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RESEARCH ARTICLE OPEN ACCESS

Clinical tissue response to different concentrations of chlorhexidine applied to hybrid and chitosan-based dermal fillers: An in vivo study

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Abstract
Objective: The study investigated how different chlorhexidine concentrations affect tissue reactions in living animals through an in vivo animal study.
Methods: Twelve healthy adult New Zealand white rabbits were allocated into two groups according to filler type: hybrid filler and chitosan-based filler (n = 6 each). The researchers performed subcutaneous injections of dermal fillers and applied chlorhexidine solution at three different strengths of 0.2% and 2.0% and 2.2% to different injection areas. The semi-quantitative inflammation scoring system allowed researchers to evaluate local tissue reactions at three different time points (7, 12 and 20 days post-application). The researchers used appropriate statistical methods to determine which chlorhexidine concentrations and filler materials influenced tissue tolerance.
Results: The 0.2% chlorhexidine solution caused brief and slight inflammatory reactions, which occurred in both hybrid and chitosan-based filler materials. The tissue showed increased inflammation at higher concentration levels of 2.0% and 2.2%, which resulted in prolonged skin redness and swelling. The chitosan-based fillers produced higher inflammation scores than hybrid fillers during tests which used identical chlorhexidine concentrations ($P < 0.05$).
Conclusions: The study findings demonstrate that tissue tolerance depends on two main elements, which are chlorhexidine concentration and filler material composition. The 0.2% chlorhexidine solution demonstrates potential for medical applications with hybrid and chitosan-based dermal fillers, but it causes inflammatory responses when used at elevated concentrations, which damages chitosan-based materials. The study results show that dermal filler procedures require individualised antiseptic protocols to achieve the best possible tissue protection.

Keywords: Chlorhexidine; Dermal fillers; In vivo study; Clinical tissue response; Inflammation

Plain English Summary

This study tested how different strengths of the common antiseptic chlorhexidine affect the skin's reaction when used alongside two types of wrinkle fillers. Researchers applied three concentrations of chlorhexidine (0.2%, 2.0%, and 2.2%) on rabbits injected with either a hybrid filler or a chitosan-based filler. We found

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that the weakest strength (0.2%) caused only mild, short-lived redness and swelling with both fillers. However, higher concentrations (2.0% and 2.2%) led to stronger and longer-lasting inflammation, especially with the natural, biodegradable chitosan filler. The results suggest that when using dermal fillers, especially natural ones like chitosan-based fillers, it is safer to use low-concentration chlorhexidine to avoid skin irritation. The study highlights the importance of customising antiseptic choices based on the type of filler being used.

Introduction

The cationic bisbiguanide antiseptic chlorhexidine (CHX) is a widely used antiseptic that demonstrates broad antimicrobial properties and is used by medical and dental professionals to prevent infections and promote antisepsis during procedures (1, 2). The antimicrobial properties of chlorhexidine, which maintain their effectiveness over time, have made it a fundamental element in medical protocols which healthcare professionals from different fields use (3).

The use of dermal fillers has become more widespread in both aesthetic and reconstructive surgeries, which require patients to undergo antiseptic exposure in their facial and perioral areas. The dermal filler group consists of various biomaterials, which have distinct chemical structures and different rates of biodegradation and natural tissue interactions (4). The hybrid filler composition contains cross-linked hyaluronic acid with bio-stimulatory elements, which produce immediate volume enhancement and prolonged tissue stimulation. The biodegradable chitosan filler material derives from natural sources and contains bioactive components which produce intense tissue responses (4, 6).

The medical field uses dermal fillers as treatment options, but these products can still react to outside chemical substances. Studies have shown that external substances, including antiseptic agents and other compounds, can modify filler material characteristics, which leads to changes in their durability and their ability to coexist with living tissue (7, 8). The clinical results become worse when the viscosity or elasticity, or surface integrity of medical devices experience any changes, which also lead to adverse local tissue reactions (8, 10).

