Original Article

The effects of surgicel and bone wax hemostatic agents on bone healing: An experimental study

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Abstract

Background: The biological effects of hemostatic agends on the physiological healing process need to be tested. The aim of this study was to assess the effects of oxidized cellulose (surgicel) and bone wax on bone healing in goats' feet.

Materials and Methods: Three congruent circular bone defects were created on the lateral aspects of the right and left metacarpal bones of ten goats. One defect was left unfilled and acted as a control; the remaining two defects were filled with bone wax and surgicel respectively. The 10 animals were divided into two groups of 5 animals each, to be sacrificed at the 3rd and 5th week postoperatively. Histological analysis assessing quality of bone formed and micro-computed tomography (MCT) measuring the quantities of bone volume (BV) and bone density (BD) were performed. The results of MCT analysis pertaining to BV and BD were statistically analyzed using two-way analysis of variance (ANOVA) and *posthoc* least significant difference tests.

Results: Histological analysis at 3 weeks showed granulation tissue with new bone formation in the control defects, active bone formation only at the borders for surgicel filled defects and fibrous encapsulation with foreign body reaction in the bone wax filled defects. At 5 weeks, the control and surgicel filled defects showed greater bone formation; however the control defects had the greatest amount of new bone. Bone wax filled defects showed very little bone formation. The two-way ANOVA for MCT results showed significant differences for BV and BD between the different hemostatic agents during the two examination periods.

Conclusion: Surgicel has superiority over bone wax in terms of osseous healing. Bone wax significantly hinders osteogenesis and induces inflammation.

Key words: Bone defects, bone wax, oxidized cellulose, goat, histology, micro-computed tomography

Introduction

Hemostasis during surgery benefits the patient, the surgical team and the health care facility.[1] The choice of proper hemostatic agent and the time of its application requires understanding of the mechanism of action, efficacy and possible adverse events of various hemostatic agents,[2] including absorbable hemostatic agents, biologically active topical hemostatic agents and systemically administered agents.[3]

Bone wax and oxidized cellulose (surgicel) are among the commonly used hemostatic agents for controlling hemorrhage from the surgical site. Bone wax is a sterile mixture of 85-90% white bees' wax and 10-15% isopropyl palmitate,[4] a palm oil-based emollient, moisturizer, thickening and antistatic agent. In addition commercially available bone wax may contain up to 30% soft paraffin wax as a softening agent. Bone wax is a nonabsorbable hemostatic sealant and it functions as a tamponade to control bleeding from bone in patients undergoing thoracic, orthopedic, craniofacial and neurosurgery.[4,5] Surgicel is a sterile cellulose based thrombogenic material used to control bleeding originating from delicate and/or friable tissues.[6] It is commercially available as a gauze like material and is generally inert and bioabsorbable.[6] The hemostatic action of surgicel is by formation of a gelatinous mass upon saturation with blood, which leads to formation of a stable clot.[6,7]

In spite of the development of newer materials for hemostasis, the more commonly used materials have not

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changed in last 50 years. Furthermore, the use of hemostatic agents is not free from health risks and complications can arise as a result of physical attributes of the hemostatic material like mechanical compression or due to phlogistic effects secondary to their chemical nature.[4,7-9] The objective of the present study was to compare the early healing response in bone defects created in goats' feet and filled with surgicel and bone wax hemostatic agents by evaluating qualitatively and quantitatively the newly formed bone using micro-computed tomography (MCT) and histology. The null hypothesis being that the hemostatic agents do not have any effect on the healing of the bone defects.

Materials and Methods

The animal study protocol was approved by the "College of Dentistry Research Center", King Saud University, Saudi Arabia, duly governed by its "Ethical Consideration for Animals" document, in conformity with National Institute of Health guidelines for the care and use of laboratory animals (NIH Publication #85-23 Rev. 1985).

