International Journal of Clinical Medicine, 2014, 5, 875-883
Published Online July 2014 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2014.514117

Efficacy of Haemocoagulase as a Topical Haemostatic Agent after Minor Oral Surgical Procedures—A Prospective Study

Kaberi Majumder[1], Shalender[2*], J. K. Dayashankara Rao[2], Neelima Gehlot[2], Varun Arya[2], Vijay Siwach[2]

[1]Department of Orthodontics, SGT Dental College, Gurgaon, India
[2]Department of Oral and Maxillofacial Surgery, SGT Dental College, Gurgaon, India
Email: [*]sharma.shalender@rediffmail.com

Received 31 May 2014; revised 30 June 2014; accepted 15 July 2014

Abstract

Purpose: Haemocoagulase is a topical haemostatic agent which provides the adequate haemostasis after minor oral surgical procedures and it has also been proved to be beneficial in promoting wound healing. The aim of this study was to check the efficacy of haemocoagulase in stopping the bleeding and its effect over wound healing after the minor oral surgical procedure. Material & Method: This study is comprised of 150 surgical sites in 75 patients. The subjects were divided into 2 groups in which Group 1 consists of 50 surgical sites in 25 patients and Group II consists of 100 surgical sites in 50 patients. Group I comprised of the group of simple extraction. In these patients one tooth socket was selected as haemocoagulase site and the other socket was the control group in which no drug was used to control haemorrhage. Group II comprised of the group of patients with bilateral impactions. 50 sockets and surgical sites were sprinkled with Haemocoagulase, and 50 sockets and surgical sites were used as control side in which no drug was used to control haemorrhage. Results: In Group I bleeding was stopped with the average time of 1.35 minutes, while at control side bleeding was stopped with the average time of 2.25 minutes. In Group II bleeding was stopped with average time for haemostasis being 1.46 minutes, while at control side the bleeding was stopped in an average time of 2.43 minutes. Conclusion: Haemocoagulase after minor oral surgery not only provides faster haemostasis but also enhances healing.

Keywords

Local Haemostatic Agents, Haemocoagulase, Botox

[*]Corresponding author.

How to cite this paper: Majumder, K., Shalender, Rao, J.K.D., Gehlot, N., Arya, V. and Siwach, V. (2014) Efficacy of Haemocoagulase as a Topical Haemostatic Agent after Minor Oral Surgical Procedures—A Prospective Study. *International Journal of Clinical Medicine*, **5**, 875-883. http://dx.doi.org/10.4236/ijcm.2014.514117

1. Introduction

Persistent bleeding from the inaccessible part of the oral cavity can cause distress, agony and discomfort to the patient and also distract the oral surgeon from operating field leading to frustration and consumption of time. Haemostasis, a physiological arrest of haemorrhage at the site of vascular injury, is a wondrous feat of evolution [1].

Bleeding control in the oral cavity is more concerned as compared to extra oral operating site because already access is less, and if there is bleeding it further decreases the visibility at the surgical site [2]. Bleeding can be due to a variety of local or systemic factors. Predisposing factors include negligence of following post surgical instructions including an avoidance of gargling or rinsing and constant spitting. Pre-existing local infections such as pericoronitis, periapical granulomas and presence of nutritional deficiency such as anaemia may also be sited as being significant to the development of excessive bleeding which may require additional haemostatic agents.

Local haemostatic agents are the compounds that are applied locally to control surface bleeding and capillary oozing. A good agent should achieve haemostasis in a short period; it should be biocompatible, should not retard the healing and should work best for a particular surgical procedure [2].

In the past several of these problems with bleeding required the use of various haemostatic measures such as pressure packing and suturing the socket, and the use of adrenaline pack or acrylic splint, however some time bleeding is primarily from capillaries which cannot be controlled by mechanical means hence haemostatic drug would be of particular value in these procedures.

From the very beginning we are using various topical haemostatic agents like Microfibrillar collagen, gelatine sponge, topical thrombin, feracryllum, bone wax etc. These agents however tend to cause infection and delay the wound healing.

Haemocoagulase is the first pharmaceutical preparation to be used therapeutically and is based on the coagulative and antihaemorrhagic properties of those fractions isolated from the venom of "*Bothrops jararaca*" or "*Bothrops atrox* 2, 3". Haemocoagulase reduces the bleeding time, and promotes wound healing by promoting the growth of capillaries in wound space [3].

