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Role of topical hemocoagulase in postoperative wound healing following dentoalveolar extraction: A systematic review

Dyna Albert*
Postgraduate Student, Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India
*Corresponding author

M. R. Muthusekhar
Program Director, Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India

Sudharsan Sivashanmugam
Fellow in oral and maxillofacial trauma, Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India

Geetha Sridharan
Fellow in orthognathic surgery, Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India

***Abstract*---**Background: Wound healing consists of sequential overlapping events, namely, hemostasis, inflammation, proliferation and remodelling. Disruption of one or more of these events results in impaired healing of the wound which causes functional, esthetic and emotional burdens in the future. Hemocoagulase is an enzyme derived from snake venom which is widely used for its hemostatic properties. In recent times, it has shown to enhance wound healing and reduce scar formations. The objective of this systematic review is to compare the effectiveness of topical hemocoagulase and placebo/control in postoperative wound healing following dentoalveolar extraction. Methodology: A systematic review was carried out to explore the use of hemocoagulase in wound healing of dental extraction sockets. The Databases of PubMed, Cochrane and Google scholar were searched for the related topics along with a complimentary manual search of all oral surgery journals till December 2020. Results: A total of eleven

studies were revealed on data search. After application of inclusion and exclusion criteria based on the filtering process, two clinical trials were included for final appraisal. Of the two clinical trials, one compared topical hemocoagulase with placebo and one clinical trial compared topical hemocoagulase with control. Both trials included patients undergoing bilateral dental extraction. The quality of randomized controlled trials included in this review are of moderate risk of bias according to Higgins and Green Cochrane checklist and is varied to state that there is a difference in the postoperative wound healing. Conclusion: There was statistically significant better wound healing where hemocoagulase was used. However, the limitation was the smaller number of literature available. Hence, more properly designed randomized clinical trials are needed to evaluate the role of topical hemocoagulase in the healing of surgical wounds.

***Keywords*---**hemocoagulase, topical, hemostatic agent, wound healing, infection, dental extraction.

Introduction

Skin and mucosa contribute to the innate immunity by serving as a mechanical barrier to microorganisms and foreign bodies[1]. Insult to the skin or mucosa disrupts the barrier function and the restoration of the same is directly related to the healing of the wound[2]. Wound healing is a complex process with a series of overlapping events which commences from the moment of injury or insult and is sequenced as follows: haemostasis (0–several hours after injury), inflammation (1–3 days), proliferation (4–21 days) and remodelling (21 days–1 year)[3]. Deregulation of any of the above steps results in impaired wound healing, which if related to the skin, imposes functional, esthetic and emotional burdens[4]. In general, postoperative wound healing is affected by patient related factors, intraoperative management and postoperative wound care[5]. Interventions are designed to modify the above factors in favour of improved quality of wound. These interventions range from general wound care to systemic or topical agents and LASER therapy[6].

Hemocoagulase is a hemostatic agent isolated from the venom of poisonous snakes like Bothrops jararaca or Bothrops atrox. It is an enzyme complex with coagulative and antihemorrhagic properties which intervenes from the first step of wound healing (ie) hemostasis[7]. The mechanism of action is such that it accelerates the conversion of fibrinogen to fibrin polymer thereby increasing the interaction of platelets with fibrin clot to coagulate the blood. The fibrin called so formed is highly resistant to the action of plasmin thereby increasing the quality and quantity of collagen fibrils under it[8]. Hence, hemocoagulase improves wound healing by reducing bleeding time, increasing cell division and capillary network formation while also serving as an effective hemostatic agent. It is commercially available as injections and topical agents[9,10]. The aim of this systematic review was to analyse the existing literature to compare the effectiveness of topical hemocoagulase used in wound dressing/closure with placebo or conventional dressing/closure technique in aiding postoperative wound healing following dentoalveolar extraction

Methodology

Protocol registration

This systematic review was registered in PROSPERO under the registration number CRD42021239534.

Study eligibility and selection

The structured question is "Does the use of topical hemocoagulase in postoperative wound dressing/closure improve wound healing, reduce incidence of surgical site infection and reduce scar tissue formation at the surgical site?

Search strategy

The Databases of PubMed Advanced Search, Cochrane Database of Systematic Review and Google scholar were searched independently by two authors with no publication date restriction using MeSH terms. The search strategy is detailed in Figures 1, 2 and 3. We used free-text terms to search the following journals: British Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, Journal of Cranio Maxillofacial Surgery and Quintessence International Journal. Only articles in English and human species were applied during the electronic search to include all the possible clinical trials that are relevant for the search phase of the systematic review. Reference list of the identified randomized trials were also checked for possible additional studies. Difference of opinion concerning inclusion of a study was resolved by discussion and no article from the reference list was included after reviewing abstracts.

