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# Chlorhexidine Versus Drug-Loaded Thermosetting Hydrogel in the Prevention of Alveolar Osteitis: A Multi-Center Clinical Study


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***Abstract:*** ***Background***: Alveolar osteitis (AO) affects 0.5-5% of routine extractions and up to 30% of mandibular third molar extractions. Current prevention strategies include chlorhexidine irrigation, but novel thermosetting hydrogels loaded with lidocaine and metronidazole offer a dual-action approach combining anesthesia with antimicrobial prophylaxis.***Objective***: To compare the efficacy of chlorhexidine irrigation versus dual-action thermosetting hydrogel (0.5% lidocaine HCl and 0.1% metronidazole) in preventing alveolar osteitis, and to evaluate pain relief, patient satisfaction, and safety in a Pakistani population across multiple tertiary care centers.***Methods:*** This prospective, multi-center, randomized controlled trial was conducted at four institutions in Punjab and Karachi, Pakistan between 23 January 2025 - 25 October 2025. A total of 672 patients aged 18-65 years undergoing tooth extraction were randomly allocated to receive either 0.12% chlorhexidine irrigation (control group, n=336) or thermosetting hydrogel application (intervention group, n=336). Primary outcome was AO incidence at 7 days post-extraction. Secondary outcomes included pain scores (Visual Analog Scale), analgesic consumption, patient satisfaction, and adverse events.***Results:*** The incidence of AO was 5% (16/318) in the chlorhexidine group versus 1.6% (5/321) in the hydrogel group (p=0.008, RR=0.31, NNT=29). Mean pain scores at 24 hours were significantly lower in the hydrogel group (2.3 ± 1.4 vs 4.9 ± 2.1, p<0.001). Patient satisfaction was significantly higher in the hydrogel group (4.6 ± 0.6 vs 3.8 ± 0.9, p<0.001). No serious adverse events were reported in either group.***Conclusion***: Thermosetting hydrogel loaded with lidocaine and metronidazole demonstrated superior efficacy compared to chlorhexidine irrigation in preventing AO, with additional benefits of improved pain control and higher patient satisfaction. This dual-action approach represents a promising advancement in post-extraction socket management, particularly relevant for resource-constrained settings in Pakistan and similar healthcare systems.



***Keywords:*** Alveolar osteitis; dry socket; chlorhexidine; thermosetting hydrogel; lidocaine; metronidazole; tooth extraction; Pakistan.

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## INTRODUCTION

### Background and Epidemiology

Alveolar Osteitis (AO) commonly known as 'dry socket' is one of the most frequent post extraction complications, especially for the extraction of the third molar of the lower jaw. This pain after surgery is caused by inadequate formation of the protective blood clot in the tooth socket or early loss of it prior to the time it is intended to remain there, leaving the underlying bone open to the oral environment [4, 5]. This exposed alveolar bone is extremely sensitive and commonly complains of a very severe, throbbing pain that starts 2-4 days after the extraction and radiates from the dental area to the ear, temple or neck on the side of the extraction [6].

The rates of AO worldwide depend on the type of extraction used [7, 8]. The prevalence of molar impaction in the mandible is 25-30% using the surgical removal of the impacted tooth as a model, while routine extraction of single rooted teeth ranges from 0.5-5% [9, 10]. In the Pakistani scenario, very little literature is available and the AO rates are reported to be higher than these ranges as there is delayed presentation to dental services, inadequate prophylactic measures and a high prevalence of tobacco use among certain population segments [11, 12].

AO is also a significant economic problem, especially in low-income communities [13, 14]. Research has shown that 45% of those patients who develop AO will need multiple unscheduled postop visits which contributes greatly to cost of healthcare and loss of productivity [15]. According to Akinbami and Godspower, the management of AO in the tertiary hospitals in Nigeria wasted significant time in the clinics and resources were estimated at necessitating an average of 3.2 extra visits by patients [29]. The introduction of the management system of AO in the public health sector where the dental services are already limited makes it difficult for the delivery of dental services and consequently less satisfactory for patients.

### Etiology and Pathophysiology

Although the exact pathogenesis of AO remains unclear, present evidence suggests a complex interaction between mechanical trauma, bacterial contamination and increased fibrinolytic activity [3, 16]. Birn suggested that trauma caused by the extraction of the tooth produced tissue activators which activated plasminogen to plasmin, the potent fibrinolytic enzyme which would dissolve the blood clot [3]. While this fibrinolytic theory does not account for all cases, it is the most accepted mechanistic theory [17].

There are several risk factors that have been consistently reported to be associated with higher incidence of AO. Perhaps the most important modifiable is surgical trauma – the harder the extraction, the longer the surgery, the more extensive the bone removal, the higher the AO rate is [18, 19]. MacGregor and Hart showed that there is a mixed bacterial flora in normal extraction sockets, while the microbial composition in AO-affected sockets is different, with an increase in the anaerobic activity [7]. In recent years, some anaerobic microorganisms, such as Treponema denticola, Prevotella intermedia and Fusobacterium nucleatum, have been found to be specifically abundant in dry sockets [20, 21].

The factors of patients are significant in AO risk. Multiple mechanisms have been identified that contribute to the 2-3 times higher incidence of AO associated with tobacco use, especially smoking: vasoconstriction, decreasing oxygen tension of tissues, and direct inhibition of fibroblast attachment [11, 22]. Sweet and Butler's classical study set the stage for the dose-response relationship between cigarette smoking and dry socket, showing that smoking within 24 h after extraction increased the risk of AO almost 4 times [11]. The use of oral contraceptives has been linked to higher AO risk, which is likely related to the different phases of the hormonal cycle which lead to higher fibrinolytic activity [12]. Garcia et al. found that women who were taking oral contraceptives were 1.8 times more likely to get AO after a third molar extraction [12]. Other factors related to poor oral hygiene, pre-existing infections, and systemic diseased conditions that interfere with healing, such as diabetes or immunosuppressive conditions play a role in the development of AO [13, 23]. In Pakistan, high prevalence of smoking among males, chewing of betel nuts and inadequate access to oral hygiene education contribute to these risk factors [24, 25].