Based on its therapeutic uses we have used haemocoagulase as a topical haemostatic agent. With haemocoagulase adequate haemostasis is achieved after the minor oral surgical procedures and it is also proved to be beneficial in promoting wound healing.

2. Materials and Methods

Present study involves the subjects for the simple blind trial comprised of 150 surgical sites in 75 patients indicated for minor oral surgical procedures (impactions, simple extractions, transalveolar extractions), selected serially from the OPD of department Oral and Maxillofacial Surgery under the approval of ethical committee.

Inclusion and exclusion criteria:

1) No bias of gender, age of the patients was 20 - 50 years.

2) Without any local pathology like cyst, tumors, generalized jaw bone or systemic diseases interfering with or influencing haemorrhage, clotting or wound healing.

3) Patients with haemogram, bleeding time and clotting time within normal limits and without any bleeding and clotting disorder.

4) Patients with a fairly good general health (ASA I & II) without any contraindication for minor surgery and/or local anesthesia.

5) Pregnant patients are excluded from the study.

The subjects were divided into 2 groups in which Group I consist of 25 patients with 50 surgical sites and Group II consists of 50 patients with 100 surgical sites.

Group I—comprised of patients who undergone more than one extractions like full mouth extraction for denture, & orthodontic extraction. In these patients one tooth socket was selected as haemocoagulase site in which haemocoagulase was used topically by local irrigation to control haemorrhage and the other socket was the control group in which no drug was used to control haemorrhage. On stoppage of bleeding pressure pack is given on both sites.

Group II—comprised of 50 patients of bilateral impactions (**Figure 1**) in which 50 sockets and surgical sites were sprinkled with haemocoagulase (**Figure 2**, **Figure 3**) so as to stop haemorrhage (**Figure 4**) and 50 sockets and surgical sites were used as control side in which no drug was used to control haemorrhage. On stoppage of

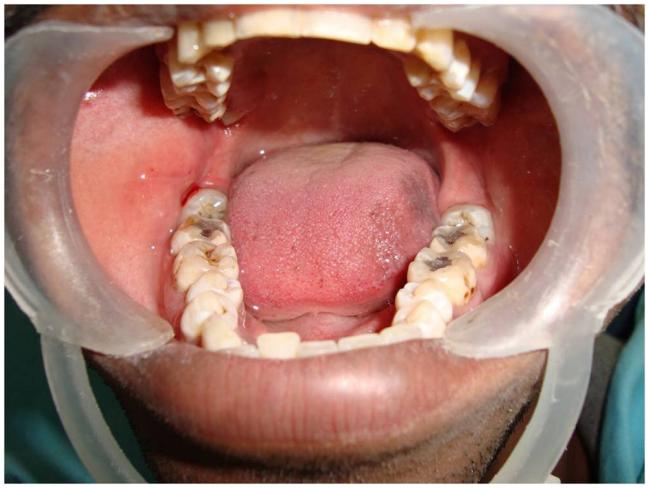

Figure 1. Impacted 48.

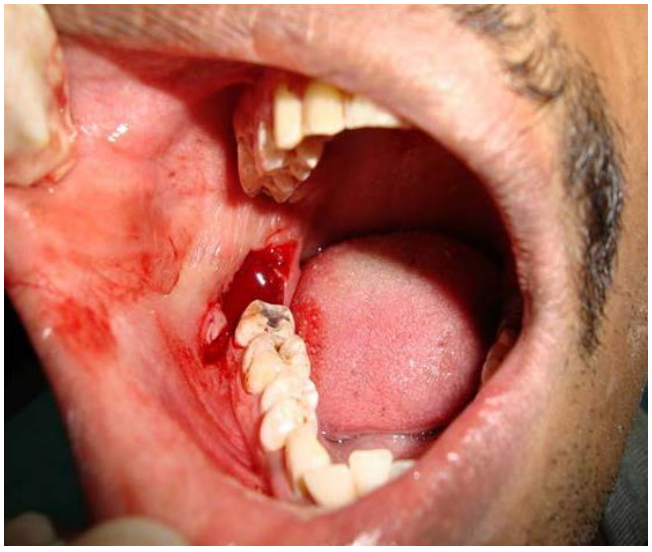

Figure 2. Extraction of impacted 48 done.

