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Efficacy of Ketorolac Tromethamine Polymeric Wafer on Postoperative Pain Relief after Periodontal Surgery – An Observational Study

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Abstract

Pain is a common feature of the early postsurgical stage. Studies have been conducted to investigate the effect of NSAIDs to control post-operative pain after periodontal surgery, with favorable results. Ketorolac tromethamine is NSAID that blocks prostaglandin synthesis by preventing the conversion of arachidonic acid to the endoperoxides. The aim of the study is to develop and assess the efficacy of ketorolac tromethamine polymeric wafers for pain control in soft tissues following periodontal surgeries.Ketorolac tromethamine polymeric wafers were developed and studied for its efficacy. 20 patients were included in the study and the formulated ketorolac wafer was placed in the patients who are undergoing periodontal surgery (test group)patients and in the following week the same group of patients were advised to take ketorolac tromethamine dispersible tablets orally in the control group after periodontal surgery on the other quadrant(

Control group). Pain was evaluated using visual analogue scale from the 3rd hour following periodontal surgery. Significant difference was observed in overall pain scale where the mean values in visual analogue scale for intensity of pain using ketorolac wafers was 1.75 and mean values for ketorolac dispersible tablets was 3.35 when compared using Mann Whitney U test ($p< 0.001$). In addition, statistically significant difference was observed in mean score for duration of pain by ketorolac wafer which was 3.05 and 6.4 for ketorolac dispersible tablets. Significant statistical difference was found in ketorolac wafer group with $p< 0.001$.Thus to conclude, ketorolac polymeric wafer proved to be an effective delivery system for reducing pain and discomfort following periodontal surgery.

Keywords: Ketorolac Tromethamine; Post-operative pain; Periodontal surgeries; Sodium alginate.

Introduction

Periodontitis is an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both. Pain after periodontal surgical procedures is a common occurrence. Many factors may influence intensity of pain, such as the nature, duration, extent of the surgery, and psychological aspects, such as stress and anxiety[1]. Postoperative pain has been reported to peak in the first 24 hours after periodontal surgery. The intensity of this pain is related to the surgical procedure itself[2].Studies have been conducted to investigate the effect of various non steroidal anti-inflammatory drugs (NSAIDs)which are administered to control post-operative pain after periodontal surgery, with favorable results. Ketorolac tromethamine (KT) is an NSAID with an analgesic potency comparable to morphine, but without the opiate-receptor-associated side effects[3] .The beneficial effects of ketorolac are due to the drug's ability to block prostaglandin synthesis by preventing the conversion of arachidonic acid to the endoperoxides.

Oral drug administration is the preferred and most common route for drug delivery. But it also suffers from disadvantages such as first pass effect, gastrointestinal enzymatic degradation and delay between the time of administration and absorption, which is detrimental in the case of drugs with rapid onset requirements. These difficulties have provided the impetus for exploring alternative routes for the delivery of drugs. Transmucosal routes of drug delivery which is comprised of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer excellent opportunities and potential advantages over per oral administration for systemic drug delivery. In fast dissolving drug delivery systems, oral flash release wafer drug delivery system is an alternative to tablets, capsules, and syrups for the patients who face difficulty in swallowing oral solid dosage forms. Thin wafer drug delivery systems are the solid dosage forms when they are kept in the mouth they dissolve in a short period of time without drinking water or chewing. These are also referred as fast dissolving oral wafers, buccal films and oral strips[4]. Wafers are prepared by freeze-drying of polymeric solutions to yield solid porous structures that can be easily be applied to wound surfaces[5] and have proven potential for mucosal wound healing[6]. Wafers offer multiple advantages over other wound delivery systems including tensile strength, hydration, bioadhesivity, rheological properties, resistance to compressive forces and controlled drug release characteristics, all combined critically influence the performance of formulations applied to moist surfaces[7]. Due to their porous nature and higher surface area, they have a higher drug loading capacity compared to films[8]. The purpose of the present study is to

develop and assess the efficacy of ketorolac tromethamine polymeric wafers for the co-delivery of ketorolac tromethamine to soft tissues for pain control following periodontal surgeries.

Materials and Methods

Materials : Sodium alginate, Methyl cellulose and Ketorolac tromethamine was procured from Yarrow Chem Products Pvt Limited, Mumbai. Lyophillizer (Martin Christ, Germany), Magnetic stirrer (Remi Lab, Bangalore) and UV-visible spectrophotometer (Shimadzu 1700, Japan) were used for the study. All other chemicals and reagents used were of AR grade.