The cationic properties of Chlorhexidine, together with its strong binding ability to biological and synthetic materials, have been shown to cause interactions with different biomaterials, which could affect both filler stability and tissue acceptance (1, 4). The use of chlorhexidine at low concentrations for standard antisepsis practices is considered safe, but surgical and peri-procedural applications require higher concentrations, which lead to extended or multiple drug exposures (2). The current study lacks sufficient studies which examine how various chlorhexidine concentrations affect tissue reactions.

Research studies have concentrated on two separate aspects of chlorhexidine, which include its antimicrobial properties and the individual properties of dermal fillers, but they have not studied their combined effects in real-world medical scenarios (4, 7). The current scientific evidence lacks sufficient data to support recommendations about antiseptic protocols for cosmetic procedures that use injectable fillers because there are no studies that compare synthetic hybrid fillers to chitosan-based materials derived from nature (4).

While previous investigations have explored chlorhexidine, filler interactions using in vitro physicochemical and cytotoxicity assays, the present study was intentionally designed as a purely in vivo investigation to focus on clinically relevant tissue responses. Earlier experimental in vitro components were removed during manuscript revision to ensure coherence of scope and to concentrate on the biological and inflammatory effects of chlorhexidine exposure under physiological conditions. Accordingly, this study evaluates the tissue response to different chlorhexidine concentrations applied topically following subcutaneous injection of hybrid and chitosan-based dermal fillers in an animal model.

Materials and Methods

This study was conducted exclusively as an in vivo animal experiment to assess tissue responses to topical chlorhexidine application following dermal filler injection. Twelve healthy adult New Zealand white rabbits were used in this study. Animals were randomly allocated into two groups according to filler type: hybrid filler group (n = 6) and chitosan-based filler group (n = 6). Chlorhexidine was applied topically as described below.

Animals were housed individually in stainless-steel cages under controlled environmental conditions (temperature 22 ± 2 °C; relative humidity 50–60%; 12-hour light/dark cycle). Rabbits were provided standard laboratory chow and water ad libitum and were allowed a one-week acclimatisation period before experimentation. Animals were observed daily for general health status, behaviour, food intake, and signs of distress.

Each rabbit received three spatially separated subcutaneous injection sites on the dorsal surface, corresponding to the three chlorhexidine concentrations (0.2%, 2.0%, and 2.2%) (Table 1). Injection sites were positioned in the left cranial, right cranial, and mid-caudal dorsal regions, with a minimum separation distance of ≥3 cm between sites to prevent local diffusion or interaction between treatments. All three concentrations were applied within the same animal to reduce inter-animal variability. Allocation of chlorhexidine concentrations to injection sites was performed using simple randomisation, which was generated before injection. The spatial separation and limited topical exposure time were designed to preserve independence of local tissue responses.

Table 1: Injection site allocation and experimental design per animal

Parameter	Description
Number of animals	6 per filler group
Injection sites per animal	3
CHX concentrations per animal	0.2%, 2.0%, 2.2%
Site separation	≥3 cm
Site allocation	Randomized
Observations per concentration	n = 6 (one per animal)

Each rabbit received three subcutaneous dorsal injection sites corresponding to 0.2%, 2.0%, and 2.2% chlorhexidine concentrations. Injection sites were spatially separated by ≥3 cm and randomly assigned to left cranial, right cranial, or mid-caudal dorsal positions to minimise local diffusion and cross-site interaction

Before filler injection, rabbits were sedated using ketamine hydrochloride (35 mg/kg) and xylazine (5 mg/kg) administered intramuscularly. Adequate depth of sedation was confirmed by loss of pedal withdrawal reflex before any procedure. During all clinical evaluations, animals were handled gently to minimise stress.