### Current Prevention and Management Strategies

Three main strategies have been adopted for AO prevention: surgical technique optimisation, antimicrobial prophylaxis, and socket protection. [26, 27]. The fundamental principle of prevention is the atraumatic extraction technique which involves handling the tissues gently, with minimal removal of bone and shorter surgical duration [14]. Larsen found that extractions involving more bone removal showed 4.2 times the frequency of AO (incidence) than simple forceps extractions. Technical issues, however, do not rule out the possibility of AO, especially in the case of complex extractions that involve tissue trauma [28].

Chlorhexidine gluconate is now the most widely studied

antimicrobial agent for use in AO prevention [2, 16]. Hermesch et al. showed that the incidence of AO was 42% lower following mandibular third molar extraction when 0.12% chlorhexidine was used during the operation (relative risk reduction of 42%) [2]. These results were verified by a subsequent meta-analysis by Caso et al. which found a pooled OR of 0.53 (95% CI: 0.37-0.74) in favor of chlorhexidine over placebo [16]. The mechanism is presumably both antimicrobial activity and chlorhexidine's substantivity (which lasts for several hours after it has been applied orally) [29]. The addition of chlorhexidine gel to the socket was also found to be more effective than chlorhexidine rinse in preventing AO by Haraji and Rakhshan [18]. In spite of this evidence, use of chlorhexidine is not widespread in Pakistan dentistry, partially due to the cost of chlorhexidine and lack of knowledge of evidence-based protocol.

The use of systemic and topical antibiotics for AO prevention has been studied, and there is special interest in metronidazole use. [6, 30] Rood and Murgatroyd [6] showed that the prophylactic use of metronidazole had a very impressive preventative effect in high-risk extractions, reducing the incidence by 76-80%. It is hypothesized that the activity of metronidazole is due to its excellent anaerobic activity and that it has a specific activation mechanism in the anaerobic environment, which results in a high level of activity in hypoxic tissue and low systemic activity [31]. There is, however, a degree of reluctance to continuing with routine systemic antibiotic use for AO prevention due to worries about antibiotic resistance and the concept of antimicrobial stewardship [32, 33]. Treatment for an established AO currently involves socket debridement, pain control using obtundent dressings (eugenol-based materials) and protection from debris; however, there are limitations and problems with these treatments such as multiple dressing changes and only symptomatic relief [19, 23, 24].

**Thermosetting Hydrogels: An Emerging Technology**

Thermosetting hydrogels are a novel drug delivery system which overcomes most of the drawbacks of traditional socket dressings [1,34]. At room temperature, these formulations are low-viscosity liquids and they undergo a sol-gel transition when they are heated to body temperature, thereby forming semi-solid gels with a well-defined geometry of the socket and adhering to the tissue surface in an exact manner [8,35]. One of the most studied thermosetting polymers is Pluronic F-127 (poloxamer 407) which is a triblock copolymer of polyoxypropylene (POP) with polyoxyethylene (POE) blocks which shows this temperature dependent phase transition due to micelle formation and packing [8].

Aduan et al. reported groundbreaking work related to the dual-action thermosetting hydrogels for AO treatment that was compounded with lidocaine and metronidazole [1]. The formulation consisting of 23.38% Pluronic F-127 and 0.13% Carbopol 934P exhibited the most desirable gelation properties; sol-gel transition started at 23°C and the resultant gel was completely formed at 37°C (physiological temperature) within 60 seconds [1]. Carbopol was a high molecular weight crosslinked polyacrylic acid polymer that was responsible for the mucoadhesive properties due to the hydrogen bonding network between carboxylic acid groups and mucosal glycoproteins, thus showing an excellent retention in the moist socket environment [36]. Escobar-Chávez et al. extensively studied thermoreversible pluronic gels and identified their benefits of being biocompatible, easy to sterilize and have a controlled drug release [8].

The drug release mechanism from the hydrogels is through diffusion, surface erosion and matrix dissolution [1, 37]. Bender's group showed that the release of lidocaine and metronidazole was of a therapeutic level for a 24-48 hour period. Lidocaine is more hydrophilic and has smaller molecular weight, and showed fast release as it attained about 60% of the loaded dose at 24 hours, affording sustained local anesthesia in the critical early post-operative period [1]. It was found that metronidazole release is slower (around 20% at 24 hrs), resulting in higher concentration of metronidazole than the minimum inhibitory concentration (MIC) for anaerobes during the critical period of 72 hrs after extraction, when AO most often occurs [1,38].

The cytotoxicity of the formulations was evaluated on primary human gingival fibroblasts, and the cell viability was higher than 90% when using formulations containing up to 0.5% lidocaine and 0.1% metronidazole, which is comparable with the negative control [1]. But this in vitro result should be taken with a grain of salt: in vivo, there are only surface cells that interact with the hydrogel, and the deeper tissues will be supplied with drugs by the diffusion of lower concentrations. There is safety data from animals, but few long-term human data [39, 40].

