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Effect of a New Sternal Sealant on Marrow Bleeding and Blood Product Use after Adult Cardiac Surgery

To minimize sternal bleeding, cardiac surgeons have experimented with several hemostatic topical agents. Bone wax, a historically popular substance, is a mixture of sterilized honeybee wax and paraffin wax. Although effective, the material is not readily absorbed, which prevents bone regrowth, and can lead to foreign body granuloma formation, increasing risk of infection.[1] The water-soluble polymer wax (WSW), Ostene® (Ceremed, Inc., Los Angeles, CA), an alkaline oxide copolymer bone hemostatic material, has been shown to achieve immediate hemostasis similar to bone wax; however, unlike bone wax, the material is water soluble. The substance completely dissolves in 48 hours, and after three weeks, bone regrowth has been observed, although it does not seem to promote bone growth.[2] The hydroxyapatite and polylactic acid (HA/PLA), BoneSeal (Hemostasis, LLC, St. Paul, MN), is an absorbable synthetic bone hemostatic agent, with beeswax consistency that also contains PLA, polyethylene glycol polymer, and hydroxyapatite, which supports bone regrowth. *In vitro* testing has shown that the solubility of hydroxyapatite is enhanced when mixed with a PLA oligomer.[3] Presently, there is no relevant, specific clinical data regarding BoneSeal®. BoneSeal® has been cleared by the Food and Drug Administration based on the determination that the product is substantially equivalent to presently cleared and marketed predicate products. Given promising preclinical studies, we designed a prospective, randomized, double-blinded clinical study to compare the efficacy of BoneSeal and Ostene in reducing blood product transfusion in adult cardiac surgery.

Approval was obtained from the Institutional Review Board of Loma Linda University Medical Center. Study subjects were identified by diagnosis and by the anticipated need for cardiac surgery through a median sternotomy. The subjects were prospectively randomized just before their surgery to either the WSW or to the HA/PLA group. A 3.5-g bar of either product was used. Inclusion criteria were age >45 years, elective cases, and first-time sternotomy. Exclusion criteria included lack of consent, known bleeding diathesis, immune system disorder, known hypersensitivity to components in BoneSeal® or Ostene® and need for emergency surgery. Once sternotomy was performed, the degree of osteoporosis and the severity of the sternal edge bleeding was assessed on a scale of 1 (none) to 5 (severe). One of the two products was then applied, and the ease of spreading the topical sealant was graded on a scale of 1 (easy) to 5 (difficult). Hemostasis were observed and similarly graded after initial application and at the end of surgery after reversal of heparin and before closure of the sternum. Rebleeds and the use of extratopical hemostatic products were also recorded. Standard sternal wound closure was performed. Postoperative chest tube drainage and the use of blood products were recorded. All patients were followed for 30 days. Wound infections and/or complications were recorded.

Means and SDs for normally distributed quantitative variables and median with range for skewed quantitative variables were used to present the descriptive statistics. We also used frequencies with percentages to present the descriptive statistics for the qualitative variables. Repeated measures analysis of variance with one within subject factor (pre-post) and one between subject factor (product) was used to compare post-intervention measures to baseline measures between the products. Repeated measures analysis of variance

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was also run after adjusting for age because age was significantly different between the two groups at baseline. Chi-squared test was used to assess the association of the qualitative variables and the two products, whereas the Mann-Whitney test was used to compare the two products with regard to the ordinal variables representing severity. The mean of the quantitative variables was compared between the two products using two independent samples *t* test. SPSS (version 25; IBM Corp., Armonk, NY) was used for data analysis. Statistical significance was set at $\alpha = 0.05$.

