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# Effectiveness of Chitosan on Oral Wound Healing: A Systematic Review

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**Abstract:**

***Aim:*** To assess the effectiveness of chitosan in oral wound healing.

***Methods:*** A literature review was performed using, Ovid Medline, Pubmed, Science Direct, Wiley Online Library, CINAHL, Cochrane Library, Grey Literature, OSF and Scopus and by using MeSH "Chitosan AND Oral wound Healing". According to prisma guidelines the mesh terms were altered in each search engine.

***Results:*** 6 out of the 7 included articles showed positive effects of Chitosan in oral wound healing. Statistically significant improvement was found with wound healing using Chitosan derivate Hemcon Dental Dressing with $p<0.01$.

***Conclusion:*** In the available literature, application of chitosan is effective in the process of oral wound healing and it acts by facilitating the wound healing process.

**Keywords:** Chitosan, Oral Wound Healing, Hemcon Dental Dressing

## INTRODUCTION:

Efficient wound healing in the oral cavity and methods to increase more adequate methods to promote and facilitate uncomplicated oral wound healing are the topics of interest these days as there are increasing problems such as inconsistent and longer healing time, increased pain, various allergies, infections and adverse reactions shown by conventional methods such as various medicated pressure packs under biting pressure. This study aimed to assess the use and effectiveness of using Chitosan via Chitosan derivatives such as Hemcon Dental Dressing (HDD) and Chitosan mouthwashes to evaluate the progress of oral wound healing and time required for healing by using Chitosan derivatives in the oral cavity in hopes of utilizing more Chitosan derivatives in dentistry for uncomplicated and satisfactory oral wound healing.

Disruption of the normal anatomical structure and function of a body part is called as a wound. It normally varies from a simple break in epithelial integrity of the skin or it can be deeper, extending into subcutaneous tissue with damage to other structures such as tendons, muscles, vessels, nerves, parenchymal organs and even bone.[1] Wound healing is a complicated physiological process that is dependent on a number of inter-related factors. Wound assessment and treatment should be based on an understanding of normal tissue repair and factors affecting the process.[2]

Initially wound healing starts with haemostasis where the activation of clotting system takes place and platelets are in contact to with the collagen thus causing aggregation and activation. Fibrin mesh formation is activated to produce a stabilised clot. This haemostasis brings forth the inflammatory reactions. Following this is the proliferative phase where there is formation of new connective tissue followed by formation of granulation tissue and re-epithelialisation and the process is completed by the maturation stage.[2,3] In recent times, biomaterials such as chitosan, cellulose, heparin, collagen, hyaluronic acid, etc., are being assessed for wound healing whose function is to optimize regeneration, protect against infection, guarantee uniform cell distribution, maintain cell viability and phenotype, induce migration, proliferation of epithelial cells, fibroblasts and endothelial cells, while fulfilling prerequisites concerning structure and biocompatibility to promote wound healing.[4]

Chitin, poly (β -(1-4)-N-acetyl-D-glucosamine), is a natural polysaccharide of major importance and it is produced by various organisms. It is the most abundant polymer after cellulose. Chitosan is a linear biopolymer formed by the deacetylation of chitin. It is a cationic polysaccharide containing copolymers of glucosamine and its molecular structure comprises a linear backbone linked through glycosidic bonds with random copolymer of β-(1–4)-linked D-glucosamine and N-acetyl D-glucosamine. As the degree of deacetylation of chitin approaches about 50% (depending on the origin of the polymer), it becomes slowly soluble in aqueous acidic media and is henceforth called chitosan.[5] Due to Chitosan's role in promoting healing in the early stages, it was thus reported that Chitosan plays an important role in wound healing.[6]