Preparation & characterization of wafers

Ketorolac tromethamine wafers were prepared using sodium alginate and methyl cellulose as polymers. In brief varying concentrations of sodium alginate was dissolved in distilled water to produce a stock solution of concentration 2.5%w/w. Increased amounts of methyl cellulose was dispersed in weighed amount of this stock solution. The solution was stirred using a mechanical stirrer with hot plate at 300 rpm with a temperature of 70^0C for 30 minutes. After cooling to room temperature, ketorolac tromethamine was incorporated in to this solution with mechanical stirring. The resulting solution was poured into petri plate(internal diameter 8.5 cm) and frozen in a deep freezer at -30^0C. The frozen samples were lyophilized in a freeze dryer for 6 hours. The wafers obtained were removed from the petriplate, sealed in aluminium foil and stored in a desiccator until further evaluation studies. A total of 3 formulations were prepared.

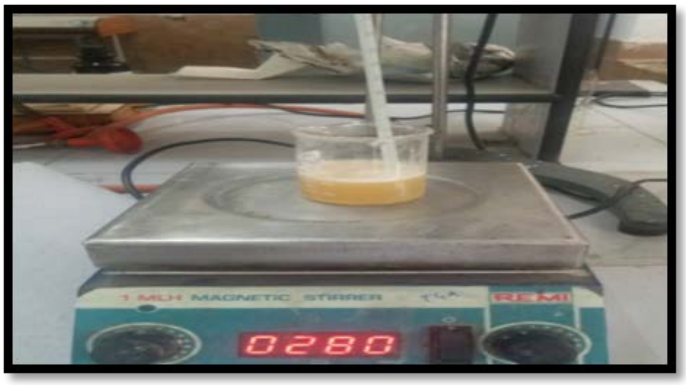

Fig 1: Mixture of methyl cellulose, sodium alginate and ketorolac drug

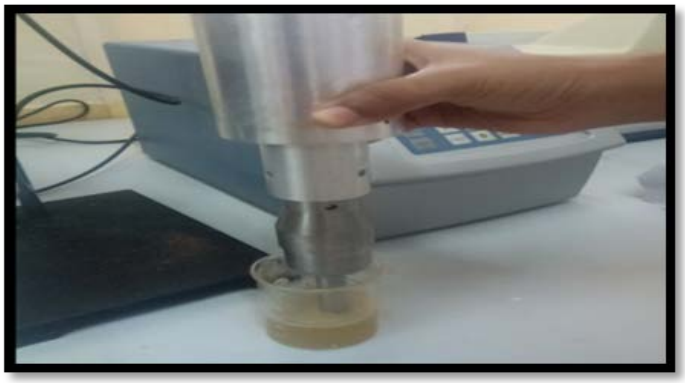

Fig 2: Sonification

Drug content test: 1cm² area of wafer was cut accurately and triturated with a small quantity of distilled water in a glass mortar and pestle and transferred to a 100 ml volumetric flask. The volume was made up with distilled water and the absorbance was measured after development of colour with ninhydrin reagent at 568nm.

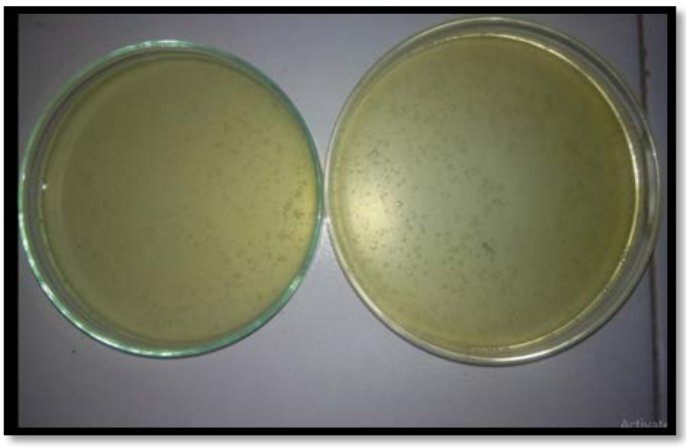

Fig 3: Ketorolac tromethamine before lyophillization.

Fig 4: Ketorolac tromethamine wafer after lyophillization

In-vitro drug release test: Drug release studies of ketorolac tromethamine liberated from dried films were investigated using Keshary-Chien diffusion cell. A clean, dried receptor cell was filled with phosphate buffer solution (PBS) pH 7.4 and was allowed to equilibrate at 37^0C. Cellulose acetate membrane was mounted between receptor and donor compartment and maintained at 37^0C with circulating water jackets throughout the entire experiment. Using a glass syringe, volume of 1 ml sample were withdrawn from the receptor compartment at regular time intervals for 8 hours and receptor volume was replaced with equal volume of fresh PBS solution. Absorbance of the resulting solutions was measured using UV-visible spectrophotometer at 468nm after development of colour with 1% ninhydrin solution. The amount of ketorolac released in mg is plotted against time.