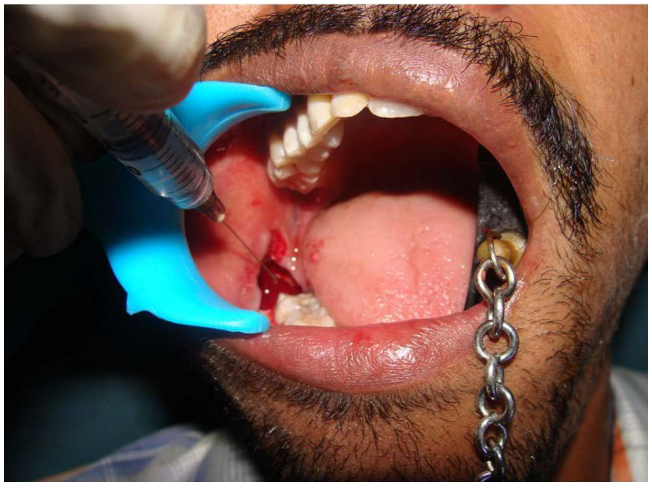

Figure 3. Extraction socket is sprinkled with botroclot.

Figure 4. Clot formation.

bleeding pressure pack is given on both sites.

The criteria for evaluation were:

1) Time taken for bleeding to cease—the time was measured from application of solution into the socket or surgical site up to the complete stoppage of bleeding by using a stopwatch. Bleeding time checked on study and control side by using no other haemostatic measures.

2) Post operative pain and swelling.

3) Nature of wound healing.

4) Complication and side effect.

Post operatively one information chart in the form of a visual analogue scale was given to each patient for evaluating the post operative bleeding, pain, & swelling and patient has informed how to evaluate these parameters.

No patient suffered from uncontrolled bleeding in our study.

Composition—Each ml of Botroclot[1] contains:

- Aqueous solution of haemocoagulase 0.2 cu.
- Chlorhexidine gluconate solution 0.1 %V/V added as preservative and antiseptic.
- Water for injection quantum sufficient (q.s.).

Mechanism of action:

1) Haemocoagulase

Haemocoagulase has two different enzymatic activities, which promote blood coagulation. One of these accelerates the conversion of prothrombin to thrombin (thromboplastin like enzyme), while the other one causes a direct transformation of fibrinogen to fibrin monomer, which can be converted by thrombin into fibrin clot (thrombin like enzyme) [2].

2) Chlorhexidine

a) It acts on bacterial cell wall and gets immediately absorbed on the surface of bacteria. This effect depends upon the concentration of Chlorhexidine solution.

b) It is an antiseptic and acts by disrupting the bacterial cell membrane.

Dosage:

1) Local haemorrhagic therapy—in localized haemorrhage after extraction capillary haemorrhage due to surgical intervention 5 to 10 drops of haemocoagulase placed at socket site.

2) Prophylaxis for haemorrhage—1 ampoule of 1cc (contains haemocoagulase > 1 NIH unit) I.M. 2 to 3 hours prior to intervention and 1 ampoule of 1 cc I.V. 30 minutes prior to surgical intervention.

3) Treatment for haemorrhage—1 ampoule of 1 cc (contains haemocoagulase > 1 NIH unit) I.M or I.V repeated after a few hours (8 hourly) until desired effect obtained.

[1]Market preparation for haemocoagulase.

Contraindication:

- Venous and arterial thrombosis.
- Disease with tendency to intravascular coagulation.

3. Results

In this study 150 surgical sites in 75 patients are divided into two groups. The student t-test for equality of means was used to draw the results.

In Group I bleeding was stopped at haemocoagulase side in a range of 1.00 - 1.75 minutes in all the patients with average time to achieve haemostasis being 1.35 minutes. While at control side bleeding was stopped in range of 1.75 - 2.75 minutes with average time to achieve haemostasis was 2.25 minutes. Hence faster haemostasis achieved at haemocoagulase side (P = 3.95) statistically significant (**Table 1**).