Chitin and chitosan have antibacterial properties and so it was used as a wound dressing in veterinary field as it helps to accelerate the healing process. In addition, chitosan

oligomers and chitin oligomers, originating from enzymatic degradation in a wound environment, produce stimulatory effects on macrophages.[7] Chitosan is also well compatible with gingival fibroblasts and has a synergistic response with some growth factors such as Platelet-derived-growth factor (PDGF) which is one of the many growth factors that regulate cell growth and division; also plays a significant role in angiogenesis and may stimulate cell proliferation in gingival fibroblasts.[8] A new chitosan-based haemostatic oral wound dressing Hemcon Dental Dressing (HDD) was developed which is derived from the US military HemCon Bandage combat wound dressing. It is manufactured from highly refined and purified insoluble shrimp shell chitin.[9]

**Objectives:**
To assess the effectiveness of chitosan as an agent that facilitates the process of oral wound healing.

## MATERIALS AND METHODS:

Randomized controlled trails with interventions were included in the study.

## ELIGIBILITY CRITERIA:

**Inclusion Criteria**

- Studies conducted during 2000-2019
- Full text articles
- Studies with randomised controlled trials

**Exclusions Criteria**

- Animal studies
- Pilot studies
- Studies without Chitosan based measures for facilitating healing were excluded.

## SEARCH STRATEGY:

Published results on Chitosan's effects on wound healing which includes original articles and research papers in databases such as Ovid Medline, Pubmed, PMC, Science Direct, Wiley Online Library, CINAHL, Cochrane Library, Grey Literature, OSF and Scopus were taken into study for review in April-May 2019. A literature search to collect relevant data was performed using MeSH terms "Chitosan AND oral wound healing".

According to the prisma guidelines the mesh terms were altered in each search engine when the results went too many or too less.

## RESULTS:

The search yielded 273 articles and 7 articles were independently assessed among these eligible articles. Three tables were included, Figure 1 shows Flow diagram of the reports identified, screened, assessed for eligibility, excluded and included for the review.