Clinical Study

Split mouth design was chosen for the present study because it minimizes the inter-subject factors such as age, sex, anatomic factors and bone metabolism and any differences that may be present (Lobo & Pol, 2015).Formulation that was having better drug content and drug release was chosen for further studies in patients. A total of 20 patients who reported to the Department of Periodontology, Faculty of Dental Sciences, MSRUAS, Bangalore were included in the study**.**Patients with age ranging between 20–60 years diagnosed with chronic generalized periodontitis or localized periodontitis and systemically healthy patients requiring periodontal surgeries were included in the study; Patients with history of antibiotic therapy, corticosteroid therapy and hormonal drugs in the past two months and patients with the history of diabetes mellitus, aggressive periodontitis and with the history of smoking were excluded from the study.The formulated ketorolac wafer was placed on the study site in the test group (Group A) and in the following week ketorolac tromethamine dispersible tablets were prescribed to the control group (Group B) orally after periodontal surgery. Pain was evaluated using visual analogue scale from the 3rd hour for every 1 hour following periodontal surgery.

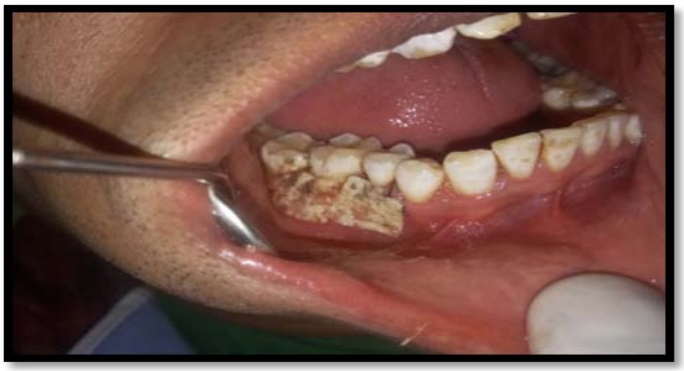

Fig 5 : Placement of ketorolac wafer after periodontal flap surgery

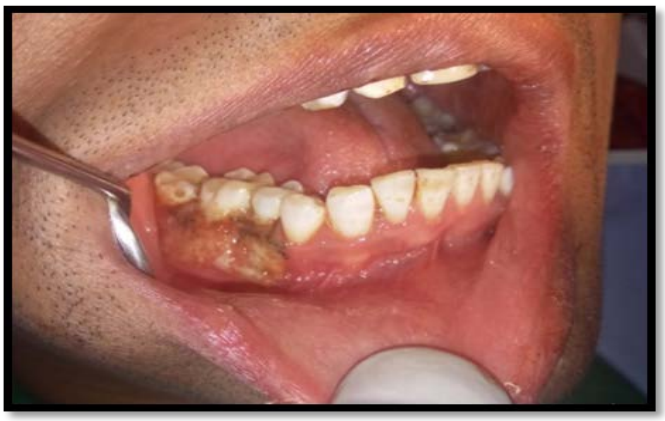

Fig 6 : After 3 minutes

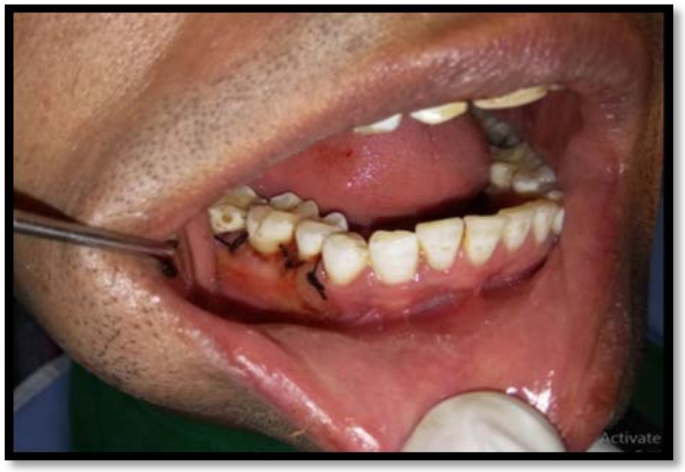

Fig 7: After 8 Minutes

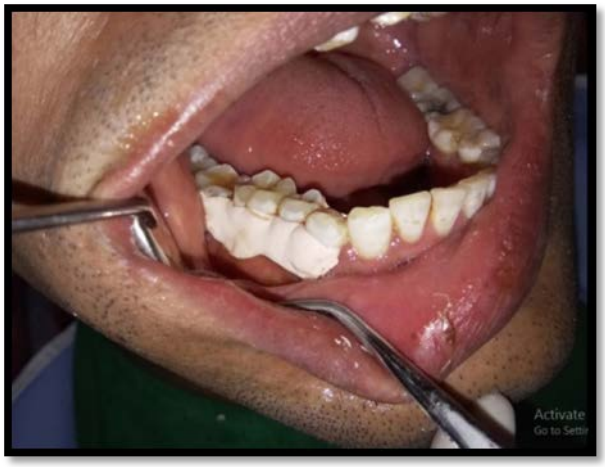

Fig 8 : Periodontal pack placed over the wafer

Statistical Analysis

The statistical analysis was done using SPSS v.20 software, and sample size was determined by G – power software. Mean values of visual analogue scale for ketorolac wafers and ketorolac dispersible tablets were compared using Mann Whitney U test ($p< 0.001$).The level of significance was set at $p<0.001$.