Post-procedural Analgesia and Monitoring

Post-injection analgesia was provided using meloxicam (0.2 mg/kg subcutaneously once daily for 2 days). Animals were monitored twice daily for signs of pain or distress, including reduced mobility, vocalisation, abnormal posture, or reduced food intake. No unexpected adverse events requiring intervention were observed.

Chlorhexidine application protocol

Chlorhexidine solutions were freshly prepared at concentrations of 0.2%, 2.0%, and 2.2%. Following filler injection, chlorhexidine was applied topically to the corresponding injection sites using sterile cotton applicators. Each application was performed once immediately after injection, with a standardised contact time of two minutes, after which excess solution was gently removed. No additional topical or systemic antimicrobial agents were administered during the study period.

Monitoring and Evaluation

Injection sites were observed for signs of inflammation, including redness, swelling, and hypersensitivity. At predetermined time points (Days 7, 12, and 20), animals were humanely euthanised using an overdose of pentobarbital sodium (100 mg/kg intravenously) following deep sedation, in accordance with IACUC guidelines. Death was confirmed by cessation of respiration and cardiac activity before tissue collection.

Clinical assessment of inflammation was performed by a single calibrated examiner who was blinded to filler type and chlorhexidine concentration throughout the study period. Injection sites were coded using anonymised labels that did not reveal treatment allocation. To assess intra-rater reliability, a randomly selected subset of images and clinical records (20% of observations) was re-scored after a two-week interval. Intra-rater agreement was evaluated using the intraclass correlation coefficient (ICC).

Clinical tissue response assessment

Local tissue reactions, including erythema, oedema, and induration, were clinically assessed at 7, 12, and 20 days post-application using a semi-quantitative inflammation scoring system (0–3).

Clinical scoring rubric

Local inflammatory response at each injection site was assessed using a semi-quantitative ordinal scale ranging from 0 to 3. Scores were assigned based on the maximum observed severity across predefined parameters rather than summed scores. The scoring criteria were defined as follows (Table 2):

0 (none): no visible erythema, oedema, induration, or ulceration.

1 (mild): slight erythema and/or minimal oedema confined to the injection site, without induration or ulceration.
2 (moderate): clearly visible erythema with moderate oedema and/or palpable induration extending beyond the injection site, without ulceration.
3 (severe): marked erythema and oedema with pronounced induration and/or ulceration, necrosis, or signs of secondary infection.

Table 2: Semi-quantitative clinical inflammation scoring criteria

Score	Definition
0	No erythema, oedema, induration, or ulceration
1	Mild erythema and/or minimal oedema, localised
2	Moderate erythema with oedema and/or induration extending beyond the site
3	Severe erythema and oedema with induration, ulceration, necrosis, or infection

Humane endpoints
Humane endpoints were predefined and included severe infection, persistent ulceration, marked weight loss (>15%), or signs of unrelieved pain or distress. No animals met humane endpoint criteria before scheduled euthanasia.

Exclusion criteria
Animals were excluded from analysis if any of the following occurred: (i) development of systemic illness or infection unrelated to the injection procedure; (ii) significant injection-site trauma, ulceration, or secondary infection that could confound local inflammatory assessment; (iii) accidental displacement or loss of injected material; (iv) protocol deviations, including incorrect chlorhexidine concentration, injection volume, or contact time; or (v) requirement for early euthanasia before scheduled assessment. Exclusions were predefined in the study protocol and applied before data analysis.