Table 2 showed that at haemocoagulase side 18 patients (36%) had pain after 2 hours increasing up to 20 patients (40%) by 3 hours while by 6 hours number of patients reduced to 8 (16%). While on a control side 8 patients (16%) had pain after 3 hours increase up to 25 patients (50%) by 6 hours and reduced to 12 patients (24%) by 9 hours (P = 0.703).

Table 2 also showed that at haemocoagulase side 13 patients (26%) had swelling after 1 hour and reduced to 7 patients (14%) by 2 hours. At the control side 20 patients (40%) had swelling after 1 hour and reduced to 16 patients (32%) by 3 hours (P = 0.273).

In Group II bleeding was stopped in a time range of 1.00 - 2.00 minutes in all the patients on haemocoagulase side with average time for haemostasis being 1.49 minutes. While at control side the bleeding was stopped in a time range of 1.75 - 3.00 minutes with an average time for haemostasis being 2.47 minutes. Hence faster haemostasis was achieved at haemocoagulase side (P = 4.23). Statistically significant (**Table 3**).

Table 4 showed that 13 patients (26%) had swelling after 9 hours increasing to 23 patients (46%) by 2nd day and reduced to 3 patient (6%) by third day in the haemocoagulase side patients, while 10 patients (20%) had swelling after 9 hours increasing to 19 patients (38%) by 2nd day and reduced to 13 patients (26%) by 3rd day in control patients (P = 0.706).

Table 1. Time required for stoppage of bleeding.

Time\minute	Haemocoagulase side	Control side
0.0 - 1.0	05	00
1.0 - 1.25	20	00
1.25 - 1.50	18	00
1.50 - 1.75	07	08
1.75 - 2.00	00	22
2.00 - 2.25	00	09
2.25 - 2.50	00	08
2.50 - 2.75	00	03

Table 2. Duration of pain and swelling post operatively.

Time\minute	Haemocoagulase side (pain)	Control side (pain)	Haemocoagulase side (swelling)	Control side (swelling)
1 hour	04	03	13	20
2 hours	18	02	07	16
3 hours	20	08	01	09
6 hours	08	25	00	00
9 hours	00	12	00	00

Table 3. Time required for stoppage of bleeding.

Time\minute	Haemocoagulase side	Control side
0.0 - 1.0	03	00
1.0 - 1.25	16	00
1.25 - 1.50	20	00
1.50 - 1.75	09	06
1.75 - 2.00	02	16
2.00 - 2.25	00	15
2.25 - 2.50	00	10
2.50 - 2.75	00	03

Table 4. Duration of pain and swelling post operatively.

Time\minute	Haemocoagulase side (pain)	Control side (pain)	Haemocoagulase side (swelling)	Control side (swelling)
1 hour	00	00	00	00
2 hours	00	00	00	00
3 hours	02	06	06	02
6 hours	09	05	05	06
9 hours	11	09	13	10
2nd day	25	18	23	19
3rd day	03	12	03	13

Table 4 also showed that 11 patients (22%) had pain 9 hours after procedure increasing up to 25 patients (50%) by 2nd day. While on the third day number of patients reduced to 3 (6%) in the haemocoagulase side patients while in the control patients 9 (18%) had pain 9 hours after procedure increasing up to 18 patients (36%) by 2nd day and reduced to 12 patients (24%) by 3rd day (P 0.604).

4. Discussion

Bleeding at the surgical site is very disturbing both for the patient and the surgeon. There are several conventional haemostatic techniques to minimize blood loss. Mechanical means include manual pressure, ligature and the application of a tourniquet. However, these methods can be labour intensive and add time to the operative procedure [4]. Sealing of bleeding vessels can also be achieved by thermal methods such as electro cauterization or laser cauterization, but these create areas of char and necrotic tissue, increasing the likelihood of infection and damaging wound edges. This may lead to impaired healing [5]. Conventional methods are also less effective in controlling bleeding from complex injuries and where access to the area of bleeding is difficult. Topical haemostatic agents may be particularly useful in such situations.

Several topical haemostatic agents are currently available in a range of configurations. They exert their effect in a variety of ways. Some improve primary haemostasis, whereas others stimulate fibrin formation or inhibit fibrinolysis [6]. Some are a preparation of a procoagulant substance in combination with a vehicle such as collagen matrix. Others use a matrix to provide a template for the endogenous coagulation cascade to achieve haemostasis. Factors affecting the selection of an appropriate topical haemostat include the type of procedure, cost, severity of bleeding, and the personal experience and preference of the surgeons.

