Mechanical Breast Compression following Stereotactic-Guided Breast Biopsy

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Micro Abstract:

Mechanical breast compression with an experimental device was compared with standard manual compression following large gauge vacuum-assisted stereotactic-guided breast biopsy in a prospective single arm study using historical controls. Mechanical breast compression was shown to be non-inferior ($p<0.0001$) to standard manual breast compression in limiting hematoma formation following large core vacuum assisted stereotactic-guided breast biopsy.

MECHANICAL COMPRESSION OF BREAST BIOPSY SITES FOLLOWING STEREOTACTIC-GUIDED BREAST BIOPSY

INTRODUCTION: The use, safety and efficacy of a proposed mechanical compression device was assessed and compared to standard manual breast compression in achieving hemostasis and limiting hematoma formation following stereotactic-guided breast biopsy.

PATIENTS AND METHODS: A prospective single-arm study, utilizing historical-controls, was undertaken to evaluate the safety and efficacy of the use of a proposed mechanical compression device following 120 stereotactic-guided breast biopsies. Patients discontinued most antithrombotic therapy to be eligible for the study. A 9 gauge vacuum-assisted needle biopsy system was used for all procedures with mammograms and supplemental ultrasound evaluations used to detect and measure hematomas following mechanical breast compression. Patient and staff perceptions relative to the use of the compression device, delayed hematomas and other complications were also assessed on follow up.

RESULTS: Nine hematomas (7.5%) were detected following use of mechanical compression which was maintained for an average of 11 minutes. Four delayed hematomas were detected on follow-up out to one week. No clinically significant hematomas or infections were observed and no previously undetected hematomas were identified in the thirty study patients who later required mammographic localization prior to surgical biopsy or lumpectomy. The compression experience was rated "good to excellent" by 97% of the patients.

CONCLUSION: Use of an experimental mechanical compression device following stereotactic breast biopsy was well tolerated and non-inferior ($p<0.0001$) to standard post-biopsy manual compression in incidence of hematomas detected on immediate post-biopsy imaging. Use of the mechanical device(s) saved staff time and reduced staff blood exposure. Further study of the device with patients maintained on antithrombotic agents is anticipated.

INTRODUCTION/BACKGROUND

There is broad consensus in the literature that minimally invasive breast biopsy (MIBB), including ultrasound-guided breast biopsies (USGBB) and stereotactic-guided breast biopsies (SGBB), are accurate cost-effective procedures with significant complications rarely reported. [10,3,5,25] Minimally invasive, non-surgical breast biopsy techniques have evolved and increased in frequency over the past twenty-five years with an estimated 1.6 million minimally invasive breast biopsies performed each year in the U.S including 700,000 performed utilizing stereotactic guidance.

In an effort to improve pathologic accuracy, primarily to diminish underestimation of pathology, there has been evolution from initial fine-needle aspiration biopsy (FNA) to core needle biopsy (CB) and more recently to vacuum-assisted breast biopsies (VABB). Although the use of core- biopsy techniques for ultrasound directed biopsy remains common, the use of larger vacuum-assisted needle-biopsy systems has largely replaced core-biopsy technique for the sampling of small masses, regions of architectural distortion and suspicious clusters of calcifications typically targeted during stereotactic-guided procedures. [2, 5]

Stereotactic-guided biopsy techniques initially employed 16- and 14-gauge coring needles, but, beginning in 1994, moved to 14-gauge and, more recently, to larger 8- and 9-gauge vacuum-assisted needle-biopsy systems. [2,3,4,5,6] Concurrently, for stereotactic- guided procedures, there has also been a significant increase in the number of cores obtained as well although, in reported studies, the variation in the average number and range of biopsy core specimens obtained during SGBB is marked. Most recent

large series report averages of 10 to 24 cores obtained per lesion sampled, but reported averages vary widely from 6 cores up to 96 or more cores retrieved in several "extended protocols." [3,5,20] The greater tissue volume obtained has achieved a desired reduction in the underestimation of pathology by approximately one half [12,13,14] but, predictably, there has also been an associated significant increase in observed intra-procedural bleeding and post-biopsy breast bruising and hematoma formation.[3,4,5,6,11, 20]