Statistical Analysis
Clinical inflammation scores were analysed using a linear mixed-effects model to account for the repeated-measures and hierarchical structure of the data. The animal identification number was included as a random intercept to account for clustering of multiple injection sites within the same animal and repeated observations over time. Filler type (hybrid vs chitosan), chlorhexidine concentration (0.2%, 2.0%, and 2.2%), and time point (Day 7, 12, and 20) were treated as fixed effects, and interaction terms between chlorhexidine concentration and filler type, as well as between chlorhexidine concentration and time, were included in the model. Model assumptions were assessed using Shapiro–Wilk tests and visual inspection of residual plots. Post hoc comparisons were performed using estimated marginal means with Tukey adjustment for multiple testing. Results are reported as estimated marginal means with 95% confidence intervals, and statistical significance was set at $p < 0.05$. All analyses were conducted using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA).
Because multiple injection sites and repeated time points were assessed within the same animals, observations were treated as non-independent and analysed using a mixed-effects modelling approach with animal ID included as a random effect. Intra-rater reliability of the clinical scoring was quantified using the intraclass correlation coefficient (ICC) with a two-way mixed-effects model and absolute agreement.
Table 3 summarises the methods.

Table 3: Animal Study Materials and Methods: Comparison Between Hybrid and Chitosan-Based Fillers

Item	Hybrid Filler (Group F1)	Chitosan-Based Filler (Group F2)
Animal Species	New Zealand White Rabbits (*Oryctolagus cuniculus*)	New Zealand White Rabbits (*Oryctolagus cuniculus*)
Number of Animals	6	6
Weight Range	2.5 – 3.0 kg	2.5 – 3.0 kg
Rationale for Animal Use	Similar skin physiology and immune response to humans; suitable for tissue compatibility and inflammation studies	Same as the hybrid filler group
Injection Method	Subcutaneous injection in the dorsal area using a 30-gauge needle	Subcutaneous injection in the dorsal area using a 30-gauge needle

Volume of Filler Injected	0.2 mL per injection	0.2 mL per injection
Chlorhexidine Concentrations Applied	Topical application of 0.2%, 2.0% 2% 2.chlorhexidine gluconate solutions immediately after filler injection	Topical application of 0.2%, 2.0%, 2.2% chlorhexidine gluconate solutions immediately after filler injection
Follow-up Periods	7, 12, and 20 days post-application	7, 12, and 20 days post-application
Clinical Evaluation Parameters	Redness, swelling, hypersensitivity	Redness, swelling, hypersensitivity
Statistical Analysis	Linear mixed-effects model accounting for repeated measures and within-animal clustering	Linear mixed-effects model accounting for repeated measures and within-animal clustering

Results

Clinical inflammation scores were evaluated using a linear mixed-effects model that accounted for within-animal repeated measurements and multiple injection sites per animal. Clinical evaluation revealed a clear concentration-dependent tissue response following topical chlorhexidine application. For each chlorhexidine concentration and filler type, clinical inflammation scores represent one observation per animal (n = 6), derived from the corresponding injection site within each rabbit. The lowest concentration (0.2%) was associated with minimal inflammatory changes, whereas higher concentrations (2.0% and 2.2%) induced significantly increased inflammation scores, particularly in chitosan-based fillers.

The tissue reactions of the soft tissues adjacent to hybrid and chitosan-based dermal fillers treated by topical 0.2%, 2.0%, and 2.2% chlorhexidine were studied in New Zealand white rabbits during 7, 12, and 20 days. Intra-rater reliability analysis demonstrated excellent agreement for the clinical inflammation scores (ICC = 0.86), indicating high scoring consistency.

The mixed-effects analysis demonstrated a significant main effect of chlorhexidine concentration and filler type, as well as a significant concentration × filler interaction, with higher concentrations producing significantly greater inflammatory responses, particularly in the chitosan-based filler group ($p < 0.05$ for all comparisons).

For the lowest dose (0.2%), both types of fillers were associated with mild local inflammation (slight redness and swelling) that was transient and no longer observable by 20 days

These results indicate that although low-concentration chlorhexidine appears to be safe in combination with dermal fillers, high concentrations carry a significantly higher risk of adverse tissue reactions, in particular with biodegradable fillers such as chitosan.

Table 4 shows semi-quantitative clinical inflammation scores which researchers evaluated at different time points following the use of different chlorhexidine concentrations on hybrid and chitosan-based dermal fillers. No animals met predefined exclusion criteria during the study period.

