar extraction. Br Dent J 2004; 197: 407–11.
5. Dionne RA, Berthold CW. Therapeutic uses of non-steroidal anti-inflammatory drugs in dentistry. Crit Rev Oral Biol Med. 2001;12:315–330.
6. Euler-Ziegler L, Vélicitat P, Bluhmki E, et al. Meloxicam: a review of its pharmacokinetics, efficacy and tolerability following intramuscular administration. Inflamm Res. 2001;50(Suppl 1): S5–9.
7. Nekoofar MH, Sadeghipanah M, Dehpour AR. Evaluation of meloxicam (A cox-2 inhibitor) for management of postoperative endodontic pain: a double-blind placebo-controlled study. J Endod. 2003;29:634–637.
8. Miranda HF, Pinardi G. Lack of effect of naltrexone on the spinal synergism between morphine and non steroidal anti-inflammatory drugs. Pharmacol Rep. 2009; 61:268–274.
9. Gillies GW, Kenny GN, Bullingham RE, McArdie CS. The morphine sparing effect of ketorolac tromethamine: A study of a new, parenteral non-steroidal anti-inflammatory agent after abdominal surgery. Anaesthesia. 1987;42(7):727-31.
10. Rosenblum M, Weller RS, Conard PL, et al. Ibuprofen provides longer lasting analgesia than fentanyl after laparoscopic surgery. Anesth Analg. 1991;73:255–259.
11. Gold BS, Kitz DS, Lecky JH, et al. Unanticipated admission to the hospital following ambulatory surgery. JAMA. 1989; 262:3008–3010.
12. Govindaraju L, Gurunathan D. Effectiveness of Chewable Tooth Brush in Children-A Prospective Clinical Study. J Clin Diagn Res. 2017;11:ZC31–ZC34.

13. Christabel A, Anantananarayanan P, Subash P, et al. Comparison of pterygomaxillary dysjunction with tuberosity separation in isolated Le Fort I osteotomies: a prospective, multi-centre, triple-blind, randomized controlled trial. Int J Oral Maxillofac Surg. 2016;45:180–185.

14. Soh CL, Narayanan V. Quality of life assessment in patients with dentofacial deformity undergoing orthognathic surgery -a systematic review. Int J Oral Maxillofac Surg. 2013;42:974–980.

15. Mehta M, Deeksha, Tewari D, et al. Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. Chem Biol Interact. 2019;308:206–215.

16. Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. J Oral Pathol Med. 2019;48:115–121.

17. Campeau PM, Kasperviciute D, Lu JT, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. Lancet Neurol. 2014;13:44–58.

18. Kumar SS. Knowledge and awareness regarding antibiotic prophylaxis for infective endocarditis among undergraduate dental students. Asian J Pharm Clin Res. 2016;154.

19. Christabel SL. Prevalence of type of Frenal Attachment and morphology of frenum in children, Chennai, Tamil Nadu. World J Dent. 2015;6:203–207.

20. Kumar S, Rahman R. Knowledge, awareness, and practices regarding biomedical waste management among undergraduate dental students. Asian J Pharm Clin Res. 2017;10:341.

21. Sridharan G, Ramani P, Patankar S. Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Cancer Res Ther. 2017;13:556–561.

22. Ramesh A, Varghese SS, Doraiswamry JN, et al. Herbs as an antioxidant arsenal for periodontal diseases. J Intercult Ethnopharmacol. 2016;5:92–96.

23. Thamaraiselvan M, Elavarasu S, Thangakumaran S, et al. Comparative clinical evaluation of coronally advanced flap with or without platelet rich fibrin membrane in the treatment of isolated gingival recession. J Indian Soc Periodontol. 2015;19:66–71.

24. Thangaraj SV, Shyamsundar V, Krishnamurthy A, et al. Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations. Plos One. 2016;11:e0156582.

25. Ponnulakshmi R, Shyamaladevi B, Vijayalakshmi P, et al. In silico and in vivo analysis to identify the anti diabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. Toxicol Mech Methods. 2019;29:276–290.

26. Ramakrishnan M, Shukri M. Fluoride, Fluoridated Toothpaste Efficacy And Its Safety In Children-Review. International Journal of Pharmaceutical Research. 2018;10(04):109-14.

27. McQuay HJ. Pre-emptive analgesia: a systematic review of clinical studies. Ann Med. 1995;27: 249–256.

28. Isiordia-Espinoza MA, Sánchez-Prieto M, Tobías-Azúa F, et al. Pre-emptive analgesic effectiveness of meloxicam versus tramadol after mandibular third molar surgery: a pilot study. J Oral Maxillofac Surg. 2012;70:31–36.

29. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.

30. Ong CK, Lirk P, Seymour RA, et al. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg. 2005;106:757–73.

31. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. Lancet. 1993;342:73–75.