**Rationale and Research Gap**

Although thermosetting hydrogels loaded with drugs have shown to have promising in vitro and ex vivo features, there is no clinical study to date assessing the efficiency of these drug-loaded thermosetting hydrogels for preventing AO in actual patients. This is an important research question because lab tests do not always correlate with clinical results [41]. There were a number of key questions left unanswered: What is the most effective AO prevention effect of the dual-action approach versus that of the current standard approach? How safe is this in the real world in different patient groups? What are the benefits on the population level, where risk factors are already very high? [42]

The Pakistani healthcare setting offers its own set of opportunities and challenges for assessing this technology. Developing clinical trials that are adequately powered to detect clinical differences is possible with high AO incidence rates without the need for large

sample sizes [43]. Multi-center public healthcare system provides for a wide spectrum of patient recruitment from diverse population reflecting Pakistan's demographic and socioeconomic diversity, which would increase the external validity [44]. Outcomes may differ by the low level of resources in these centers, differing oral surgical skill across centers, and by patient factors such as low health literacy, smoking prevalence and betel nut chewing in low-income countries, where most oral surgical research is conducted, [45].

The objective of this study is to fill these knowledge gaps by performing first time multi-center randomized control trial comparing the prevention of AO with irrigation using chlorhexidine (CHX) and dual action thermosetting hydrogel in Pakistani population. This research provides high quality clinical evidence in a resource limited context which may guide practice in Pakistan and other healthcare systems around the globe similar to Pakistan's in South Asia.

## MATERIALS AND METHODS

### Study Design and Setting

This was a prospective, multi-center, parallel group randomized controlled trial with a 1:1 allocation ratio in four tertiary care institutions and hospitals of Lahore, University of Lahore, Islamic International Dental Hospital Islamabad and Altamash Institute of Dental Medicine and Dow International Dental College, Karachi respectively, from 23 January 2025 till 25 October 2025. Study procedures were designed in accordance with CONSORT 2010 guidelines and approved by institutional review boards from all institutions before enrollment of the first participant.

The four institutions involved are public tertiary care teaching hospitals which cater to a wide variety of patients. All centers with a standardized clinical protocol, have specific oral surgery units and account for about 25% of enrolments. A two-day training workshop was held for site investigators on study procedures, intervention techniques and outcome assessment in January 2025.

### Participants

#### Inclusion Criteria

Patients were eligible to participate in the study if they were: (1) between 18-65 years of age (inclusive); (2) scheduled for either a single or multiple tooth extraction(s) for any indication (cariosis, periodontal disease, orthodontic, impaction etc); (3) able to understand study procedures and provided written informed consent in either Urdu or English; (4) willing to follow study follow-up schedule; (5) living within 50 km radius of the study site so that follow-up visits could be made.

#### Exclusion Criteria

Patients were excluded if they had: (1) any known allergy or hypersensitivity to study medications (chlorhexidine, lidocaine, metronidazole, or excipients in any study medication); (2) known diagnosis of active infection with indication for systemic antibiotic use at time of enrollment; (3) history of immunocompromised state (HIV/AIDS, active malignancy, chronic course of oral corticosteroid therapy >10mg prednisone daily); (4) uncontrolled diabetes mellitus (HbA1c >8.5% within 3 months prior to enrollment); (5) pregnancy or breast-feeding (confirmed with urine β-hCG for women of childbearing age); (6) current or prior (0–12 months) bisphononate therapy; (7) history of bleeding disorders and/or therapeutic anticoagulation (warfarin, direct oral anticoagulants) (except for aspirin ≤100 mg daily).

### Randomization and Allocation Concealment

To achieve randomisation, computer-generated block randomisation with variable block sizes and stratified by site and extraction difficulty (simple vs surgical) was used.computer-generated block randomisation with variable block size and stratified by extraction difficulty (simple vs surgical) and by site. The R software (version 4.3.1) with the 'blockrand' package was used by an independent statistician not related to patient care to create the randomization sequence.

Allocation concealment was achieved by using sequentially numbered, opaque, and sealed envelopes that were locked in cabinets at each site. Only after informed consent was acquired had envelopes been opened; they were opened immediately before extraction by the treating clinician. Because of observer detection of differences in the interventions, blinding of both the participants and the treating clinicians was not feasible. However, outcome assessors who followed up the evaluations and data analysts were blinded with respect to allocation during the whole study period.

### Interventions

#### Control Group: Chlorhexidine Irrigation

Upon completion of the tooth extraction and hemostatic control, the extraction site was well irrigated with 10 mL of 0.12% chlorhexidine gluconate solution, using a disposable 10mL syringe fitted with a blunt irrigation tip. Irrigation was done gently, and along the sides of the sockets: 30 seconds (total time) Excess solution was suctioned and 2 minutes was provided for socket to stabilize.

A 200 mL bottle of chlorhexidine mouthwash 0.12% was given to the participants and they were asked to rinse twice a day (morning and evening) for seven consecutive days using 15 mL (one tablespoon) of the mouthwash solution. The instructions were written and illustrated in Urdu with special stress on the importance of rinsing for 30 seconds and not eating or drinking for 30 minutes after rinsing. The amount of compliance was determined at follow up after asking participants to return the bottle and estimating volume.

**Intervention Group: Thermosetting Hydrogel**

The thermosetting hydrogel formulation comprised of Pluronic F-127 23.38% w/w, Carbopol 934P 0.13% w/w, lidocaine hydrochloride 0.5% w/w, and metronidazole 0.1% w/w and purified water. The product formulation was made in the CMH Lahore Medical College Pharmacy Department & followed the guidelines of Good Manufacturing Practice. Quality control testing was effected which confirmed pH: 6.8-7.2, viscosity at 25°C: 150-180 cP, drug content: within 95-105% of nominal levels and gelation temperature: 32-34°C.

Hydrogel was canned into light-protected containers, maintained for 2-8°C and had a known shelf life of 7 days. The viscosity of the hydrogel syringe was reduced for easier injection with the syringe allowed to reach room temperature before application (approx. 5 minutes). After the extraction of teeth and the achievement of hemostasis, hemi-hydroxyapatite was gently inserted into the tooth socket using a sterile 5 mL syringe with blunt tip from the apex toward the coronal opening of the socket to make sure that no hole remains in the socket after insertion.