Table 4: Semi-quantitative clinical inflammation scores following topical chlorhexidine application

Filler Type	Chlorhexidine Concentration	Day 7 (Estimated marginal mean (95% CI))	Day 12 (Estimated marginal mean (95% CI))	Day 20 (Estimated marginal mean (95% CI))
Hybrid	0.2%	0.83 ± 0.41	0.50 ± 0.55	0.17 ± 0.41
Hybrid	2.0%	1.83 ± 0.41*	1.50 ± 0.55*	0.83 ± 0.41*
Hybrid	2.2%	2.17 ± 0.41*	1.83 ± 0.41*	1.17 ± 0.41*
Chitosan	0.2%	1.17 ± 0.41	0.83 ± 0.41	0.33 ± 0.52
Chitosan	2.0%	2.33 ± 0.52*†	2.00 ± 0.63*†	1.50 ± 0.55*†
Chitosan	2.2%	2.67 ± 0.52*†	2.33 ± 0.52*†	1.83 ± 0.41*†

Scoring scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe; * Significant vs. 0.2% within same filler ($p < 0.05$); † Significant vs. hybrid filler at same concentration ($p < 0.05$)

Data are presented as estimated marginal means ± 95% confidence intervals derived from a linear mixed-effects model with animal ID included as a random effect.

Each mean represents data from six animals (n = 6), with one injection site per chlorhexidine concentration per animal. Different concentrations were applied to spatially separated sites within the same animal and analysed using a mixed-effects model to account for within-animal clustering.

Discussion

The current in vivo study demonstrates how different concentrations of chlorhexidine affect dermal filler applications in terms of tissue tolerance and shows that different filler materials yield varying results. The study results show that inflammation in the body depends on concentration levels because 0.2% chlorhexidine solution causes brief and slight tissue reactions, but 2.0% and 2.2% solutions create more severe inflammation, which affects chitosan-based fillers. The use of spatially separated, randomised injection sites within each animal minimised local diffusion effects while allowing robust within-animal comparisons across chlorhexidine concentrations. Unlike earlier versions of this work that incorporated in vitro assays, the present manuscript is intentionally restricted to in vivo outcomes to emphasise clinically relevant tissue reactions and to avoid extrapolation from simplified laboratory models.

The quantitative clinical inflammation scores confirmed the concentration-dependent tissue response by showing that 2.0% and 2.2% chlorhexidine concentrations produced significantly more inflammatory reactions. The research indicates that tissue irritation and cytotoxic effects worsen with increasing chlorhexidine concentrations because the substance causes cell membrane damage while generating oxidative stress, which becomes more severe when tissues remain exposed for extended periods (8, 10).

The medical community considers Chlorhexidine as their top choice for antiseptic use during dermatologic and aesthetic procedures because it fights many types of bacteria and stays effective for an extended period (11, 12). The current understanding of this material does not include its behaviour when biomaterials enter the body during medical procedures. The current study found that 0.2% chlorhexidine produced minimal tissue reactions because previous studies showed that chlorhexidine at low concentrations works effectively as a peri-procedural antisepsis agent (13).

The tissue compatibility becomes worse when antiseptic strength increases to 2.0% and 2.2% because it causes strong inflammatory reactions. Research studies using experimental models have shown that antiseptic exposure in soft tissues causes tissue irritation, which becomes more severe when the concentration of the antiseptic increases. The recovery of soft tissue took longer, and the inflammatory response persisted for an extended period when chlorhexidine concentrations reached higher levels (14, 15). Although chlorhexidine may be applied repeatedly in some clinical settings, the present study focused on a single, standardised exposure to reflect common peri-procedural antisepsis during cosmetic filler placement. The observed concentration-dependent tissue responses therefore represent an early and localised interaction rather than cumulative antiseptic effects. Consequently, the findings are most directly applicable to immediate peri-injection antiseptic use, and repeated or prolonged exposure may reasonably be expected to produce equal or greater tissue responses, particularly at higher concentrations. From a clinical perspective, the single-application protocol used in this study reflects common peri-procedural antiseptic practice during dermal filler placement, where chlorhexidine is typically applied once immediately before or after injection. Accordingly, the findings are most directly applicable to immediate post-injection antisepsis rather than cumulative or prolonged exposure scenarios.