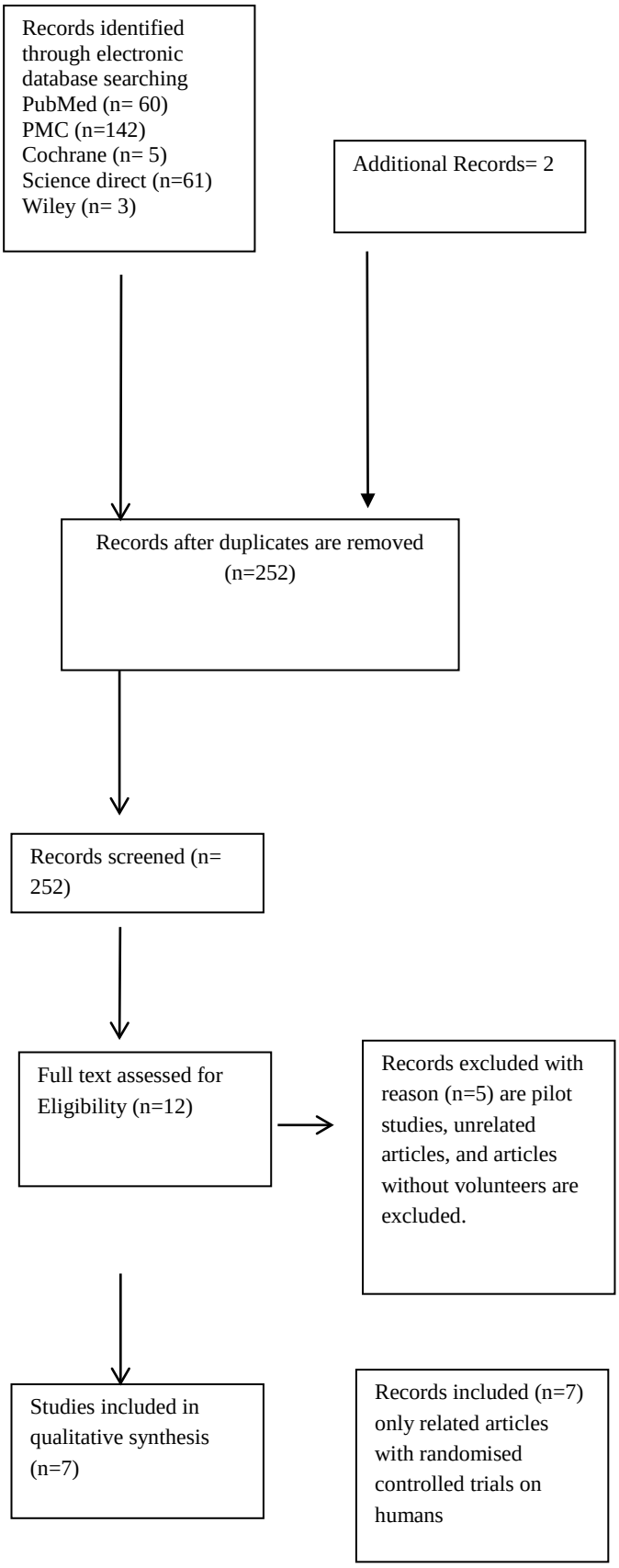


**FIGURE 1:** FLOW DIAGRAM SHOWING NUMBER OF STUDIES IDENTIFIED, SCREENED, ASSESSED FOR ELIGIBILITY AND INCLUDED FOR SYSTEMATIC REVIEW

**TABLE 1: CHARACTERISTICS OF INTERVENTIONS IN THE STUDY:**

| AUTHOR NAME | YEAR | SAMPLE SIZE | DURATION | INTERVENTIONS |
|---|---|---|---|---|
| Jay P. Malmquist et al[10] | 2008 | 17 (8 males and 9 females) | 7 days | Test Group: Trimmed custom-cut HDD material was placed in extraction socket (74 sites) Control Group: Conventional treatment with standard folded sterile cotton gauze dressings placed with biting pressure in the extraction socket (52 sites) |
| Tejraj P. Kale et al[11] | 2012 | 40 (33 males and 7 females) | 7 days | Test Group: Trimmed custom-cut HDD material was placed in extraction socket Control Group: Conventional treatment with standard folded sterile cotton gauze dressings placed with biting pressure followed by suturing if necessary in the extraction socket |
| Roberto Pippie et al[12] | 2015 | 20 (15 males and 5 females) | 6 days | Test Group: HDD Control Group: Common haemostatic sponge (CollaPlug, Zimmer Dental) stabilized in situ with a Vicryl Plus external criss-cross inverting horizontal mattress suture |
| K.R. Ashok Kumar et al[13] | 2016 | 30 (12 males and 18 females) | 7 days | Test Group: Hemcon dental dressing applied under finger pressure in extraction site Control Group: Conventional method of pressure pack with a sterile gauze piece under biting pressure in the socket |
| Marta Madrazo-Jiménez et al[14] | 2016 | 25 (Gender unspecified) | 43 days | Test Group: 10 ml of topical gel composed of chitosan, 0.2% chlorhexidine, allantoin and dexpanthenol on the surgical wound three times a day for 10 days was applied after antibiotics were taken. Control Group: Only antibiotics were taken |
| Fatemeh Rahmani et al[15] | 2018 | 20 (8 males and 12 females) | Duration unspecified | Group 1: Chitosan mouthwash Group 2: Triamcinolone Mouthwash Group 3: Biogel preparation |
| Akshat Gupta et al[9] | 2019 | 27 (Gender unspecified) | 12 weeks | Test Group: HDD was placed followed by pressure packs given with sterile cotton gauze dressing Control Group: Pressure packs given with sterile cotton gauze dressing |

Table 1 shows the characteristics of the studies that have been chosen for the systematic review. The following characteristics were studied: Name of the author, year of study, sample number including their details such as gender and the interventions involved in the study. All the included studies were randomised controlled trials and were conducted strictly in the oral cavity. HDD which is a chitosan derivative has been used majority of the times in the test group for assessing wound healing and it was compared with others such as Triamcinolone and conventional pressure packs.