The socket was observed for 2 minutes to verify gelation (no longer could flow a gel, there was increased opacity inside the socket). A sterile gauze pad was then set over the socket and participants were asked to apply gentle pressure for 10 minutes. Study subjects were told not to eat hot foods or to vigorously rinse their mouths for 24 hours, so the gel could set. No supplements or other treatments were given.

**Standardized Extraction Protocol**

All the extractions were conducted by an experienced oral surgeon and senior dental resident under guidance with a standardized technique to limit procedural variation. Local anesthesia was attained through the use of 2% lidocaine and epinephrine 1:80,000 (up to 7 cartridges). Extracts were categorized as easy or difficult by the Pederson index (for teeth 3rd molars) or a simplified classification:Score: 1 = simple extraction (Forceps without any bone removal); Score: 2 = Forceps extraction with only a little mucoperiosteal reflection; Score: 3 = surgical extraction (flap and bone removal <25% of crown); Score: 4 = complex surgical extraction (flap and bone removal >25% of crown).

Direct pressure with gauze was used for at least 5 minutes to achieve hemostasis. Simple extraction (Score 1-2) was not routinely done with primary wound closure (PWC) while surgical extraction (Score 3-4) held the surgeon to his/her discretion. The same post-operative instructions were given to all the participants: avoid smoking and the use of cigarettes for 72 hours, avoid spitting large quantities and rinsing excessively for 24 hours, take the prescribed analgesics as and when needed, soft diet for 48 hours.

**Outcome Measures**

**Primary Outcome**

The main outcome was the presence of alveolar osteitis at 7 days after tooth extraction, assessed by applying modified Blum's criteria [10]. Patients diagnosed and seen for AO were those who experienced all four of the following: (1) moderate-severe pain at the alveolar extraction site (VAS ≥4) which persisted beyond 48 hours post extraction; (2) partial or total disintegration of the blood clot in the alveolar extraction site; (3) clinical visibility of the alveolar bone; (4) pain extending beyond the site of extraction to the ear, temple, or neck. A blinded outcome assessor (senior oral surgeon involved in neither the procedure nor the patient examination) confirmed diagnosis during a face-to-face exam at day 7 or sooner if the participant had symptoms.

**Secondary Outcomes**

Pain Intensity: Visual Analog Scale (VAS) questions is a 100mm anchored by 'no pain' (0) and 'worst pain imaginable' (100), which were re-scored to 0-10 for analysis. Evaluation was performed at 6 hrs, 12 hrs, 48 hrs, 72 hrs and 7 days after extraction. At each timepoint (home visit) participants filled out a paper-based VAS, which was returned at day-7.

**Use of Analgesics**

A standardized prescription of Ibuprofen 400mg tablets (max 6/24h) and paracetamol 500mg tablets (max 8/24h) was given to participants for rescue. They kept a chart of medicines, noting dates, times and medicines administered. For each participant, the amount of tablets used across 7 days was determined.

Patient Satisfaction: Measured on a change of the validated 5-point Likert scale (1 = very dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, 5 = very satisfied) at day 7. Attendees responded to their experience of the overall treatment for pain and healing.

**Adverse Events**

Adverse events were reported for the entire 7 day follow-up period. Pinpointed events were put into one of three categories: mild (no intervention), moderate (intervention, but not hospitalization), or severe (hospitalization or permanent disability or death). The adverse events that were sought and reported were: taste changed, mucosal irritation, allergic reaction, continued bleeding, and secondary infection.

**Sample Size Calculation**

The sample size was determined according to the primary outcome (incidence of AO) from two-sided chi-square test with $\alpha$=0.05 and power=80%. Previous literature estimated 5% incidence of AO in the chlorhexidine group [2, 16] and this is what we predicted. We assumed there would be a clinically relevant 70% relative risk reduction, which equated to an absolute risk reduction of 1.5%. The minimum number of participants required for each group (total = 584) was calculated using these parameters. With 15% of the loss to follow-

up or protocol violations, a sample size of 336 per group (672 total participants) was targeted.

**Statistical Analysis**

The analysis was conducted based on the pre-specified statistical analysis plan, using SPSS version 28.0 (IBM Corp, Armonk, NY, USA). The primary analysis was carried out based upon the intention to treat (ITT) principle, which included all patients randomized as per the treatment condition regardless of treatment administered. As sensitivity analysis a per protocol analysis was performed with only those subjects presenting without significant protocol deviations.

Descriptive statistics (in terms of mean ± SD when normally distributed or median (IQR) when skewed for continuous variables and frequencies with percentages for categorical variables) are used for summarising baseline characteristics. Independent t-tests were used to compare groups for continuous variables and chi-square tests for categorical variables.

Chi-square test was used to compare the incidence of AO between the groups for the primary outcome. Treatment effect was reported as risk ratio (RR) with associated 95% confidence interval (CI) based on the Koopman asymptotic score method. The absolute risk reduction (ARR) was calculated as the inverse of the number needed to treat (NNT) with 95% confidence interval (CI). The p-values < 0.05 (two-sided) were considered significant.

For secondary outcomes: Pain scores were compared using independent t-tests at each time point, and other scores were compared using Mann-Whitney U test; adverse event rates were compared using chi-square or Fisher's exact test (if expected cell frequency <5).

Subgroup analyses were pre-specified: extraction difficulty (simple vs surgical), smoking status (current vs non-smoking) and gender. Interaction terms were tested using logistic regression. The primary outcome was analysed by complete case analysis, whereas the secondary outcomes were analysed by multiple imputation by chained equations with 10 imputations was performed for missing data.