Topical haemostats can be broadly classified as follows:

1) Collagen based haemostats *i.e.* avitene, helistat. The helical structure, and large surface area it provides, are important for the haemostasis [4]. Contact with a bleeding surface attracts platelets. These agents are commonly

combined with a procoagulant substance, often thrombin, in order to enhance the result. Adverse effects of these agents are very rare like formation of granulomatous masses, adhesion formation, and allergic reactions.

2) Gelatine based haemostats *i.e.* surgifoam, gel foam. The mechanism of action of gelatine-based haemostats is not fully understood, but seems likely to involve physical surface effects rather than any action on the blood clotting mechanism. Gelatine-based devices have been reported to induce a better quality clot than collagen based haemostats [7]. The safety of these agents and the extent of tissue reactions against them have not been clearly elucidated. However, transient granulomatous inflammation of variable intensity was observed.

3) Cellulose based haemostats *i.e.* surgicel. Oxidized cellulose and oxidized regenerated cellulose have been in use for several decades. A number of mechanisms are thought to contribute to their haemostatic action, including blood absorption, surface interactions with proteins and platelets, and activation of both the intrinsic and extrinsic pathways [8]. These agents raise significant safety concerns. Surgicel granulomas have been reported at a number of sites and postoperative neurological complications [9] are also seen in some cases.

4) Albumin derived haemostats *i.e.* bioglue. Tissue adhesives have been used widely for decades, for both their haemostatic and sealant properties. The main disadvantage of bioglue is that it can leak through suture tracks.

5) Polysaccharide based haemostats *i.e.* traumadex, MPH. These are the agents based on polysaccharides are a relatively recent addition to the haemostatic arsenal. Two broad categories are currently available, the first consisting of *N*-acetylglucosamine-containing glycosaminoglycans and the second microporous polysaccharide haemospheres (MPH) [10].

6) Inorganic haemostats *i.e.* quick clot. Inorganic agents are also a relatively recent addition to the range of haemostats. QuikClot is based on zeolite, a substance that has been used previously for ion exchangers and catalysts [11]. The manufacturer suggests that its mechanism of action is related to the absorption of water from the bleeding site, leading to an increase in the concentration of platelets and clotting factors. Others have reported that it is able to activate coagulation directly [12] and it has also been suggested that the exothermic reaction associated with the absorption of water might lead to cauterization of local bleeding vessels. Unfortunately, the exothermic reaction associated with QuikClot, while possibly being partially responsible for its efficacy, can produce injuries. Partial and full-thickness burns have been described in swine after QuikClot application.

Rakoz suggested various newer local haemostatic agents in extraction site which include TranexamicAcid mouth wash, fibrin glue, cyanoacrylate, thrombin, microfibrillar collagen and oxidized cellulose [3]. It is conceivable however that mouthwash may have effect on superficial clot but not on bleeding from the depth of the socket, a region not accessible to mouth wash. Resorbable haemostatic agents such as gel foam, absorbable collagen, microfibrillar collagen etc. have risk of adherence and infection especially if any portion remains unabsorbed by tissue [13] [14]. Biological agents such as thrombin, fibrin glue are technically difficult to manipulate especially in wet regions. All these agents are very costly.

Haemocoagulase is an enzyme complex, based fundamentally on coagulant and antihaemorrhagic properties of fractions isolated from the poison *Bothrops jararaca*. Its main function is conversion of fibrinogen to fibrin even in the absence of clotting factors. This thrombin like action is present even in the presence of antithrombin and is not absorbed in fibrin clot hence the action of haemocoagulase is prolonged.

It is completely free of neurotoxins and other toxic substances. It is pale yellow crystalline powder which is sparingly soluble in water but readily soluble in phenolated saline. It is active over a wide pH range of 4 to 8. A clotting enzyme of the venom *Bothrops jararaca* denoted FC-Bj was purified by gel chromatography on Sephadex G-100. The clotting factor coagulates fibrinogen to fibrin. The protein was of serine type. The amidolytic activity of this enzyme was resistant to inhibitors such as heparin, aprotinin, EDTA. The importance of the disulfide bridges for the structural integrity of the purified enzyme was indicated by the loss of amidolytic activity in the presence of beta-mercaptoethanol [15].