Study selection and data collection

The PICOS of the study was as follows: P- patients of any age and gender undergoing dentoalveolar extraction, I- topical hemocoagulase, C- control/placebo, O- wound healing, wound infection, scar formation, S- randomized clinical trial, prospective clinical trial.

Data synthesis

Only randomized controlled trials and prospective clinical trials were included in this review while case reports, case series, invitro and experimental studies, retrospective studies, review articles, studies in which statistical analysis was not mentioned and studies published in languages other than English were excluded. Data extraction for general characteristics of studies and variables of outcome was done independently by two authors. For each trial the following data were recorded: author, journal, study design, sample size, participants/ groups, methodology, parameters, statistical analysis and result.

Quality Assessment and Risk of Bias

Quality Assessment criteria to evaluate the studies were decided by the two

review authors in accordance with CONSORT guidelines. The risk of bias for each study was independently assessed by the review authors and conflicts concerning risk of bias were sorted by discussion. Guidelines according to Higgins and Green Cochrane reviewer's handbook 2009 was followed.

Results

Study selection

Electronic search was carried out using the keywords in the Search engines- PubMed, Cochrane and Google Scholar which yielded a total of 11 articles. Hand search yielded 1 article which was the same as that obtained in electronic search. Based on pre-set inclusion and exclusion criteria, the titles of the studies identified from the search were assessed independently by two review authors. Conflicts concerning inclusion of the studies were resolved by discussion. Three articles were excluded after reading titles. Seven titles were identified from the search after excluding four duplications. Abstracts of selected articles were reviewed independently. No articles were excluded after reading the abstract. Full text articles were retrieved for four relevant studies. One article was excluded after reading the full text and three articles were included in the qualitative synthesis (Figure 1) . The characteristics of included and excluded studies are detailed in Table 1 and Table 2.

Risk of bias

Both the trials included in this review have a level of evidence 1b. Both are randomized clinical trials; thus, the level of evidence is high (Table 3). Risk of bias is low to moderate. The quality of evidence is low (Tables 4 and 5).

Narrative synthesis

Wound healing: There was no uniformity in the assessment tool used for wound healing among the two studies. Aslam et al assessed wound healing by blood smear quantification and histological evaluation while Shenoy et al used clinical and histological assessments of wound healing. Both studies showed significant improvement of wound healing. Wound infection: Only Aslam et al studied wound infection in the form of microbial colonization and found no statistically significant difference between hemocoagulase and placebo group. Scar Formation: None of the included studies assessed the quality of scar formed. (Table 6)

Discussion

Surgical wound healing may occur by primary, secondary and tertiary intention depending on the nature, duration and the extent of injury[11]. Surgical wounds may be classified as clean, clean-contaminated, contaminated and dirty[12]. Well approximated clean wounds heal by primary intention with minimal scarring. Unapproximated or improperly approximated wounds heal by secondary intention with granulation tissue formation and have more tendency to scar. Healing by tertiary intention occurs when there is an intentional delay in the closure of wounds[13]. Patient factors that affect wound healing are patients age, body mass,

nutritional status, oxygenation, systemic condition and medication[14,15,16]. Intraoperative management of wounds include incision planning, tissue handling, wound closure devices and techniques[17]. Postoperative wound management includes general wound care, topical scar reducing and antimicrobial agents[18,19]. Treatment for scars includes dermabrasion, micro needling, injections, pressure therapy, radiotherapy, fillers and surgical revision of scars[20,21,22,23,24]. It is prudent to reduce the occurrence of postoperative scar as effectively as possible in order to void future aesthetic, functional and financial burdens associated with scarring[25,26].

Hemocoagulase is being used popularly as an hemostatic agent and its role in wound healing remains unpopular[27,28]. Hemocoagulase has thrombin-like actions with the exception that it is not inhibited by Antithrombin and can remain in the blood stream along with antithrombin. Also, unlike thrombin, hemocoagulase is not absorbed by the fibrin clots and is therefore not neutralized by that mechanism[29]. It hastens the process of hemostasis which is the first step in wound healing. Studies have illustrated the role of hemocoagulase in improving the collagen content, inducing angiogenesis, enhances epithelialization, increased fibrin deposition and reduced inflammation[10,29]. Commercial formulations of hemocoagulase are available under trade names botroclot, botropase, reptilase etc[10,30,31]. Several invitro and few invivo studies have, in recent years, demonstrated the role of hemocoagulase in wound healing. Studies have demonstrated the effect of systemic hemocoagulase on human volunteers[10,32,33].

There were 2 randomized controlled trials included in this systematic review and both were split mouth designs. Aslam et al compared topical hemocoagulase and placebo while Shenoy et al compared topical hemocoagulase and control. Both trials included patients undergoing bilateral dental extraction.