**Ethical Considerations**

The study was carried out in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants signed an informed consent after listening to and reading detailed information which was provided to them in their preferred language (Urdu or English). Participants were briefed on their right to drop out without impacting their usual care. An independent Data Safety Monitoring Board was used to monitor the study for safety data, reviewing the data after 100, 300 and 500 patients were enrolled, and had the authority to recommend ending the study if safety concerns arose.

## RESULTS

**Participant Flow**

Of all the 745 patients who were evaluated for eligibility in the four participating centers, 711 were eligible for this study. Of these, 73 did not participate; 41 were outside age range (18) or had uncontrolled diabetes (12), received bisphosphonates (6), had an active infection (needing antibiotics) (3) or were pregnant (2). A total of 672 patients were successfully randomized with a half going to the chlorhexidine group and a half to the hydrogel group.

There was 18 participants (5.4%) lost to follow-up in chlorhexidine and 15 participants (4.5%) lost to follow-up in hydrogel. Reasons for loss to follow-up were: moved out of area (n=14), withdrew consent (n=8), multiple attempts to contact patient (n=11). Thirty-one-eight men and women finished the chlorhexidine arm of the final analysis, and 321 men and women completed the hydrogel arm (follow-up rate of 95.1%).

| **Characteristic** | **Chlorhexidine (n=318)** | **Hydrogel (n=321)** |
|---|---|---|
| Age (years), mean ± SD | 34.2 ± 12.8 | 33.8 ± 13.2 |
| **Gender, n (%)** | | |
| Male | 187 (58.8%) | 192 (59.8%) |
| Female | 131 (41.2%) | 129 (40.2%) |
| **Smoking status, n (%)** | | |
| Current smoker | 98 (30.8%) | 95 (29.6%) |
| Non-smoker | 220 (69.2%) | 226 (70.4%) |

| **Extraction difficulty, n (%)** | | |
|---|---|---|
| Simple (score 1-2) | 189 (59.4%) | 194 (60.4%) |
| Surgical (score 3-4) | 129 (40.6%) | 127 (39.6%) |

**Primary Outcome: Alveolar Osteitis**

The incidence of alveolar osteitis at 7 days after tooth extraction was 5.0% in the chlorhexidine group and 1.6% in the hydrogel group. This difference was statistically significant (p=0.008). The absolute risk reduction was 3.4% (95% CI: 0.8% to 6.0%), corresponding to a risk ratio of 0.31 (95% CI: 0.12 to 0.79). The number needed to treat to prevent one case of AO was 29 (95% CI: 17 to 125), meaning that 29 patients would need to be treated with hydrogel rather than chlorhexidine to prevent one additional case of AO.

Results were similar when using per protocol sensitivity analysis (excluding protocol violations): RR 0.31 (95% CI: 0.12 to 0.80); p=0.009, indicating the results were robust.

| **Outcome** | **Chlorhexidine** | **Hydrogel** |
|---|---|---|
| AO cases, n (%) | 16 (5.0%) | 5 (1.6%) |
| Risk Ratio (95% CI) | 1.00 (reference) | 0.31 (0.12-0.79) |
| P-value | --- | 0.008 |
| NNT (95% CI) | --- | 29 (17-125) |

**Secondary Outcomes**

**Pain Scores**

The hydrogel group demonstrated significantly lower pain scores at all assessed time points compared to the chlorhexidine group (all p<0.001). The difference was highest at 6 hours post-extraction (2.8 points on VAS scale 0-10, 95% CI: 2.4 to 3.2) suggesting significantly better early pain relief with the lidocaine-containing hydrogel. This benefit remained at 72 hours with clinically meaningful differences (differences > 1 point) remaining at 72 hours. Both groups had very low pain scores by 7 days, with the hydrogel group having lower scores (0.3 ± 0.5 vs 0.8 ± 0.7, p<0.001)

| **Time Point** | **Chlorhexidine (mean±SD)** | **Hydrogel (mean±SD)** |
|---|---|---|
| 6 hours | 6.2 ± 1.8 | 3.4 ± 1.5 |
| 12 hours | 5.8 ± 1.9 | 3.1 ± 1.6 |
| 24 hours | 4.9 ± 2.1 | 2.3 ± 1.4 |
| 48 hours | 3.2 ± 1.8 | 1.6 ± 1.2 |
| 72 hours | 2.1 ± 1.5 | 1.0 ± 0.9 |
| 7 days | 0.8 ± 0.7 | 0.3 ± 0.5 |

**Analgesic Consumption and Patient Satisfaction**

The mean (IQR) number of tablets used over the seven-day period for this follow-up was significantly less in the hydrogel group than in the chlorhexidine group: 4 (2-6) and 8 (6-12) tablets, respectively (p<0.001). This is a 50% reduction in the amount of analgesics required, which may have consequences regarding the decrease of the adverse effects of NSAIDs and therefore patient comfort.

The patient satisfaction scores were significantly greater for the hydrogel group than the chlorhexidine group at day 7: mean 4.6 ± 0.6 versus 3.8 ± 0.9 (p<0.001). In the hydrogel group, 83.5% rated their satisfaction as 4 or 5 (satisfied and very satisfied) while 64.2% rated their satisfaction as 4 or 5 in the chlorhexidine group.

**Safety and Adverse Events**

During the study period, there were no serious adverse events reported in either group. In both groups, adverse events were minor and self limiting, and the safety profile was good. In the chlorhexidine group, 26 subjects (8.2%) had transient taste changes, while 7 subjects (2.1%) in the hydrogel group had similar changes (p=0.002), which is typical of chlorhexidine. Ten participants (3.1%) in chlorhexidine group and 5 participants (1.6%) in hydrogel group reported slight tissue irritation (p=0.18).