The vast majority of MIBB-related hematomas are considered "non-clinically significant," with clinically significant hematomas variably described in the literature to include MIBB-related continuous bleeding, large or expanding hematomas with significant pain or bleeding requiring surgical consultation, close interval follow-up, transfusion or hospitalization for observation or surgical control. "Clinically significant" hematomas are reported in the literature at 0.0% to 4%. [3,4,5,6,10,11,15,25]

"Non- clinically significant" hematomas are reported at much higher rates. (Summarized Table 1) Chetlen et al.[3] reported a 10% (2/20) rate of hematomas with 12- gauge vacuum-assisted needles utilizing ultrasound guidance while Liberman et al. reported a 30.5% hematoma rate following SGBB with 14-gauge vacuum–assisted biopsy needles.[6]. Melotti and Berg reported a hematoma rate of 45% (71/171) for non-anticoagulated patients utilizing an 11-gauge VABB probe with similar rate of 38% (3/8) noted for a small cohort of anticoagulated patients. [4] Schaefer et al. reported a 42% (11/26) rate for hematomas detected after stereotactic-guided biopsy utilizing a 9-gauge ATEC VAAB probe, including a 19% rate for hematomas measuring greater than 1.5 cm in diameter (1.8cm^3).[5] Combining Schaefer et al. 8-gauge Mammotome and 9-gauge ATEC VABB needle biopsy cohorts shows a 39% rate of hematoma formation.

A larger and more recent study by Chetlen et al. [3] was also reviewed for guidance in establishing a historical-control group. Within their study of 617 ultrasound, stereotactic- and MRI-guided biopsies evaluating the incidence, size and clinical significance of hematomas among patients on and off a variety of antithrombotic therapies, Chetlen et al. reported a 25.5% (51/200) rate of hematoma formation utilizing 9-gauge ATEC VABB for the stereotactic-guided biopsy cohort. The average reported size of the hematomas for the entire study population was 2.6 cm in diameter, (9.2 cm^3), with a reported range in hematoma volume of 0.52 cm^3 to 134 cm^3. The number of cores obtained for individual cohorts and the distribution of those patients on antithrombotic agents (16.5% of all patients), including high- and low-dose ASA, warfarin, clopidogrel and other agents, including the 9-gauge stereotactic-biopsy cohort, was not separately reported. The mean number of cores obtained for the entire study, including the much larger USGBB cohort utilizing 14-gauge needles, was 6.5, although "more cores were obtained using the larger, 9-gauge VAB needles," which were used exclusively for all stereotactic and MRI-guided breast biopsies (MRGBB).

Subjects and Methods

Institutional review board approval was obtained for this HIPPA-compliant prospective study. FDA review and input was considered and incorporated into the scope and design of this trial. The study was registered with Clinicaltrials.gov.

Patient recruitment

Beginning on March 4, 2015, through termination of accrual on November 4, 2015, all non-pregnant, non-lactating women 18 years of age and older presenting for approved stereotactic-guided biopsy of calcifications, small masses (<1.5 cm) and sites of architectural distortion who met inclusion and exclusion study parameters were offered participation in the study. Patients were required to have discontinued the use of most anticoagulant therapy including coumadin, clopidogrel and high-dose aspirin (more than 81 mg) for 5 days. NSAIDS were not restricted. Heparin was restricted for the study, but no patients presented for biopsy who were recently on heparin or other short-acting antiplatelet therapy (bridge therapy). Patients with known bleeding disorder or uncorrected coagulopathy with a platelet count of ≤80,000 and or an INR ≥1.5 were excluded from the study. Coagulation parameters were not routinely assessed unless there was suspicion of coagulopathy, including known deficiencies including Factor Vlll and Xl, DIC, Uremia, Liver Failure, Myeloproliferative Disorder, Alpha 2 Antiplasmin deficiency, Monoclonal Gammopathy and Lupus Anticoagulant.

Patients could show no evidence of cognitive impairment for inclusion in the study.

Two site biopsies within opposite breasts were included for this study, but multisite biopsies in the same breast were excluded (FDA advice).

Informed consent was obtained from all patients prior to inclusion in the study using SecureConsent® software and data storage provided through Enforme Interactive, Frederick, Maryland.