A platelet aggregating enzyme PA-Bj was also isolated from the venom of snake *Bothrops jararaca* [16]. Haemocoagulase has two different enzymatic activities, which promote blood coagulation. One of these accelerates the conversion of prothrombin to thrombin (thromboplastin like enzyme), while the other one causes a direct transformation of fibrinogen to fibrin monomer, which can be converted by thrombin into fibrin clot (thrombin like enzyme). In vitro the thrombin like enzyme coagulates fibrinogen by gradually splitting off fibrinopeptide A and B. This gives rise to des-A-fibrin monomer, which polymerize end to end to form fibrin clot. In the circulating blood the des-A-fibrin monomer produced by haemocoagulase remains in solution because it forms a complex with native fibrinogen. These complexes of high molecular weight accelerate the platelet ag-

gregation also helped by the enzyme PA-Bj and reduce capillary permeability at the site of vascular injury.

The thromboplastin like enzyme activates factor X essentially in the presence of factor III released from the platelets aggregates at the bleeding site. The activated factor Xa then supports thrombin formation at the site of haemorrhage. However in vitro thromboplastin like enzyme can convert prothrombin to thrombin even in the absence of factor III and factor X.

Haemocoagulase induced fibrin deposition librates structurally different degraded products. These products may have decisive role in improving the wound repair on haemocoagulase. However this warrants future prospective research.

In the present study haemocoagulase is applied topically on the extracted tooth socket and compared with the extracted socket without haemocoagulase. The average time for stoppage of bleeding at the test side was 1.35 minutes compared to 2.25 minutes at the control side. Duration of post operative pain and swelling was also less on the haemocoagulase side as compared to control side. Haemocoagulase is also applied topically after removal of impacted tooth. In all these surgical procedures the average time of stoppage of bleeding was 1.46 minutes at the test side compared to 2.43 minutes at the control side. Duration of postoperative pain and swelling was also less.

K. V. Ramesh, D. R. Kulkarni, in 1990 [17] done a study in view of the importance of blood coagulation in wound healing, botropase, a fractionated snake venom used as systemic haemocoagulant, to arrest bleeding, is studied on different wound models in albino rats. Physical, biochemical and histological evaluation revealed that botropase promotes reparative process. Pro-coagulation effect and other enzymatic actions of botropase may be responsible for augmentation of healing.

Dr. Babu S. Parmar, Dr. Samir mansuri in 2006 [2] done a study and stated that use of haemocoagulase after lower third molar surgery not only provides faster hemostasis but also enhances healing by rapid formation of healthy tissue and reducing the amount of infection which may alter the normal healing process. Although physical, biochemical and enzymatic catalytic reaction may still be required for correct evaluation of wound healing process with haemocoagulase. This could not be evaluated in our study and is one limitation in our study. Also haemocoagulase is said to be ineffective rarely in the presence of low fibrinogen level in the blood. In this study preoperative antibiotics, enzymes and other drugs were not used therefore reduction in pain and improvement in wound healing could be attributed to the action of the drug only. We have not encountered any complication like dry socket, trismus or altered sensation at the surgical site.

5. Conclusion

In the present study haemocoagulase is applied topically on the extracted tooth socket which has been acted as the test side and compared with the extraction socket where no additional haemostatic measure has been applied which has been acted as the control side. It is concluded from this study that the use of haemocoagulase after the minor oral surgery not only provides faster haemostasis but also enhances healing by rapid formation of healthy tissue and less chances of infection. Based on our results further studies are required where we can prove the use of haemocoagulase in haemophilic patients and other surgical patients.

Conflict of Interest Statement

I have no conflict to declare.

References

[1] Kim, S.H. and Lee, H.S. (1993) Efficacy of Intravitreal Haemocoagulase for Control of Bleeding in Rabbit Experimental Model of Vitrectomy. *Japanese Journal of Ophthalmology*, **37**, 379-384.

[2] Parmar, B.S. and Mansuri, S. (2006) Efficacy of Haemocoagulase as a Topical Haemostatic Agent after Third Molar Surgery (A Study of 50 Cases). *Journal of Maxillofacial Surgery*, **5**, 5-9.