Operative procedures

Ten adult male goats, 12-months old with a mean body weight of 26 kg (±3.2 kg) were used. The goats were anesthetized by intramuscular injection of xylazine (5 mg/kg, Lloyd Laboratories, Shenandoah, IA, USA), acepromazine (1.5 mg/kg, Vedco, St. Joseph, MO, USA) and ketamine (20 mg/kg, Sigma Chemical St. Louis, MO, USA). The goats were administered antibiotics procaine penicillin (20,000 units/kg, IM) and gentamicin (6.6 mg/kg intravenous [IV]) at the start of the surgery and for after 24 h postoperatively and analgesic paracetamol (10 mg/kg IV every 8th hourly) for 3 days.[10]

The left and right anterior feet were shaved and the surgical site was cleaned and disinfected using 10% Povidone Iodine solution (Riyadh Pharma, Riyadh, Saudi Arabia). The lateral aspect of each metacarpal bone was exposed through a 7-cm linear skin incision followed by periosteal elevation. Three circular bone cavities, each 4 mm in diameter, were drilled into the anterior part of each metacarpal bone using a high torque, low speed trephine drill (Kohler, Stockach, Germany) under constant and copious saline irrigation. Defects were randomly assigned to one of the following groups: (1) Control defect - where hemostasis was achieved only with gauze packing which was removed prior to wound closure and no filling material was placed (2) test defect to be filled with oxidized cellulose (Surgicel™ Nu-Knit™; Johnson and Johnson Medical, Arlington, TX, USA) and (3) test defect to be filled with bone wax (Aesculap AG and Co., KG Tuttlingen, Germany). A total of 60 bone defects were made in the bilateral metacarpal bones of the ten goats, out of which 10 defects were used per treatment group for each examination period.

Following placement of hemostatic agents in the test defects and achievement of hemostasis in the control defects, the surgical site was closed primarily using 4-0 black silk (Futura Surgicare Pvt. Ltd., Bangalore, India). The goats were monitored daily for the 1st week and every 2 days thereafter for any adverse events. During the 3rd and 5th weeks, five goats were euthanized and sacrificed at each time interval using an overdose of 3% sodium pentobarbital (Vortech Pharmaceuticals Limited, Dearborn, MI, USA). The right and left metacarpal bones were then osteotomized 20 mm proximal and distal to the region of interest (ROI) and fixed immediately in 10% phosphate buffered formaldehyde (pH = 7.4).

MCT analysis

After fixation in 10% phosphate-buffered formaldehyde (pH = 7.4) and dehydration in 70% ethanol, three-dimensional MCT images were made using SkyScan 1176 "High resolution X-ray MCT (Skyscan, Kontich, Belgium). The specimens were wrapped in parafilm (West Chester, PA, USA) to prevent drying during scanning and scanned at 70 kV and 343 μA with a resolution of 12.39 μm pixel using an aluminum filter (1 mm). The rotation step was 0.6° and the exposure time was 15-20 min. The frame averaging was 4 while the tomographic rotation was 1800 and the camera was adapted as standard (1000 pixel field width). Cone-Beam acquisition and reconstruction saved all projection images as 16 bit TIF files. The scanning and reconstruction parameters were identical for all specimens. After scanning, NRecon (Skyscan, Kontich, Belgium) reconstruction software, data Viewer scan viewing software and a computed tomography (CT) analyzer analysis programs were launched.

The parameters acquired via MCT were bone volume (BV, mm^3) and bone density (BD, mg/cm^3) of mineralized tissue within the ROI. BV was defined as the volume of mineralized tissue formed at the defect site during healing and is a quantitative indicator of newly formed mineralized tissue and BD was defined as the density of mineralized tissue within the volume of interest and is an indicator of the quality of mineralized tissue.[11] Following MCT analysis, the ROI for BV were identified using the computer program. The area of new bone formed was measured in each section of the MCT scan and the product of the measured area and the slice thickness of the scan section was the BV in that particular scan section. The sum of the BVs of each scan section was calculated to determine the total BV of new bone formed.

To calculate the BD of the newly formed bone, four representative sites were selected from the specimen as the ROI. Each site was selected to represent either the superior or the inferior aspect of the proximal and distal portions of the bone cavities, 2 mm away from the edges. The mean of the individual BD obtained from each site was calculated to obtain the total BD of new bone formed.

Light microscopy

Immediately after MCT scanning, the excised metacarpal bone segments were fixed in a 10% neutral formalin solution for 1 week. They were decalcified in a solution containing equal parts of 50% formic acid and 20% sodium citrate for 10 weeks respectively. The decalcified specimens were washed in running water, dehydrated in an ascending ethanol series and embedded in paraffin. 5-μm thick serial sections were prepared and stained with hematoxylin and eosin to be investigated under the light microscope (Olympus B×41, Tokyo, Japan). The ROI was evaluated only qualitatively based on the histological findings.