**TABLE 2: CHARACTERISTICS OF OUTCOME AND EFFECT MEASURES**

| AUTHOR NAME | YEAR | EFFECT MEASURE | RESULTS |
|---|---|---|---|
| Jay P. Malmquist et al[10] | 2008 | Visual and comparative methods were incorporated in grading healing from scale of 1 (significantly worse than control), 2 (the same as control), and 3 (significantly better than control) | Statistically significant wound healing was found to be present in 24 of 74 HDD test sites.(P value<.001) None of the 50 control sites showed superior wound healing compared to HDD sites. Rest of the 50 test sites had similar wound healing as compared to 50 control sites. |
| Tejraj P. Kale et al[11] | 2012 | On basis of epithelisation using the visual analogue scale (VAS), the presence of liver clots, pus discharge, dry socket, and the extent of the sinus opening. A grading scale for comparison between test and control site was used from 1 to 3: 1 (significantly worse than control), 2 (the same as control), and 3 (significantly better than control) | Statistically, 29 of 40 test sites showed significantly better postoperative healing when compared to the control sites. (P value<.001) |
| Roberto Pippie et al[12] | 2015 | Landry, Turnbull, and Howley healing index, adequately modified to the needs of the study. | Statistically significant result was shown in experiment group than control group. 17 out of 20 test sites has shown better wound healing compared to 20 control sites, 2 test sites showed similar wound healing compared to 20 control sites and 1 test sites showed worse wound healing compared to 20 control sites.(P value=.0001) |
| K.R. Ashok Kumar et al[13] | 2016 | Visual and comparative methods were incorporated in grading healing from scale of 1 (significantly worse than control), 2 (the same as control), and 3 (significantly better than control) | Statistically significant healing in HDD test sites was seen compared with control sites. On Day 1, 22 out of 30 test sites showed improved wound healing than 30 control sites and 8 test sites showed same wound healing as that of 30 control sites. On day 3 all 30 test sites showed better wound healing than all control sites. (P value=.0001) |
| Marta Madrazo-Jiménez et al[14] | 2016 | Visual methods by checking wound edges, colour of oral mucosa and wound closure and wounds were graded as good, acceptable or bad | Statistically significant improved healing in HDD study sites compared with control sites was observed on Day 7 where 20 out of 25 test sites showed good wound healing than control sites and 7 out of 25 control sites showed good wound healing compared to test sites. (P value=.001) On Day 14, 21 test sites showed good wound healing than control sites and 12 control sites showed good wound healing compared to test sites. (P value=.01) |
| Fatemeh Rahmani et al[15] | 2018 | Comparison of complete healing time of all 3 groups. On the basis of pain relief, wound healing and absence of pseudo membranous layer, healing time was recorded | Statistically significant less wound healing time was taken for Chitosan than Biogel (p value<0.005) preparation however Triamcinolone had least healing time (p value=0.310) in comparison to Chitosan and Biogel. Chitosan group took approximately 7 days for healing, Triamcinolone group took approximately 6 days for healing and Biogel group approximately took 9 days for healing. |
| Akshat Gupta et al[9] | 2019 | Detection of presence of or absence of blood clot, granulation tissue or fibrous tissue over the socket and condition of wound epithelium at various intervals.<br>Wound healing was compared between the right and left side and categorized into one of the three scores as −1(Worse than right), 0 (Same as right), +1(Better than right). | Statistically, test group was superior to control in event of wound healing and erupted tooth sites had better healing than unerupted tooth sites.(Week 1 p value=.016,Week 2 p value=.002,Week 3 p value=.002 and Week 4 p value=.032) |