Methods

Stereotactic biopsies were all performed with vacuum assistance using either a 9- gauge Eviva® or 9-gauge Petite Eviva® Breast Biopsy System Hologic®, Bedford MA. All of the biopsies were performed on a dedicated prone stereotactic biopsy table, MultiCare Platinum®, manufactured by Hologic ® Corporation.

All biopsies were performed by one of five radiologists with 5, 18, 23, 23 and 28 years of SGBB experience.

Following standard skin preparation, skin and superficial anesthesia was achieved with two to four ml of buffered 1% lidocaine HCL. For patients without a significant cardiac history or allergy, deep anesthesia was obtained using a maximum of 15 ml of 1% lidocaine with epinephrine (1/100,000), with the bulk administered after advancing or “firing” the needle into or astride the target lesion. Up to an additional 10 ml of lidocaine with epinephrine (1/100,000) was administered during the course of biopsy as needed.

After the biopsy was completed, the biopsy cavity was lavaged with normal saline until clear or after at least three full, 360-degree revolutions of the needle within the cavity were made. If calcifications were targeted, the system was placed on continuous suction-lavage pending review of biopsy specimen imaging. This time interval was not measured, however; with our in-suite specimen imager (Kubtec® Milford CT), this averages three to four minutes. All biopsy sites were then marked with a titanium marker clip

One of three compression devices, having many similar design elements allowing for rapid single-handed attachment to the stereo-guide/paddle was selected for breast compression. Two of the three devices feature compressive surfaces of nearly identical size (approximating two human fingers

side by side) but differing primarily in the centering of compressive force relative to the biopsy window of the stereo-guide compression paddle. One of these devices, a modified flattened sphere (**Image 1**), has its compressive surface centered within the window of the stereotactic-biopsy guide/compression paddle while the other, a modified flattened pyramidal shape, has its compressive surface offset from the center of the biopsy window to several millimeters from either the top, posterior chest-wall side of the breast (**Image 2)** or, in reversed orientation, several millimeters from the inferior, nipple side of the biopsy paddle aperture (**Image 3)**. The decision regarding which particular compression device is to be used may be influenced by a patient's breast size; however, it is primarily directed by the proximity of the biopsy incision site to the chest wall or nipple, where the offset compression-device design is required or optimal. The third device, not shown, centers a larger flat compression surface approximating roughly the width of four fingers within the biopsy paddle window. This device configuration may be used for very small breasts, for large hematomas noted prior to initiation of compression or for compression of hematomas detected after the patient has been removed from the stereotactic-biopsy table, where the collinearity and thus the predictability of the precise location, of the biopsy site has been lost.

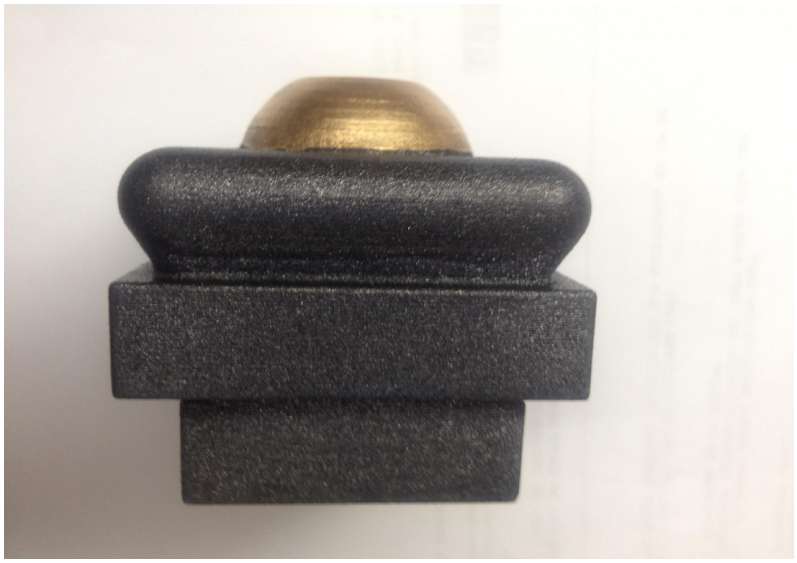


Image 1.