Statistical analysis

The sample size was estimated to be 60 test defects (n = 10/group) distributed evenly among the 3 groups during the 2 examination periods, based on a type 1 error value of 5% (α=0.05) and a power of 0.85. Sample size calculation was done using MINITAB software (Version 14, Minitab Inc., Pennsylvania, USA). Any observed difference in the values of BV and BD greater than 1, between the different hemostatic agents and during different examination periods was considered significant. Furthermore, BV and BD were compared using two-way analysis of variance (ANOVA) followed by the least significant difference (LSD) posthoc test. The factors for ANOVA were: (1) Examination period (3 or 5 weeks) and (2) hemostatic agents (surgicel, bone wax and control). $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows, version 16 (SPSS, Chicago, IL, USA).

Results

Postsurgery, all goats were healthy with good appetite and showed signs of good healing with no evidence of complications (e.g., hematoma, infection).

Histological findings

At 3 weeks postoperatively, the bone cavities of the control defects (n = 10) showed large numbers of tiny blood vessels, inflammatory cells, fibroblasts and macrophages in a collagen-rich connective tissue matrix suggesting granulation tissue formation and neovascularization. The granulation tissue was surrounded by newly formed bone trabeculae rich in cellular activity. The surface of the new bone was lined by osteoid and plump osteoblasts, indicating active bone formation. Residues of surgicel cellulose fibers that markedly slowed the rate of repair and caused inflammation were seen in the surgicel filled defects (n = 10). The cellulose fibers did not hinder the formation of new bone trabeculae at the borders of the bone defect. Although bone wax was not evident in the bone wax filled defects (n = 10) due to its dissolution during the embedding process, it had resulted in inflammation and granuloma formation comprising chronic inflammatory mass of tissue with foreign-body reaction in the form of multinucleated foreign body giant cells (macrophage fusion). New bone trabeculae could not be seen clearly around the bone wax, instead there was a fibrous tissue lining made up of bundles of collagenous white fibers interspersed with rows of connective tissue cells at the borders of the bone defect [Figure 1].

At 5 weeks postoperatively, the bone defects of the control group (n = 10) showed an increased amount of newly formed bone trabeculae at the borders at the expense of the granulation tissue at the center. There was evidence of more vigorous bone formation as the staining of the newly formed bone approximated that of the surrounding cortical bone. Residues of surgicel cellulose fibers surrounded by and intermingled with granulation tissue was found at the center of the surgicel filled defects (n = 10). Even though the amount of newly formed bone trabeculae at the borders was increased; it was less than that of the control defects. The bone wax was surrounded by a fibrous tissue lining and fibrous connective tissue septa could be seen dividing the material into more compartments. No newly formed bone trabeculae could be seen at the borders of the bone wax filled defects (n = 10) [Figure 2].

MCT results

The results of the MCT analysis supported the histological findings. The reconstructed coronal and sagittal images for the specimens examined at 3 weeks showed minute amount of newly formed bone in surgicel filled defects (n = 10) compared to control defects (n = 10). No new bone formation could be detected in the bone wax filled defects (n = 10). The specimens examined at 5 weeks showed similar quantities of newly formed bone in the surgicel filled defects (n = 10) and control defects (n = 10). However, the amount of newly formed bone in the bone wax filled defects (n = 10) was very little. There was an overall increase in the quantities of newly formed bone at the end of 5 weeks compared to 3 weeks of healing [Figure 3].

In general, the control defects (n = 10) had a greater BV of newly formed bone followed by the surgicel filled (n = 10)