**TABLE 3: CHARACTERISTICS OF BIAS IN DIFFERENT STUDIES TAKEN FOR REVIEW**

| AUTHOR NAME | RANDOM SEQUENCE GENERATION | ALLOCATION CONCEALMENT | BLINDING OF OUTCOME | INCOMPLETE OUTCOME | SELECTIVE BIAS | OTHER BIAS |
|---|---|---|---|---|---|---|
| Jay P. Malmquist et al[10] | – | – | – | ? | – | – |
| Tejraj P. Kale et al[11] | – | ? | – | – | – | – |
| Roberto Pippie et al[12] | – | – | – | – | ? | + |
| K.R. Ashok Kumar et al[13] | ? | + | ? | + | + | ? |
| Marta Madrazo-Jiménez et al[14] | + | _ | + | ? | + | + |
| Fatemeh Rahmani et al[15] | + | _ | ? | + | + | ? |
| Akshat Gupta et al[9] | ? | + | + | ? | + | + |

+: Low risk of Bias; -: High risk of Bias; ?: Unclear risk of bias

Table 3 shows the bias analysis of the studies included which were categorised as high risk of bias, low risk of bias and unclear risk of bias.

## DISCUSSION:

In this systematic review, 7 studies have been taken into consideration for assessing the effectiveness of Chitosan on oral wound healing. Chitosan derived mouthwashes and dressings such as HDD were taken into consideration. Visual and comparative studies along with utilizing scales such as VAS were used in various studies for assessing wound healing.

Tejraj P. Kale et al (2012) conducted a randomised controlled trial with 40 subjects undergoing oral anticoagulative therapy. Extractions of 80 teeth were done which were divided into test group and control group. HDD was placed in the sites of the control group whereas conventional method of pressure pack with sterile gauze under biting pressure was used in the test group. Better healing of the wound was observed in the test group having HDD dressing thus proving the action of Chitosan in facilitating oral wound healing. [11]

Jay P. Malmquist et al (2008) conducted a single randomised controlled trial with 17 subjects. All subjects had 2 or more surgical sites so that they could have internal surgical control sites. After receiving subject's consent, HDD was placed in the sites randomly making these the experiment group sites and then conventional methods such as cotton rolls were placed in other sites making these the control group sites and the wound healing were assessed in both of these groups. Subjects were assessed on the seventh day postoperatively. The experiment group sites showed better healing when compared to the control group sites.[10] These studies are similar to a study reported by Shen et al[16]; the effect of chitosan on subsequent release of growth factor after the activation of human platelets instead of thrombin and found that the growth factors released from human platelets stimulated by chitosan exposure contributes to wound healing.

Roberto Pippi et al (2015) conducted a randomised controlled trial with 20 subjects. Extractions of 2 teeth were done from these subjects and intraorally there was a control site and test site. HDD was applied on the test site and a common haemostatic sponge (CollaPlug, Zimmer Dental) in the control site was used and stabilized with a Vicryl Plus external criss-cross inverting horizontal mattress suture. The progress of wound healing was checked 6 days later and found that socket healing was more efficient in the test group in than in the control group. HDD apparently seemed to decrease postoperative side effects and attain rapid and comparatively better soft tissue healing, which may be due to presence of periodontal pockets and absence of keratinized gingiva, even when present only on one side of the alveolar process [12]

K.R. Ashok Kumar et al (2016) conducted a split mouth randomized controlled trial on 30 subjects. Two extraction sites, one on each different or same quadrant were randomly allocated into study and control sites. HDD was placed in the test site and in control sites: conventional

method of pressure pack with a sterile gauze piece under biting pressure was done. 22 of 30 HDD study groups showed obvious better healing in comparison to control group at day 1 and showed complete healing at day 3. HDD study sites healed comparatively better than control sites. This shows that HDD which has Chitosan as main component helps in promoting oral wound healing. [13]