Modified spherical compression surface. (Side view) Compressive surface is colored in gold.

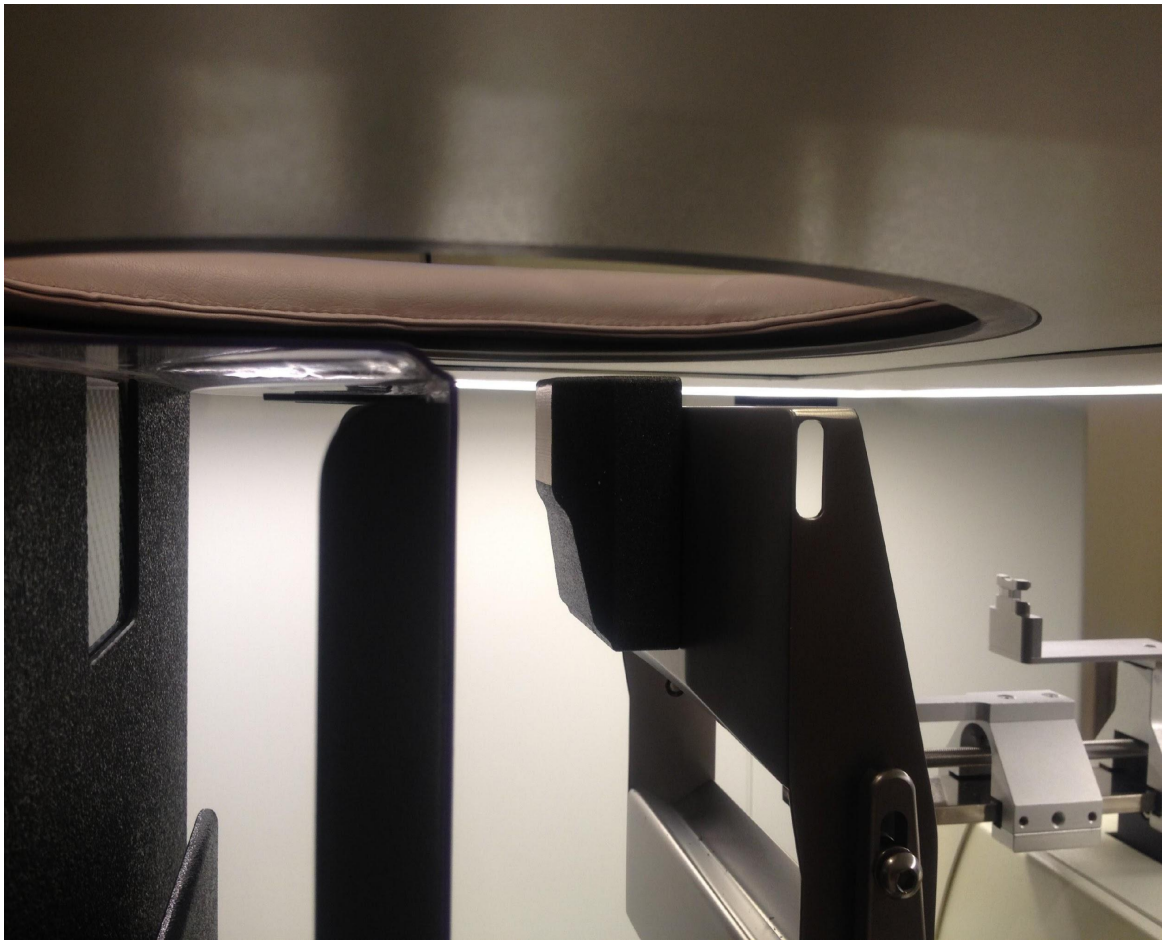


Image 2.

Modified pyramidal device.

Posterior compression orientation. Note that, in this orientation, the center of the flat compressive surface, depicted in gold, is centered 2 mm anterior to the posterior edge of the biopsy window. This device orientation allows for adequate compression of all posterior lesions reachable by biopsy.