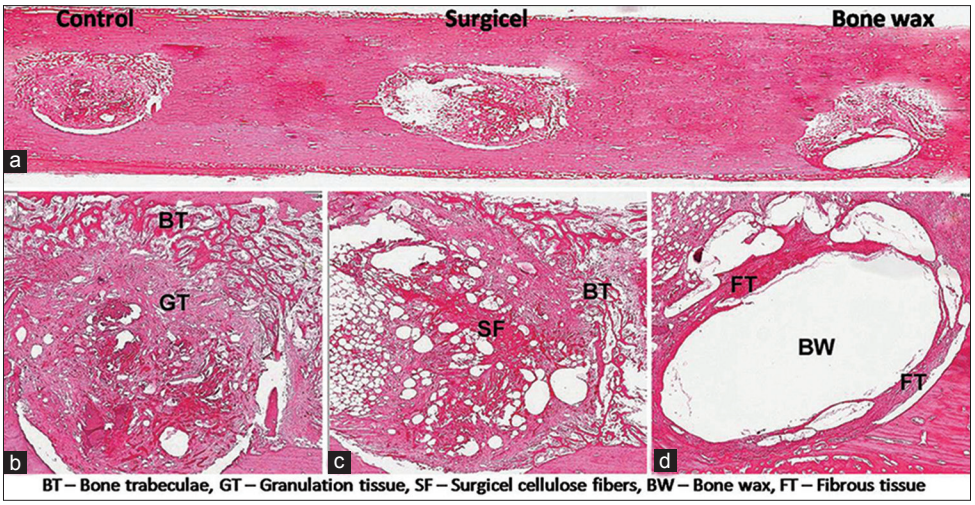

Figure 1: Histological images of control and test defects filled with surgicel and bone wax. (a) Longitudinal section of goat metacarpal bone at 3 weeks postoperatively (H and E, original magnification ×100) (b) control defect at 3 weeks (c) surgicel filled defect at 3 weeks (d) bone wax filled defect at 3 weeks (H and E, original magnification ×200)

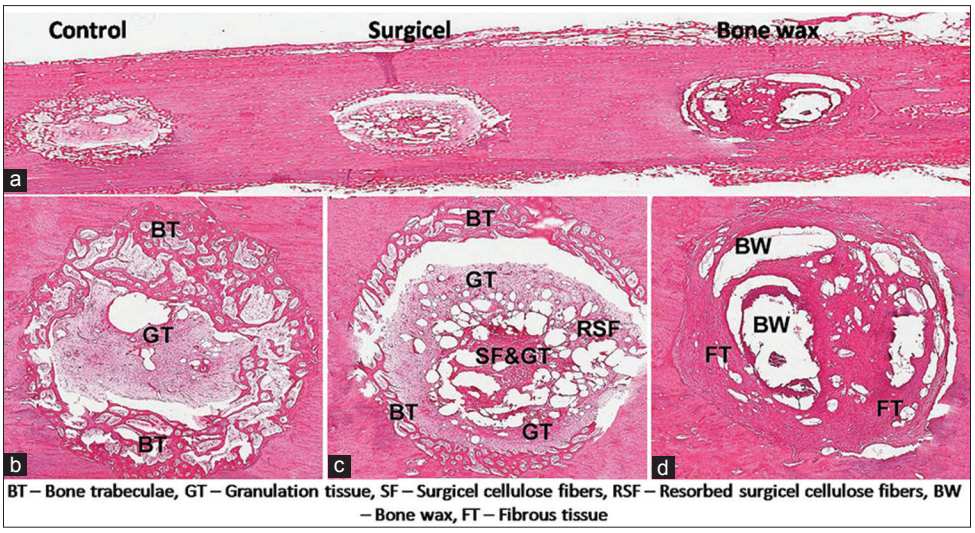

Figure 2: Histological images of control and test defects filled with surgicel and bone wax. (a) Longitudinal section of goat metacarpal bone at 5 weeks postoperatively (H and E, original magnification ×100) (b) control defect at 5 weeks (c) surgicel filled defect at 5 weeks (d) bone wax filled defect at 5 weeks (H and E, original magnification ×200)

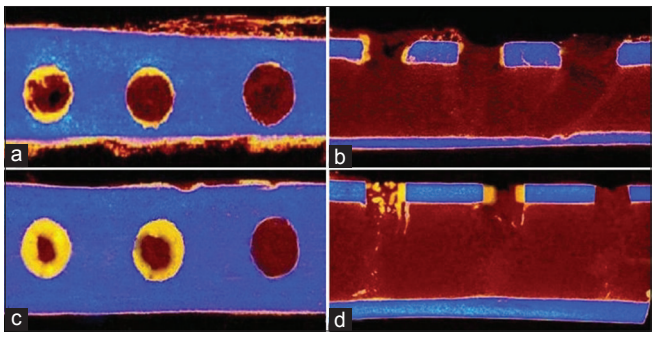

Figure 3: Micro-computed tomography sections of the goat metacarpal bones showing the control defects and the defects filled with surgicel and bone wax in order from left to right. (a) Axial reconstruction of the defects at 3 weeks (b) sagittal reconstruction of the defects at 3 weeks (c) axial reconstruction of the defects at 5 weeks (d) sagittal reconstruction of the defects at 5 weeks. The cortical bone is colored blue, the medullary bone and soft tissue are colored brown and the newly formed bone is colored yellow

and bone wax filled defects ($n = 10$) [Table 1 and Figure 4]. A similar pattern was also observed in terms of the BD of newly formed bone [Table 1 and Figure 5]. Two-way ANOVA revealed an overall significant difference in BV with respect to the examination periods ($F = 1695.871$, $P < 0.001$) and the types of hemostatic agents used ($F = 9476.238$, $P < 0.001$). Furthermore, a significant interaction was found between examination periods and hemostatic agents which affected the values of BV ($F = 858.697$, $P < 0.001$). LSD *posthoc* test for multiple comparisons regarding the hemostatic agents revealed a statistically significant difference between the volumes of newly formed bone in the control defects compared with surgicel and bone wax filled defects [Table 2].