[3] Borea, G. and Capuzz, I.P. (1993) Tranexamic Acid as a Mouthwash in Anticoagulant Treated Patients Undergoing Oral Surgery. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, **75**, 29-31. http://dx.doi.org/10.1016/0030-4220(93)90401-O

[4] Zwischenberger, J.B., Brunston Jr., R.L., Swann, J.R. and Conti, V.R. (1999) Comparison of Two Topical Collagen-Based Hemostatic Sponges during Cardiothoracic Procedures. *Journal of Investigative Surgery*, **12**, 101-106. http://dx.doi.org/10.1080/089419399272656

[5] Tan, S.R. and Tope, W.D. (2004) Effectiveness of Microporous Polysaccharide Hemospheres for Achieving Hemostasis in Mohs Micrographic Surgery. *Dermatologic Surgery*, **30**, 908-914. http://dx.doi.org/10.1111/j.1524-4725.2004.30261.x

[6] Levy, J.H. (2004) Hemostatic Agents. *Transfusion*, **44**, 58S-62S. http://dx.doi.org/10.1111/j.0041-1132.2004.04173.x

[7] Szpalski, M., Gunzburg, R. and Sztern, B. (2004) An Overview of Blood-Sparing Techniques Used in Spine Surgery during the Perioperative Period. *European Spine Journal*, **13**, S18-S27. http://dx.doi.org/10.1007/s00586-004-0752-y

[8] Kanko, M., Liman, T. and Topcu, S. (2006) A Low-Cost and Simple Method to Stop Intraoperative Leakage-Type Bleeding: Use of the Vancomycin-Oxidized Regenerated Cellulose (ORC) Sandwich. *Journal of Investigative Surgery*, **19**, 323-327. http://dx.doi.org/10.1080/08941930600889425

[9] Henry, M.C.W., Tashjian, D.B., Kasowski, H., Duncan, C. and Moss, R.L. (2005) Postoperative Paraplegia Secondary to the Use of Oxidized Cellulose (Surgicel). *Journal of Pediatric Surgery*, **40**, E9-E11. http://dx.doi.org/10.1016/j.jpedsurg.2005.01.032

[10] Favuzza, J. and Hechtman, H.B. (2004) Hemostasis in the Absence of Clotting Factors. *Journal of Trauma*, **57**, S42-S44. http://dx.doi.org/10.1097/01.TA.0000136745.89568.D9

[11] Galownia, J., Martin, J. and Davis, M.E. (2006) Aluminophosphate-Based, Microporous Materials for Blood Clotting. *Microporous and Mesoporous Materials*, **92**, 61-63. http://dx.doi.org/10.1016/j.micromeso.2005.12.020

[12] Hunt, K.E. and Crookston, K.P. (2003) Hemostatic Agent QuikClot™ Activates Coagulation Directly via the Contact Pathway. *Transfusion*, **43**, 6A.

[13] Gabay, M.L. (2006) Absorbable Haemostatic Agents. *American Journal of Health System Pharmacy*, **63**, 1244-1253. http://dx.doi.org/10.2146/ajhp060003

[14] Allison, R.T. (1994) Foreign Body Reaction and an Associated Histological Artifact Due to Bone Wax. *British Journal of Biomedical Science*, **51**, 14-17.

[15] Zaganelli, G.L. and Magalhaes, A. (1996) Purification and Characterization of a Fibrinogen Clotting Enzyme from the Venom of Jararacussu (*Bothrops jararacussu*). *Toxicon*, **34**, 807-819. http://dx.doi.org/10.1016/0041-0101(96)00006-2

[16] Serrano, S.M. and Mentele, R. (1995) Purification, Characterization, and Amino Acid Sequence of a Serine Proteinase, PA-BJ, with Platelet Aggregating Activity from the Venom of *Bothrops jararaca*. *Biochemistry*, **34**, 7186-7193. http://dx.doi.org/10.1021/bi00021a033

[17] Ramesh, K.V. and Ramanarayan, K. (1990) Effect of Botropase on Wound Healing. *Indian Journal of Surgery*, **52**, 218-221.

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or Online Submission Portal.