From June 2017 to November 2017, a total of 60 patients were randomized to either the WSW or the HA/PLA group. The two groups of subjects were comparable in terms of gender and diagnoses. The age range for the HA/PLA group was 49 to 83 years and for the WSW group, 47 to 80 years. The mean age of the HA/PLA group was younger than the WSW group (60.4 ± 8.0 *vs* 68.9 ± 7.7; $P < 0.001$) and had less severe osteoporosis (2.7 ± 1.0 *vs* 3.3 ± 1.2; $P = 0.03$) (Table 1). HA/PLA was easier to use and apply because of a softer consistency. The initial sternal bleeding was more severe in the WSW group than the HA/PLA (4 *vs* 3; $P = 0.002$), and at the end of surgery, the sternal bleeding was controlled better in the HA/PLA group (2 *vs* 4; $P < 0.001$) and hence, at the end of surgery after reversing the anticoagulation, more hemostatic products were used to control the bleeding in the WSW group (Table 1). The age-adjusted hemoglobin drop before and after surgery in the HA/PLA group (12.5 ± 2.4 to 10.8 ± 2.1) was less than that in the WSW group (12.8 ± 2.4 to 9.9 ± 2.1; $P < 0.05$) (Table 2). There was no statistically significant difference in wound infections.

The HA/PLA composite used in this experiment has similar handling characteristics to bone wax. It was designed to promote hemostasis *via* a similar tamponade-like mechanism. Because it is not water soluble and biodegrades in few weeks, it demonstrated a better hemostatic effect than WSW, which dissolves after a few minutes and may lead to rebleeding. We saw evidence of this in our study because the WSW cohort required the use of more topical sealants.

In this study, HA/PLA decreased blood products utilization by 50 per cent compared with WSW, although this did not reach statistical difference. We have shown that HA/PLA maintains the hemoglobin after surgery at a higher level than WSW. Limitations of this study include its small size and single-center design. In addition, despite randomization, the BoneSeal® group was slightly younger than the Ostene® group and had slightly less initial bleeding from the sternotomy sites. However, in a subgroup analysis of only initial bleeding severity of 3 and 4 (n = 21 for HA/PLA and n = 27 for WSW), there was no statistically significant difference in the degree of

TABLE 1. *Bone Hemostat Performance Comparison*

Outcome		BoneSeal® Intervention		Ostene® Control		*P* Value
Ease of product use [median (min.-max.)]		1 [1–3]		4 [1–5]		<0.001
Initial bleeding severity at sternum [median (min.-max.)]		3 [1–4]		4 [2–4]		0.002
End of surgery bleeding severity at sternum [median (min.-max.)]		2 [1–3]		4 [1–5]		<0.001
		Number	Per cent	Number	Per cent	
Number of rebleeds at sternum		3	11.1	25	83.3	<0.001
Additional topical hemostat (FloSeal) used during surgery	Yes	1	3.7	13	43.3	0.001
	No	26	96.3	17	56.7	
Age-adjusted intraoperative units of blood products [mean ± SD] (units)		[1.2 ± 3.6]		[1.9 ± 3.6]		0.452
Age-adjusted postoperative units of (within 24 hours) blood products [mean ± SD]		[0.3 ± 1.0]		[0.5 ± 1.0]		

TABLE 2. *Age-Adjusted Hemoglobin Change over Time*

	Preoperative Hemoglobin Level			Postoperative Hemoglobin Level			*P* Value
	Number	Mean	SD	Number	Mean	SD	Pre-Post
BoneSeal® intervention	27	12.5	2.4	27	10.8	2.1	0.045
Mean difference	Reference				–1.7		
Per cent change	Reference				–13.9		
Ostene® control	30	12.8	2.4	30	9.9	2.1	
Mean difference	Reference				–2.9		
Per cent change	Reference				–22.8		

osteoporosis ($P = 0.15$), and the end of surgery bleeding of the HA/PLA group *versus* the WSW group (2 *vs* 4, $P < 0.001$) remained statistically significant. Larger studies are needed to confirm the efficacy of HA/PLA in median sternotomy and/or cranial/spine surgery models, particularly comparing it against other common hemostatic agents. Other useful avenues for investigation would be longer term studies to ascertain the rate of HA integration in bone after application as a hemostat.

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