Two-way ANOVA revealed an overall significant

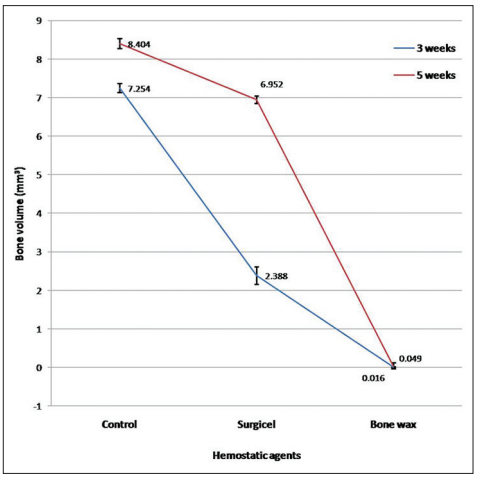

Figure 4: Profile plot with error bars showing the interaction between the hemostatic agents during different examination periods and its effect on bone volume (mm^3)

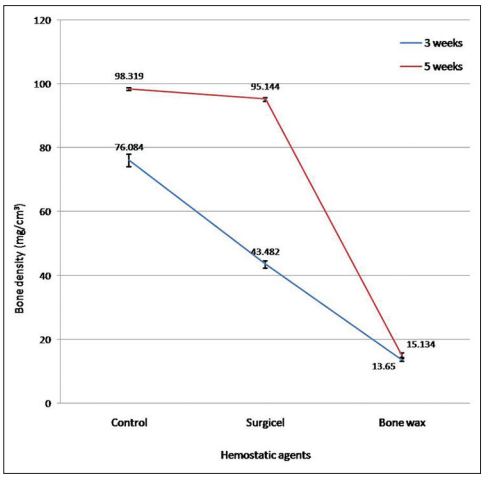

Figure 5: Profile plot with error bars showing the interaction between the hemostatic agents during different examination periods and its effect on bone density (mg/cm^3)

difference in BD with respect to the examination periods ($F = 4368.187$, $P < 0.001$) and the types of hemostatic agents used ($F = 13279.880$, $P < 0.001$). Statistically significant interaction was also found between examination periods and hemostatic agents which affected the values of BV ($F = 1466.165$, $P < 0.001$). LSD *posthoc* test for multiple comparisons regarding the hemostatic agents revealed a statistically significant difference between the BD of newly formed bone in the control defects compared to surgicel and bone wax filled defects [Table 3].

Table 1: Descriptive statistics for bone volume and bone mineral density during different examination periods and for different hemostatic agents

Examination periods (weeks)	Hemostatic agents (*n*=10)	Mean±SD	
		Bone volume (mm^3)	Bone density (mg/cm^3)
3	Control	7.254±0.112	76.084±2.013
	Surgicel	2.388±0.230	42.521±1.118
	Bone wax	0.016±0.003	13.650±0.371
5	Control	8.404±0.132	98.319±0.412
	Surgicel	6.952±0.094	95.144±0.606
	Bone wax	0.049±0.049	15.134±0.725

SD=Standard deviation

Table 2: Least significant difference *posthoc* test for the effect of hemostatic agents on bone volume and their significance

Hemostatic agents (*n*=10)		Mean difference (I-J)	*P* value
I	J		
Control	Surgicel	3.159	<0.001
	Bone wax	7.797	<0.001
Surgicel	Control	−3.159	<0.001
	Bone wax	4.638	<0.001
Bone wax	Control	−7.797	<0.001
	Surgicel	−4.638	<0.001

Table 3: Least significant difference *posthoc* test for the effect of hemostatic agents on bone density and their significance

Hemostatic agents (*n*=10)		Mean difference (I-J)	*P* value
I	J		
Control	Surgicel	17.888	<0.001
	Bone wax	72.809	<0.001
Surgicel	Control	−17.888	<0.001
	Bone wax	54.921	<0.001
Bone wax	Control	−72.809	<0.001
	Surgicel	−54.921	<0.001