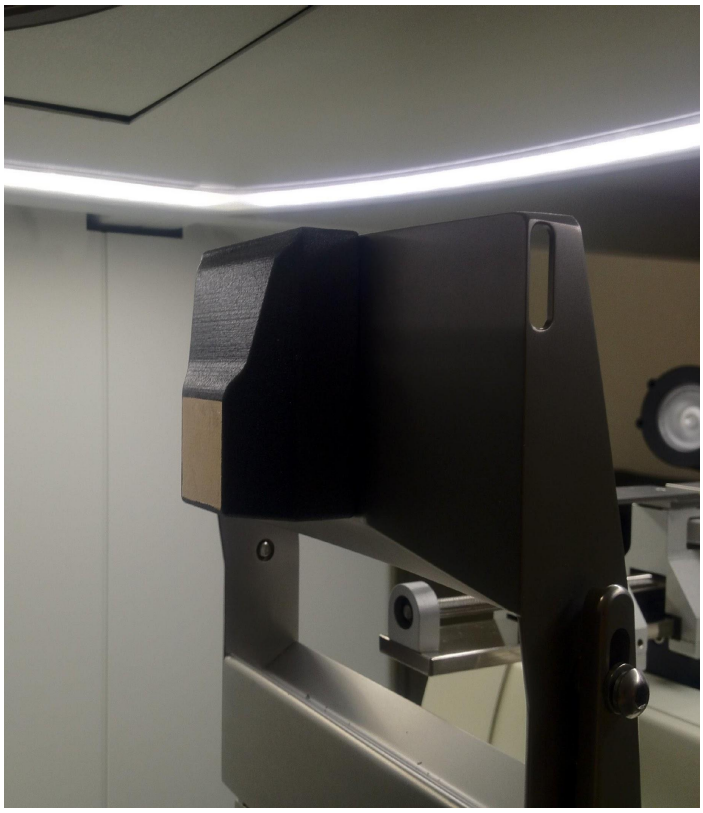


Image 3.

Modified pyramidal device.

The reverse orientation of the compression device shown is recommended for lesions close to the nipple. The posteriorly slanting surface stabilizes posterior breast tissue preventing push-back of breast tissue away from the compressive surface.

Following marker clip placement the stereotactic biopsy guide paddle was withdrawn from the breast and the selected mechanical compression device, enclosed within a sterile latex-free covering, was inserted into the biopsy window of the biopsy paddle. Several twice-folded sterile 4 X 4 inch gauze sponges and several overlain unfolded 4 X 4 gauze sponges were then compressed against the biopsy skin incision. This process takes approximately 5 seconds.

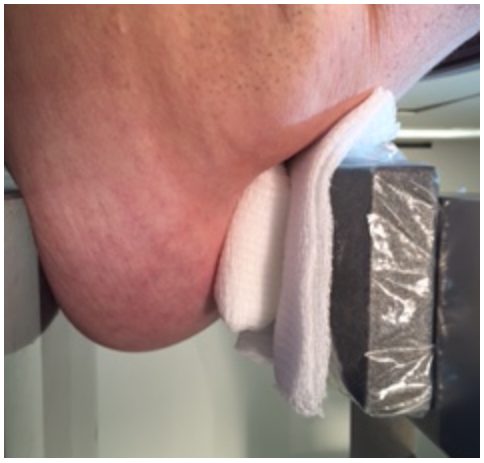


Image 4. Modified pyramidal compression device in place with a sterile gauze and sterile covering shown.

Using the needle driver “X” and “Y” guidance controls, the center of the compressive surface was aligned with the skin incision and the biopsy paddle was subsequently advanced to make contact with the breast. Following initial advancement and compression using the motorized foot control, the hand ”Z” control is then used to apply final graded pressure to the gauze-covered skin incision site. (**Image 4**) As the breast is not moved during this process, the collinearity of the incision, needle tract and deeper biopsy cavity is preserved, ensuring that all potential sites of bleeding are compressed between the compressive surface of the compression device and the posteriorly positioned rigid image detector guard. Similar to standard post biopsy manual compression and compression during mammographic imaging, the amount of pressure applied is an interactive process between the technologists and patients and may be varied depending on the patient’s tolerance of compression and breast thickness.