The chitosan-based fillers maintained higher inflammation scores than the hybrid fillers did after receiving the same amount of chlorhexidine. The tissue microenvironment interacts with chitosan-based materials through their biodegradable and bioactive properties, which produce different responses. The properties which enhance integration between cells also make tissues more vulnerable to chemical damage (16).

The study results from a medical perspective contradict the standard approach, which uses identical antiseptic treatments for all fillers regardless of their materials. The use of antiseptics in excess amounts could lead to increased post-procedural inflammation when biodegradable fillers are applied to the skin (17).

Importantly, these findings remained statistically significant after reanalysis using a mixed-effects model that accounted for repeated measurements and clustering of injection sites within animals, confirming that the observed dose-dependent effects were not attributable to violations of independence assumptions.

Several limitations of the present study should be acknowledged. The assessment of tissue response used clinical scoring methods, which did not include histological or molecular tests to evaluate only the visible inflammatory changes at the macroscopic level. The study did not evaluate tissue changes which occur during long-term periods and when inflammatory responses begin after the procedure. The evaluation of living organisms through in vivo methods across time provides vital data which standard laboratory tests

using in vitro methods fail to deliver (17). A limitation of this study is the use of a single topical chlorhexidine application; repeated or prolonged exposure, as may occur in some clinical contexts, was not evaluated and may influence the magnitude of tissue response.

The study findings demonstrate that tissue tolerance depends on two main factors, which include chlorhexidine concentration and the materials which make up the filler. Low-concentration chlorhexidine shows promise for medical treatment of hybrid and chitosan-based fillers, but high concentrations of the solution lead to increased inflammation that mainly affects materials which break down over time. The study results show that antiseptic treatment for dermal filler procedures needs to be determined by the specific requirements of each patient. The assessment of tissue response was based on a semi-quantitative clinical scoring system; histological evaluation was beyond the scope of the present study.

Conclusion

The study conducted in living tissue demonstrated that tissue tolerance to these substances depends on both the amount of chlorhexidine and the materials which make up the fillers. Low-concentration chlorhexidine is commonly used in clinical practice and demonstrated favourable tissue tolerance in this model, but chitosan-based fillers with elevated chlorhexidine levels produce increased inflammatory responses. Healthcare providers need to exercise careful selection when choosing antiseptic protocols for dermal filler procedures, according to the study findings.

List of Abbreviations

CHX: Chlorhexidine
HA: Hyaluronic Acid
CaHA: Calcium Hydroxylapatite

Declarations

Ethics Approval and Consent to Participate

All animal procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC), College of Dentistry, Al-Bayan University (approval No. 12/2023; approval date: 15 March 2023; protocol reference: BD-IACUC-CHX-FILLER-22). The study was conducted in accordance with national regulations for laboratory animal care and complied with the ARRIVE 2.0 guidelines. All procedures complied with the ARRIVE 2.0 reporting guidelines for animal research.

Consent for publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability

Data for this work are available.

Competing Interests

None.

Funding Sources

None.

Author Contributions

Basma Kamal Ahmed assisted in the development of the idea, study design and method supervision, along with manuscript reviewing. Yaqoob Sami contributed to data analysis and interpretation and helped to revise the manuscript. Asmaa Yousuf carried out the experimental work, collected data, and participated in the initial manuscript draft. Laboratory mix, Tamarah Mazin assisted with laboratory work and was involved in the organisation and validation of the data. Manar Emad participated in the literature study, data analysis, and final manuscript revision. The final manuscript was read and approved by all authors.

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