Results

Drug Content Test: In the current study 1cm² area of wafer was cut accurately and triturated with a small quantity of distilled water and volume was made up to 100 ml and absorbance was measured after development of colour with ninhydrin reagent at 568nm. The results are tabulated in table 1.

Table 1

Formulation	Drug content (%)
F1	89.5
F2	92.5
F3	93.4

In-vitro drug release test: In this study drug release of ketorolac tromethamine from the developed wafers was studied using Keshary-Chien diffusion cell. At suitable time intervals samples were withdrawn from the receptor compartment for 8 hours and absorbance was measured using UV-visible spectrophotometer at 468nm after development of colour with 1 percent ninhydrin solution. The amount of ketorolac permeated in mg is plotted against time in Fig 9. At the end of 7th hour the cumulative drug released was 90%.

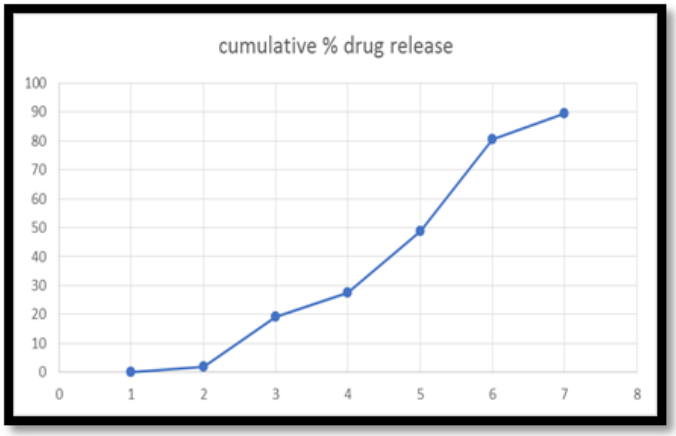

Fig 9

Visual Analogue Scale Rating and Duration of Pain

Participants of both the groups reported highest mean Visual Analouge Scale (VAS) scores of intensity of pain, 4.64 and 4.89for Groups A and B, respectively at 3rd hour after periodontal surgeries**.** Mean VAS scores declined significantly for both groups ($p<0.001$). On comparison of VAS scores for both groups from 3rd hour after periodontal surgery for every 1 hour, a statistically significant difference was observed in group B ($p< 0.001$).On comparison using Mann Whitney U test a statistically significant difference in overall pain scale was

found where the mean values of VAS for intensity of pain for ketorolac wafers was 1.75 and for ketorolac dispersable tablets was 3.35 (P< 0.001). In addition, a statistically significant difference was found in mean scores ketorolac tablets was 3.05 for duration of pain and the mean values for ketorolac wafer was 6.4which was highly statistically significant (P< 0.001).