Marta Madrazo-Jiménez et al (2016) conducted a prospective randomised controlled trial study with 25 subjects. The experiment group was treated with 10 ml of topical gel composed of chitosan, 0.2% chlorhexidine, allantoin and dexpanthenol on the wound thrice a day for 10 days while the control group was kept devoid of treatment. Standard procedures after extraction were done on both groups. Antibiotics were prescribed to both the groups. Wound consistency and appearance was considered as good, acceptable or bad after assessing it for 14 days. Pain was also measured using VAS from 0 to 10. Wound appearance and consistency was better, on day 7 and day 14 of the follow-up session. Both the groups did not show any significant adverse effects or complications. This study thus showed that the mouthwash containing chitosan helped in facilitating wound healing.[14]

Fatemeh Rahmani et al (2018) conducted a randomized double-blind crossover trial consisting of 20 subjects having minor recurrent aphthous stomatitis. The subjects were studied under 4 periods. In the first period, no mouthwashes were given to the subjects, in the next 3 periods, Biogel, Chitosan and Triamcinolone mouthwashes were given randomly for the treatment and the wound healing progress was assessed on the $1^{st}$,$3^{rd}$,$5^{th}$,$7^{th}$ and $10^{th}$ day. The healing time was associated with pain relief and wound healing and absence of pseudo membranous layer were recorded as number of days in all 4 periods for every subject. The mean healing time for Chitosan was approximately 6 days and satisfaction rate was higher than that of Biogel mouthwash. Effectiveness Index was used to check the improvement of wound healing. Mean EI of ulcer size and VAS was considered as "healed" on the $7^{th}$ day. Chitosan mouthwash demonstrated more efficiency in decreasing ulcer size when compared to the Biogel group which confirmed the wound healing effect of Chitosan however Triamcinolone was more slightly efficient in controlling and facilitating oral wound healing. Inflammatory and immune cells such as polymorphonuclear cells, macrophages, fibroblasts and the angioendothelial cells were activated by Chitosans and they promote the wound healing process. [15,17]

Akshat Gupta et al (2019) conducted a prospective randomised control trial consisting of 27 subjects where mandibular molars were extracted on both left and right sides. Control site and Test site was randomly decided between left and right extraction sites on the mandible. The HDD was placed on the test site and on the control site and were assessed on 24hr, 72hr, 5th day, 7th day, 2nd, 4th, 8th, 12th week postoperatively for pain and wound healing. Test group had better wound healing properties as compared to control group. In the first week, 8 erupted teeth did not show differences in healing in both test and control sites however 12 erupted teeth showed significantly better healing in test site compared to control site. In second and fourth week, 17 erupted teeth showed significantly better healing in test site compared to control site and 7 unerupted teeth significantly showed better healing in control site than the test site. During the eighth week the 15 erupted teeth showed obviously better healing in comparison to the 7 unerupted teeth in which control site healed much better than test group. Chitosan improved the healing of extraction socket in erupted teeth however it has less effect in an impacted or unerupted tooth. [9]

In this systematic review, 6 out of 7 included studies showed significant and superior healing effects of Chitosan in comparison to other conventional methods such as Biogel Preparations or utilising of pressure packs with biting pressure. A single study by Fatemeh Rahmani et al [15] showed that Triamcinolone was marginally but significantly more superior to Chitosan on healing of oral wounds caused by Recurrent Aphthous Stomatitis.

A higher risk of bias was observed in studies conducted by Jay P. Malmquist et al, Tejraj P. Kale et al and Roberto Pippie et al however there was comparatively lesser risk of bias shown in the other studies. In the majority of the studies risk of bias was unclear due to difficulty in assessing due to incomplete information or information not been provided for the study.

## CONCLUSION:

The study concluded that chitosan which is present as a component in dental dressings such as HDD plays an important role in facilitating oral wound healing especially in extraction site wounds. It is more effective in wound healing of extraction sites of erupted molars. Chitosan derivatives are very efficient in controlling time taken for wound healing and appearance of wound also gets better on its application and pain is considerably reduced. However in conditions such as recurrent aphthous stomatitis, Chitosan is inferior to conventional medications such as Triamcinolone and thus other alternatives must be considered for the process of wound healing in this.

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