All adverse events were self-resolving within 48 hours without intervention. There were no dropouts due to adverse events. There were no allergic reactions, secondary infections or persistent bleeding events noted in either group, indicating that both interventions are safe.

## DISCUSSION

This multi-center randomized controlled trial represents the first clinical evaluation of dual-action thermosetting hydrogel for alveolar osteitis prevention. Our findings demonstrated that the hydrogel intervention significantly reduced AO incidence compared to standard chlorhexidine irrigation, with a 69% relative risk reduction (RR=0.31, 95% CI: 0.12-0.79, p=0.008) and number needed to treat of 29. Additionally, the hydrogel provided superior pain control, reduced analgesic consumption, and achieved higher patient satisfaction, all while maintaining an excellent safety profile comparable to standard care.

**Primary Outcome Interpretation and Mechanistic Insights**

The synergistic dual-action mechanism of the thermosetting hydrogel is responsible for the observed reduction in the incidence of AO. Metronidazole is sustained released, so it can maintain antimicrobial levels above the minimum inhibitory concentration (MIC) of anaerobic organisms during the 72 hours that are crucial for the incidence of AO [1, 6].In addition, the special activation mechanism of metronidazole in an anaerobic environment makes it particularly suitable for use in the microenvironment of the extraction socket, where blood circulation is disrupted after extraction and anaerobic bacteria can thrive [31]. Anaerobic bacteria were found to be the predominant bacteria in the dry sockets, such as Treponema denticola, Prevotella intermedia, and Fusobacterium nucleatum, which are highly sensitive to metronidazole [20, 21].

Lidocaine component provides additional benefits not related to analgesia. Lidocaine can help to decrease the pain associated with the surgery, which may lead to less manipulation of the socket by the patient (tongue probing or finger exploration), and may help to prevent mechanical disruption of the socket blood clot [46]. In addition, recent studies have shown that local anaesthetics have anti-inflammatory properties which are not related to their analgesic actions, and may therefore limit the inflammatory cascade that is responsible for fibrinolysis and clot dissolution [47].
Pluronic F-127/Carbopol formulation has thermosetting properties which offer specific benefits to conventional socket dressings. This sol-gel transition at body temperature enables the formulation to be applied as a low-viscosity liquid that can penetrate to all parts of the socket and then quickly turns into a semi-solid gel with an exact fit with the socket geometry [1, 8]. This monolithic effect is inherently better than the transient antimicrobial activity of chlorhexidine irrigation that is rapidly neutralized by saliva and gingival crevicular fluid [48]. The mucoadhesive properties provided by the use of Carbopol 934P result in increased retention, even in the wet oral cavity, as Bender et al. have shown in vitro that the retention time is over 24 hours in simulated physiological conditions [1, 36].

**Pain Management and Patient-Centered Outcomes**

The marked reduction in pain scores in the hydrogel group, especially in the first few hours post-operatively (6-24 hours), is related to the immediate release of lidocaine along with its prolonged release profile. The amount of pain reduction (2.8 points at 6 hours) is far more than the minimal clinically important difference (MCID) for VAS pain scores (typically estimated at 1.3-1.5 points), meaning it is not only statistically significant, but clinically meaningful as well [49].

The prolonged pain relief up to 72 hours indicates that lidocaine is still releasing during this vital time. In an in vitro dissolution study, Bender et al. showed that ~60% of loaded lidocaine was dissolved within 24 hours, and that it continued to dissolve for 48 hours [1]. This is better than a local anesthetic injection with a single dose providing 2-4 hours of anaesthetic effect or oral analgesics, which need repeat doses and have systemic effects [50].

The 50% reduction in the consumption of analgesics is important in the public health and clinical context. Reducing the use of NSAIDs will decrease the risk of gastrointestinal complications, especially important in the Pakistani population where H pylori is found at very high prevalence (up to 80% in some studies) and NSAID-related peptic ulcer disease is an important burden [51, 52]. Also, reduced use of analgesics may contribute to better adherence to medication for patients with chronic conditions who take multiple medications daily (polypharmacy), which is linked to reduced adherence [53].

This was more likely because of a combination of benefits, including the decreased AO incidence and better pain control and treatment convenience, which led to higher levels of patient satisfaction in the hydrogel group (mean score 4.6 vs 3.8, $p<0.001$). The hydrogel is only given at the time of extraction, unlike chlorhexidine which must be taken twice a day for one week by the patient. This one time only solution is especially beneficial in low health-literate populations or in individuals who might have difficulties with regular use of medicines [54].

**Comparison with Existing Literature and Current Standard of Care**

Our control group had an incidence of 5.0%, which is in the same range as previous studies showing that 0.12% chlorhexidine decreased incidences of AO by around 40-50% when compared with placebo or no intervention [2, 16]. Hermesch et al. did a landmark study and reported 4.2% AO rate in the chlorhexidine group and 11.6% AO rate in the placebo group in the extraction of mandibular third molars [2]. Caso et al. [16] conducted another systematic review and meta-analysis which included multiple trials, and found pooled odds ratio of 0.53 (95% CI: 0.37-0.74) favoring chlorhexidine. These findings confirm these results, and offer recent evidence that chlorhexidine is effective as standard care.

However, the hydrogel AO rate of 1.6% is another 68% relative improvement over chlorhexidine, demonstrating its considerable superiority over current standard care. This level of benefit is similar to or greater than the benefit of systemic antibiotic prophylaxis. Prophylactic systemic metronidazole did not only reduce the incidence of AO by 76-80%, but also has the potential of the development of resistance, adverse effects, and drug interactions, which has restricted the use of systemic antibiotics for routine use to prevent AO [32, 33]. The topical delivery system of the hydrogel generates the

same efficacy while providing a local action and low systemic effects.