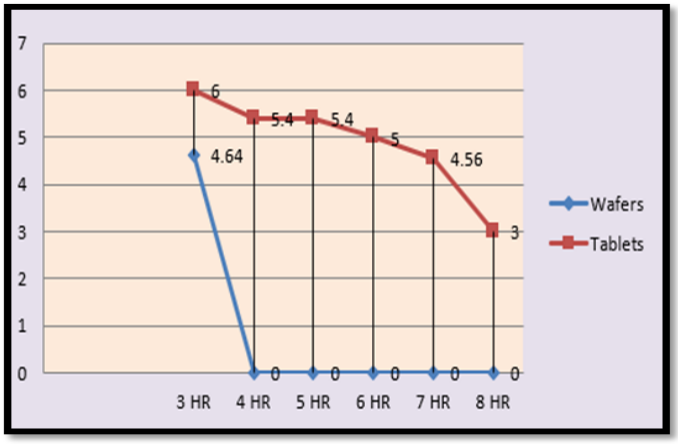

Fig 10

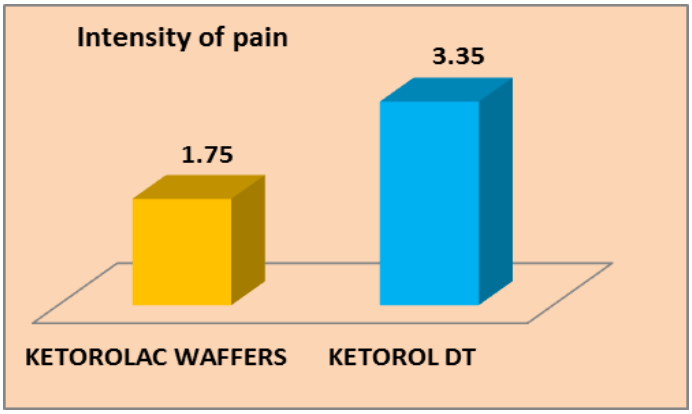

Fig 11

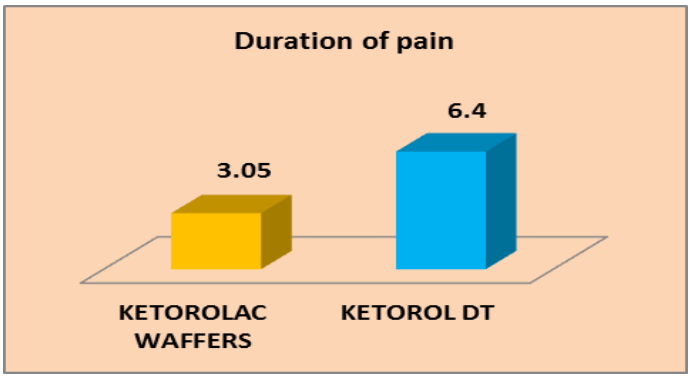

Fig 12

Discussion

In this study Sodium alginate (ALG), Polyvinyl Pyrrolidone K-25 (PVP K-25) and methyl cellulose were selected for wafer preparation for their expected inherent ability to form coherent and stable freeze-dried wafers which is in accordance with the study done by Matthews et al, 2005.[10] In the present study, significant difference in overall pain scale was found using visual Analogue scale. Ketorolac wafers and ketorolac dispersable tablets had duration (1.75) and intensity of pain (3.05), which was in accordance with the study done by Elesky et al[9] 2018 where they conducted a study on 20 patients age between 17 to 30 years, who needed gingivectomy procedures in 2 quadrants of maxillary arch. Patients received scalpel gingivectomies in the right quadrant of the arch needing treatment followed by Coepack application (group A), while on the left quadrant they received the same procedure but the wound was covered by the selected ketorolac/ lidocaine wafers (group B) and found that Mean VAS scores declined significantly for both groups (p<.05) on day 6 . However, comparing VAS values of both groups on day 6, a highly statistical significant difference in favor of group B was observed (0.7±0.47 vs. 0, for groups A and B, respectively, p<.05).

In our study more significant reduction in the mean values was seen in ketorolac wafers compared to ketorolac dispersible tablets following periodontal surgeries, this is in accordance with the study done by Shital et al 2011 & Shah et al 2014 where they conducted a study using ketorolac tromethamine dispersible tablets just before periodontal flap surgery which was efficient in providing optimal response by the patient during operative period and found that 10 mg ketorolac tablets administered before the periodontal surgery was effective.[7] Hutton et al 2016 conducted a study using ketorolac tromethamine tablets before periodontal flap

surgery. Results showed that it was effective in controlling intensity of pain. Following extensive periodontal surgeries like quadrant periodontal flap surgeries, mucogingival surgeries, ketorolac wafers and ketorolac dispersible tablets were used in our study.

Conclusion

Wafers offer multiple advantages over other wound delivery systems including tensile strength, hydration, bioadhesivity, resistance to compressive forces and controlled drug release characteristics, all combined critically influence the performance of formulations applied on moist surface. The ketorolac polymeric wafer proved to be an effective method of reducing pain and discomfort following periodontal surgery.

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