The results of postoperative wound healing following surgical procedure in both studies showed significant difference with topical hemocoagulase showing better results than placebo or control. The assessment of wound healing varied among the studies. Aslam et al quantitatively and qualitatively measured the parameters of wound healing by hematological quantification using blood smear and histological observation of biopsy specimens from the surgical site. Shenoy et al used clinical and histological scorings for qualitative assessment and histologically measured the various cellular components of wound healing using biopsy specimens from the surgical site. The only study to quantitatively assess the wound infection in terms of microbial accumulation in dental extraction sockets was done by Aslam et al and it did not show any significant difference between topical hemocoagulase and placebo groups.

Implications for practice

There is some evidence that the use of topical hemocoagulase plays a vital role in postoperative wound healing following dentoalveolar surgical procedures. Owing to its dual benefits of being a hemostatic agent and its role in positively affecting wound healing, topical hemocoagulase may be included as part of intraoperative or postoperative wound care in dentoalveolar surgeries especially extraction wounds which heal by secondary intention. The affordability and the availability

of topical hemocoagulase is an additional implication for its routine usage.

Implications for Research

The number of good quality randomized controlled trials included in this review is very limited. There is a lack of evidence supporting the findings. Hence more long term randomized controlled trials are required to prove the role of topical hemocoagulase in aiding postoperative wound healing following dentoalveolar surgeries.

Limitations

Though the level of evidence of the studies included in this systematic review is high, the risk of bias of these studies ranges from low to high. Moreover, the number of studies included in this systematic review is very less due to its stringent inclusion criteria. The included studies are heterogenous in their assessment methods used thereby making direct comparisons unreliable. The authors acknowledge the above limitations of the study and have provided a systematic review with the available evidence.

Conclusions

The number of good quality randomized controlled trials included in this review is limited to state that there is a difference in postoperative wound healing between hemocoagulase and conventional wound dressings or no wound dressing. Hence, more properly designed randomized clinical trials are needed to evaluate the role of topical hemocoagulase in postoperative wound healing and to arrive at a consensus.

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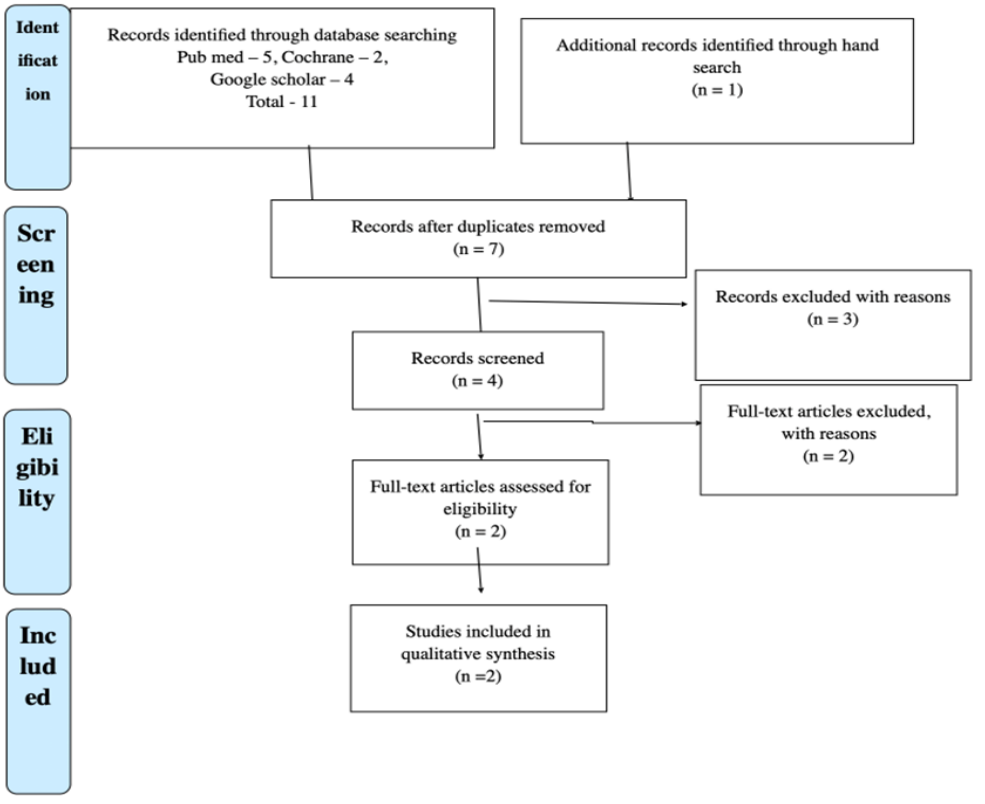