32. Ong KS, Tan JML. Preoperative intravenous tramadol versus ketorolac for preventing postoperative pain after third molar surgery. Int J Oral Maxillofac Surg. 2004;33:274–278.

33. Ong CK, Lirk P, Tan JML, et al. The analgesic efficacy of intravenous versus oral tramadol for preventing postoperative pain after third molar surgery. J Oral Maxillofac Surg. 2005;63:1162–1168.

34. Pozos-Guillen A, Martinez-Rider R, Aguirre-Banuelos P, et al. Pre-emptive analgesic effect of tramadol after mandibular third molar extraction: a pilot study.
35. Farshchi A, Ghiasi G. Comparison the analgesic effects of single dose administration of tramadol or piroxicam on postoperative pain after cesarean delivery. Acta Med Iran. 2010;48: 148–153.

36. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth. 1991;66:703–712.

37. O’Hanlon JJ, Muldoon T, Lowry D, et al. Improved postoperative analgesia with preoperative piroxicam. Canadian Journal of Anaesthesia. 1996;43:102–105.

38. Aoki T, Yamauchi H, Naito H, et al. Premedication with cyclooxygenase-2 inhibitor meloxican reduced postoperative pain in patients after oral surgery. Int J Oral Maxillofac Surg. 2006;35: 613–617.

39. De Menezes SAF, Cury PR. Efficacy of nimesulide versus meloxican in the control of pain, swelling and trismus following extraction of impacted lower third molar. Int J Oral Maxillofac Surg. 2010;39:580–584.

40. Calvo AM, Sakai VT, Giglio FPM, et al. Analgesic and anti-inflammatory dose-response relationship of 7.5 and 15 mg meloxican after lower third molar removal: a double-blind, randomized, crossover study. Int J Oral Maxillofac Surg. 2007;36:26–31.

41. Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. J Am Dent Assoc. 2002;133:861–871.

42. Ong CKS, Seymour RA. Pathogenesis of postoperative oral surgical pain. Anesth Prog. 2003;50:5–17.

43. Vijayashree Priyadharsini J. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. J Periodontol. 2019:90: 1441–1448.

44. Pc J, Marimuthu T, Devadoss P, Kumar SM. Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study. Clinical Implant Dentistry and Related Research. 2018;20(4):531-4.

45. Ramesh A, Varghese S, Jayakumar ND, et al. Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A Case-control study. J Periodontol. 2018; 89:1241–1248.

46. Ramadurai N, Gurunathan D, Samuel AV, et al. Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial. Clin Oral Investig. 2019;23:3543–3550.

47. Sridharan G, Ramani P, Patankar S, et al. Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Oral Pathol Med. 2019;48:299–306.

48. Mathew MG, Samuel SR, Soni AJ, et al. Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: Randomized controlled trial. Clin Oral Investig. 2020;1–6.

49. Samuel SR. Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life? Int J Paediatr Dent. 2021;31:285–286.

50. R H, Hannah R, Ramani P, et al. CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2020;130:306–312.

51. Chandrasekar R, Chandrasekhar S, Sundari KKS, et al. Development and validation of a formula for objective assessment of cervical vertebral bone age. Prog Orthod. 2020;21:38.

52. Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species. Arch Oral Biol. 2018;94:93–98.

53. MP SK. Knowledge, Attitude and practices regarding needlestick injuries among dental students. Asian J Pharm Clin Res. 2016;9(4):312-5.

54. SK M. Knowledge, attitude, and practices regarding infection control among undergraduate dental students. Asian J Pharm Clin Res. 2016;9(1):220-4.

55. Ak H. Knowledge and awareness about oral cancer among undergraduate dental students. Asian Journal of Pharmaceutical and Clinical Research. 2016;165-7.

56. Gayathri MM. Knowledge and awareness among patients about dental implants. Journal of Pharmaceutical Sciences and Research. 2016;8(5):351.

57. Vijayalakshmi B, Kumar MS. Knowledge of students about Local anaesthetics used during oral surgical procedures. Journal of
58. Gayathri MM. Knowledge, Awareness and Attitude among dental students about hepatitis B infection. Journal of Pharmaceutical Sciences and Research. 2016;7(11):1011.

59. Ahamed A, Kumar MS. Knowledge, attitude and perceived confidence in handling medical emergencies among dental students. Journal of Pharmaceutical Sciences and Research. 2016;8(7):645.

60. Kumar S. Knowledge, attitude and practices of dental students toward dental management of patients on antiplatelet therapy. Asian J Pharm Clin Res. 2016;9(30):270-6.

61. MP SK. Local hemostatic agents in the management of bleeding in oral surgery. Asian J Pharm Clin Res. 2016;9(3):35-41.

62. Kumar MP. Newer methods of extraction of teeth. Int J Pharm Bio Sci. 2015;6(3):679-85.

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