Earlier trials of the insertion of chlorhexidine gel (not rinse) have been successful, but not widely adopted. In another study, Haraji and Rakhshan showed that the use of 0.2% chlorhexidine gel was effective in reducing AO than with the use of a rinse alone, indicating that the sustained delivery of chlorhexidine locally is more effective at reducing AO [18]. Our Pluronic-based system, however, has the thermosetting properties that can provide the precise socket conformability and retention provided by chlorhexidine gel formulations. Additionally, chlorhexidine alone treats only the antimicrobial component of AO prevention, while the dual-drug hydrogel could treat both the antimicrobial and the pain management component - a key patient-centred outcome that is frequently not addressed in AO prevention strategies.

Although combination drug delivery is used in other medical fields, the use of the same technique in oral surgery is under-explored. Recent studies of platelet rich fibrin (PRF) and antimicrobials have demonstrated excellent results, [27] however, the collection of blood and centrifugation is not available in all settings and is restricted. Our hydrogel therapy is better than combination therapy with added convenience of having it formulated and just needing to be refrigerated.

**Pakistani Healthcare Context and Generalizability**

Male participants in our cohort smoked at high rates (around 30%), which likely resulted in a higher base level of AO risk than in other countries with lower rates of smoking, especially in high-income countries [55]. Sweet and Butler's classic study found that smoking just after an extraction was 3.8 times more likely to result in an AO, [11] and more recent studies by Muhonen et al. have confirmed this relationship in modern populations, [13]. Evidence of effectiveness in this high-risk population group adds to the growing body of compelling evidence for effectiveness in difficult real world settings, which supports implementation more broadly.

Other cultural habits like chewing of betel nut (paan) in south Asian nations also pose some difficulties, not found in the western population. Betel nut use has been related with delayed wound healing and raised risk for infections, [56] but betel nut users weren't particularly omitted from our research (except for active infections), thus giving the generalizability of our outcomes to common dental practice in Pakistan. Incorporation of these high risk practices indicates good performance in a wide range of patient groups.

The multi-center study design across four tertiary hospitals in different cities (Lahore and Faisalabad) increases the generalizability of results in other Pakistani contexts and in other health care delivery systems in South Asia. The differences in surgical experience, patient population, and surgical practice between centers were intended and the number of centers with a wide variety of practices provided a more accurate reflection of the conditions under which surgical procedures are actually performed in the real world than single centers with uniform practice. The consistency of effects across centres (not shown in the main results, but confirmed in the sensitivity analyses) gives confidence in the robustness of the intervention.

The hydrogel tackles a number of pragmatically relevant health system issues. The one application method decreases patient burden and removes compliance problems with multi-day rinse methods. The hydrogel has to be stored in a cold chain (2-8°C), but this can be readily accomplished in most tertiary centers where there is refrigerator space for vaccines and other temperature sensitive products [57]. The 7-day shelf life is shorter than ideal, but can be managed through effective meal planning. Implementation considerations - Element of cost will be important (we did not carry out a formal cost-effectiveness analysis but the extra cost of materials will probably be outweighed by reduced unscheduled visits and lost productivity due to AOs).

**Safety Profile and Tolerability**

The safety profile seen in this study, with no serious adverse events in either group and only minor and self-limiting adverse events, is reassuring, as this is a novel intervention in human populations. In vivo safety studies were needed to validate Bender et al.'s in vitro preclinical studies, which showed favourable cytotoxicity in primary human gingival fibroblasts. [1] Our results demonstrate the formulation's safety across various patient populations, including those with multiple comorbidities and of high-risk behavior.

Another patient-centred benefit of hydrogel is its lower incidence of altering taste (2.1% compared with 8.2% for chlorhexidine). With the well known ‘metallic taste' and the possibility of taste disturbance with chlorhexidine, this may lead to poor patient compliance and poor patient satisfaction, [59] while the localized delivery of the hydrogel reduces oral exposure. The incidences of mild tissue irritation were similar (1.6% vs 3.1%), indicating similar local tolerability; both were below the thresholds of clinical concern.

No allergic reaction was noted although metronidazole is known to have a potential for allergic reactions. Allergic reactions are rare with this medication (0.5-1% of people) and if they do happen, usually occur when the medication is given intravenously, but not when it is applied topically. Lidocaine allergy is very infrequent (<1% of population), [61] and true lidocaine mediated reactions are even rarer, with most allergies reported being vasovagal reactions or anxiety responses. Unexpected reactions did not occur in our group of 321

patients, although we excluded patients who had known drug allergies.

**Study Limitations and Considerations**

There are a number of limitations to be considered when drawing conclusions from our findings. The nature of the intervention does not allow for blind allocation of participants and clinicians.The nature of the intervention makes complete blinding impossible (the clear liquid irrigation vs white gel application is visually different). This can lead to treatment bias, with the clinician inadvertently adjusting procedure or post-operative care depending on the treatment group [62]. We addressed this concern, however, by implementing some standardisation regarding the protocol, training, and most importantly, blinded assessment of the primary end point (AO diagnosis). Exposed bone and clot dissolution are objective criteria, which minimize subjectivity in outcome determination for AO.

Although the one-week follow-up interval was appropriate for the diagnosis of AO, which generally occurs within 2-4 days, it was not sufficient to assess longer-term healing outcomes like complete socket epithelialization, bone remodeling or any changes in the ridge. A larger study with longer follow-up would assess if the enhanced early healing seen with the hydrogel results in better long-term anatomical results that are relevant for future prosthodontic rehabilitations or implant placement.

Relatively low and comparable loss to follow up (5.3%) may affect results if differential and/or related to outcome. This was addressed with sensitivity analyses using multiple imputation with consistent results. Those who were not followed up were younger, however, more likely to be smokers, possibly a higher risk sub-group. Differential outcomes between treatment groups may lead to bias in our estimates if these individuals differ.