Discussion

Literature suggests that the caprine (goat) animal model is suitable for testing human implants and materials as goats are considered to have a metabolic rate and bone remodeling rate similar to that of humans.[10] Hemostasis is a cascade process involving vascular contraction, platelets aggregation and activation of coagulation factors resulting in a coagulum which stops bleeding. Sometimes during a surgical procedure, it may not be practical to wait for the natural hemostatic process to occur and additive measures in the form of hemostatic agents are needed to obtain a stable coagulum.[12] A thorough knowledge and understanding about the mechanisms of action of various hemostatic agents is necessary for selecting the right material for the right indication.[2]

Bone wax was first formulated by Victor Horsley in 1885 and introduced to the field of surgery by Parker in 1892.[4,13] Since then bone wax has been used widely as a nonabsorbable hemostatic bone sealant. However, certain adverse reactions reported with its use include persistent granulomatous inflammation, foreign body reaction and promotion of infection, delayed bone healing and potential for neurological complications.[4,14-17]

The histological findings of the present study revealed a foreign body reaction to bone wax in the form of granulomatous inflammation and fibrous tissue encapsulation with the inhibition of bone healing and osteogenesis. The effect of bone wax on inhibiting osteogenesis is evident by the fact that the amount of new bone (BV) formed at the borders of the bone wax filled defects was significantly lower during both examination periods [Tables 1 and 2]. The bone mineral density (BD) too was significantly low compared to that of the control and surgicel filled defects [Tables 1 and 3] This is supported by numerous animal and clinical studies[16-19] which have demonstrated that the bone wax remains at the implantation site indefinitely and inhibits new bone formation.

Surgicel (Oxidized cellulose) is obtained by dissolving alpha-cellulose in an alkaline organic solvent.[6] It is usually placed in the surgical site to achieve hemostasis by formation of a gelatinous mass saturated with blood and left to be absorbed. Advantages of surgicel as a hemostatic agent include its inertness, bio absorbability, no foreign body reaction and *in-vitro* antibacterial effects.[6,7] Nevertheless literature suggests that surgicel can swell and increase in volume following saturation with blood thereby leading to mechanical compression on vital anatomical structures and radiographic artefacts mimicking abscesses and tumors in CT and ultrasonography.[6,20-25]

Based on the histological findings of the present study, though the cellulose fibers of surgicel resulted in an inflammatory reaction, they did not hinder formation of new bone at the borders of the surgicel filed defects. Furthermore, the effect of surgicel on delaying wound healing in the bone defects saw a steady decline from the 3rd week to the 5th week postoperatively. This could be attributable to the absorbable nature of surgicel. The volume of new bone (BV) formed in the surgicel filled defects were significantly higher than that of the bone wax filled defects and lower than that of the control defects during both examination periods [Tables 1 and 2]. However the bone mineral density (BD) of the newly formed bone which was significantly lower than that of the control defects during the 3rd week increased to a value close to that of the control defect by the 5th week [Table 1 and Figure 5]. This implies the beneficial effect of an absorbable hemostatic agent like surgicel which delayed wound healing during the initial stages, nevertheless led to a catch up osteogenesis during later stages as the material was reabsorbed.

In a study reported by Finn *et al*.[8] comparing the effect of different hemostatic agents on bone healing in dogs, the authors, suggested that surgicel was a better hemostatic agent for bone healing compared to microfibrillar collagen and gel foam and contraindicated the use of bone wax. The histological findings of the above study were comparable to the results of the present study.

Correlating the histological and MCT findings of the present study it was found that bone wax when used as a hemostatic agent in bone not only delayed wound healing by foreign body reaction, granuloma formation and encapsulation but also significantly inhibited osteogenesis as evidenced by the very small volumes of newly formed bone detectable in the bone wax filled defects. However, surgicel when used as a hemostatic agent delayed wound healing in the early stages and during the later stages when it was absorbed from the defect site it allowed unhindered wound healing and bone formation resulting in a new bone comparable in quantity and quality to that of the control group.

Based on the findings of the present study it could be concluded that surgicel (oxidised cellulose) is adequate as a hemostatic agent for bony defects as it is absorbable and allows new bone formation. The use of bone wax as a bone hemostatic agent should be guided with caution in the light of the present study results and must be contraindicated at sites where bone regeneration is expected.

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