Table 1: Characteristic of included studies

S.No	Author	Study design	Sample size	Age	Technique used	Method of evaluation	Results
1.	Aslam et al, 2013	Split mouth study Double blinded Case- control study	N=20 (total number of site -40)	11-30 years	Patients undergoing bilateral orthodontic extraction of teeth; Hemocoagulase was used on one side and placebo on the other side.	Surgical site microbial accumulation evaluated with number of microbial colonies formed; Histological quantification of blood smear to assess factors influencing wound healing ; histological observation of biopsy tissue of surgical site from 5 randomly selected patients to assess wound healing.	Microbial colonies at 6th hour: No statistically significant difference Blood smear quantification: Statistically significant difference in amount of RBC's at 6th postoperative hour; No statistically significant difference in number of polymorphs, epithelial cells and chronic inflammatory cells at 6h; No statistically significant difference in amount of RBC's and polymorphs at 3rdPOD; Statistically significant difference in number of epithelial cells at 3rdPOD Histological observation of biopsy tissue at 12thPOD (N=5): Statistically significant difference in number of fibroblasts, collagen count and epithelial cell count; No statistically significant difference in number of chronic inflammatory cells and vascularity
2.	Shenoy et al, 2014	Split mouth prospective study	N=38 (total number of site- 76)	18-70 years	Patients undergoing bilateral multiple teeth extraction; Hemocoagulase was used on one site while the other site was used as control	Clinical Scoring of wound healing. Histological Scoring of wound healing, incisional biopsy followed by histological assessment of wound healing parameters	Clinical scoring of wound healing of both groups: No statistically signoficant difference at 7th (p=0.835), 14th (p=0.09) and 21st (p=0.145) POD. Histological scoring of wound healing of both groups: No statistically significant difference at 7th POD (p=0.118) and statistically significant difference at 14th (0.021) POD. Combined analysis of clinical and histological scoring: Hemocoagulase to aid in wound healing (p= 0.004) Histological parameters of both groups: No statistically significant difference between both groups at POD 7; Statistically significant difference in epithelium, collagen quantity, collagen organisation, fibroblast activity, inflammation, degree of fibrosis and presence of fibrin mesh between both groups at POD 14. Combined analysis of histological parameters on POD 7 and 14: Statistically significant difference in epithelium, collagen quantity, collagen organisation and degree of fibrosis between both groups.

Table 2: Characteristic of excluded studies

S.NO	AUTHOR	TITLE	REASON FOR EXCLUSION
1.	Gupta et al (2018)	Efficacy of hemocoagulase as a topical hemostatic agent after dental extractions: a systematic review	Study does not evaluate wound healing.
2.	Hm Hu et al (2015)	The beneficial effects of batroxobin on blood loss reduction in spinal fusion surgery: a prospective, randomized, double-blind, placebo controlled study	Study does not evaluate wound healing.
3.	Di Silvestro et al (2006)	RBone volume reconstruction in atrophic edentulous ridges: placement method of graft-implant unity in single step together with endogenous growth factors	Study is unrelated to PICO of this systematic review.
4.	Singh et al (2016)	Role of local instillation of 1% feracrylum and hemocoagulase on wound healing	Incomplete data, statistical analysis not mentioned and study not as per PICO of this systematic review.

5.	Madhu et al (2019)	Effect of topical hemocoagulase therapy in wound healing	Study is unrelated to PICO of this systematic review

Table 3. Evidence level of selected articles (Based on Oxford Centre of Evidence Based Medicine)

Sl no	Author & Year	Study Design	Level of Evidence
1	Aslam et al 2013	Randomised split mouth study	1b
2	Shenoy et al 2014	Randomized split mouth study	1b

Table 4. Risk of bias- major criteria

S.No	Study	Randomization	Allocation concealment	Assessor Blinded	Drop outs described	RISK OF BIAS
1	Aslam et al	YES	YES	YES	NO	MODERATE
2.	Shenoy et al	YES	NO	YES	YES	MODERATE

Table 5. Risk of bias- minor criteria

S.No	Study	Sample justified	Baseline comparison	I/ E criteria	Method of error
1	Aslam et al	YES	YES	YES	NO
2	Shenoy et al	YES	YES	YES	NO

Table 6. Summation table for individual parameters

S.No	Author and Year	Evaluation period	Outcome
1.	Aslam et al, 2013	6h, POD 3 and POD 12	Wound infection No statistically significant difference was found between both groups in microbial colonisation. Wound Healing Blood smear quantification and histological evaluation showed a significant difference in wound healing between hemocoagulase and placebo groups with hemocoagulase showing better outcome.
2.	Shenoy et	Clinical	Wound Healing

	al, 2014	evaluation - POD 7,14,21 Incisional biopsy- POD 7 or 14	Clinical and histological evaluation showed a significant difference in wound healing between hemocoagulase and placebo groups with hemocoagulase showing better outcome.