Some of the challenges with the hydrogel formulation are that it must be stored under refrigerated conditions (2-8°C) and has a shelf life of 7 days. The limitations might restrict the use in primary health centers without adequate cold chain facilities [63]. Optimization of formulation is continuing to develop longer shelf life and to identify room-temperature stable formulations; however, the changes will then need to be tested separately for their gelation properties and drug release.

We did not evaluate hydrogel retention in vivo or pharmacokinetic studies of the actual concentrations of the drug in the socket tissue and gingival crevicular fluid. Although Bender et al. have shown 24 hour in vitro retention under simulated conditions, [1] this may not be the case in the dynamic oral environment as the tongue moves and saliva flows along with chewing and masticatory forces. Microdialysis or tissue sampling-based pharmacokinetic studies would help to better understand in vivo delivery dynamics for a drug and would provide an aid in formulation optimization in the future [64].

Study population were tertiary care teaching hospitals, but there was a variety of extraction types and difficulties. The generalizability to primary care or a private dental practice may vary, especially in terms of surgical skills and storage for formulations. It would be interesting to research implementation in a variety of practice contexts.

**Clinical Implications and Future Directions**

It is recommended for clinical practice, thermosetting hydrogel is a better solution than chlorhexidine irrigation to prevent AO, especially for high-risk patients (smokers, surgical extraction, patients with a history of AO). This number needed to treat of 29 is favourable when compared to other accepted preventive interventions in dentistry and medicine [65]. The other positive aspects of better pain control and patient satisfaction add to the argument for adoption, particularly when considering similar safety.

Health systems considerations for implementation include: development of local manufacturing capacity to ensure sustainable production and reduced costs through economies of scale; training programs for oral surgeons and general dentists in the technique of application of the hydrogel; setting up cold chain logistics for the distribution and storage; integration within clinical practice guidelines and SOPs.

There are a number of research directions worth pursuing. There is a lack of cost-effectiveness analysis that could help in allocation of resources and policy of reimbursement. The drug delivery platform could be further developed for other oral surgery uses such as implant placement, periodontal surgery and bone grafting [67]. Exploring different drug combinations, including the addition of growth factors for improved healing and anti-inflammatory agents like corticosteroids, could further enhance the results.

The shelf-life limitation should be taken into consideration in formulation optimization studies, which may be achieved by lyophilizing the product and reconstituting it prior to use, or by searching for other polymer systems that are stable at room temperature. Further research into patient-specific risk stratification tools may allow them to be used more selectively to achieve cost-effectiveness, with those who are most likely to benefit. Lastly, long term evaluations (3-6 months) of ridge preservation, bone quality and suitability for placement of dental implants would be useful for prosthodontic planning.

**Broader Implications for Oral Surgery and Drug Delivery**

In addition to AO prevention, this study provides evidence that thermosetting hydrogels are a versatile

drug delivery platform in the oral cavity. The sol-gel transition mechanism is a solution to the fundamental challenges that oral administration of drugs presents: the need for formulations with conformable geometry to fit into the irregular anatomy of the mouth, the high moisture environment in which they are delivered, and the need for sustained release to maintain therapeutic levels despite the clearance of the drug by saliva [8, 68]. The clinical success of the formulation from the lab to patient care will validate the developmental route for other similar technologies and possibly lead to increased investments in the study of oral drug delivery. Addressing infection prevention and pain management in the same delivery system (combination therapy) is a paradigm that may be adopted for other oral surgical procedures in which both infection prevention and pain management are desired.

Innovations which can enhance outcomes with reduced patient burden (fewer visits, less need for analgesics, compliance) have a special value for a developing country with high burden of dental disease and limited resources. The hydrogel is an example of this principle - although there is a significant investment in the research and development of the product and in cold chain systems, this may overcome the downstream costs associated with the reduction in complications and health care utilisation.

## CONCLUSION

This multi-center randomized controlled trial demonstrates level 1 evidence that dual-action thermosetting hydrogel with lidocaine and metronidazole will prevent alveolar osteitis following tooth extraction, compared to irrigation with chlorhexidine. The intervention showed a clinically significant 69% decrease in the incidence of AO (RR 0.31, NNT 29), significant decrease of pain on VAS after 6 hours (2.8-point reduction) with also substantially better pain control, 50% reduction of analgesic consumption, and significantly higher patient satisfaction (mean 4.6 vs 3.8 on 5-point scale). The good safety profile (no serious adverse events, minor and self-limiting effects) is commensurate with the acceptability of the intervention for use in routine clinical practice.

Successful translation of formulation to effective clinical use has shown the viability and clinical usefulness of the thermosetting hydrogel technology for use in oral surgery. The synergistic dual-acting mechanism - sustained antimicrobial action plus long lasting local analgesic effect - is designed to tackle multiple pathophysiological aspects of AO and to enhance patient-centered outcomes. The thermosetting properties allow for the conformability of sockets and the retention for a long period of time, which is not possible with traditional rinses and dressings.

This combination of two actions is a promising step in the post-extraction socket management for healthcare systems in Pakistan and similar resource-limited regions with high AO burden. Performance in a high-risk population with high smoking rates, cultural practices that impact healing and inconsistent access to oral hygiene resources indicates strong performance in the real world. Single application convenience removes compliance barriers introduced by multi-day protocols, possibly improving the effectiveness of the protocols in populations with low health literacy.

Studies that look at the long-term healing outcomes, cost-effectiveness on a healthcare system and societal level, best patient selection criteria for targeted application and implementation strategies in different practice settings will be critical to evidence-based clinical practice guidelines and policy decisions around adoption of this technology. Shelf life and cold chain optimization of different drug combinations and formulation could further broaden the applicability and accessibility of this promising intervention..

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