Mechanical breast compression was maintained for a minimum of ten minutes in all cases. If the physician or technologist felt it was warranted, the compression time could be extended without limit per the protocol. Time in mechanical compression could be extended for a number of reasons including note of significant bloody lavage during or following the biopsy, note of unusual bleeding during clip placement or observation of a hematoma on the immediate post-clip placement small field of view imaging obtained while the patient was still on the table. Total time in compression, measured in minutes, was recorded for all procedures.

Technologists remained in the biopsy suite throughout compression to monitor their patients but could perform other duties as long as they remained in close proximity to the patients.

After a brief assessment of the biopsy site, the patients were taken off the biopsy table and moved to an adjacent mammography suite for a standard two-view, mediolateral and cranicaudal view, mammogram of the post-biopsy breast. This was routinely accomplished within 5 to 15 minutes following compression.

The two-view mammogram was reviewed by the attending radiologist with the nature of target lesion (calcification, mass or density), number of cores obtained and compression time recorded. The mammograms were reviewed for accuracy of targeting, adequacy of clip deployment (less than 20 mm

from the target lesion or biopsy cavity) and the presence or absence of a hematoma. Hematomas for this study were assessed and measured on the immediate two- view post-biopsy mammogram or on supplemental ultrasound examination if the biopsy occurred in a dense portion of a patient's breast where detection of a hematoma could be limited. Consistent with the primary selected historical-control study methodology[3], post-biopsy collections seen as three-dimensional masses on post-biopsy imaging with a volume greater than 0.52 cm^3 were recorded as a hematoma. To enhance uniformity among radiologists, example images of hematomas and measurement techniques were reviewed by the five participating radiologists prior to initiation of the protocol, and images were maintained on display in the reading area for visual reference throughout the study.

Hematomas were measured in millimeters in thee planes, including the longest diameter, with hematoma volume calculated and recorded using the formula for an ellipsoid. (Equation 1) Using this formula, a spherical hematoma, a "special ellipsoid" measuring 1 cm in diameter in all planes, would have a volume of 0.52 cm^3, and a spherical hematoma measuring 2.5 cm in diameter in all planes would have a volume of 15.6 cm^3. If a mass, as opposed to calcifications, was targeted for biopsy, the volume of the target lesion was measured using the same technique and subtracted from the total post-biopsy volume (representing hematoma and mass) to arrive at hematoma volume.

Statistical methods

Sample Size Calculation

This study involved 120 female patients/procedures assigned to the active treatment arm. A sample size of 120 patients was determined to be appropriate on the basis of statistical power calculations (SAS®, PROC Power) to allow statistical comparison to a historical-control group (Chetlen et al. 2013). Specifically, the hematoma (>0.523cm^3) rate in the single-arm study would be compared to the lower 95% confidence interval for the Chetlen et al. ([3])historical-control data set of N=200, where 51/200, or 25.5%, of patients were reported to have a hematoma >0.523 cm^3 following biopsy. The lower 95% confidence interval for the 25.5% historical control rate is 19.46%. This calculation is provided below:

Where p = proportion of interest = 0.255

n = sample size = 200

α = desired confidence = 95%

z= z value for desired confidence = 1.96

= 25.5 ± 6.04 or 19.46 to 31.54 (95% CI) % rate for hematoma (>0.523 cm^3) following biopsy.

Assuming that being within 10% of the target rate (i.e., 0.1946) is not clinically important, then the null proportion becomes 0.1946+0.1 = 0.2946. Assuming that the likely rate of hematoma (above 0.523 cm^3) in the study will be 19.46%, equal to the target rate, then a sample size of 120 patients would provide 80% power for the ITT population and at least 76% power for the PP population, assuming that up to 14 patients (12%) do not meet PP criteria (i.e., PP≥106 patients).

Primary Safety Endpoint

Paralleling the primary historical control, the primary efficacy endpoint is defined in this study as the occurrence of a hematoma greater than 0.523 $cm.^3$ calculated using the formula for the volume of an ellipsoid (Equation 1) as detected on standard post-biopsy mammogram or post-biopsy sonogram.

Secondary Safety and Efficiency Endpoints

Following the mammogram and prior to discharge, a nursing assessment was performed and included obtaining the patient's vital signs and performing a targeted physical examination of the biopsy site. Per protocol, all patients were asked to rate their pain during the biopsy, during post-biopsy compression and at the time of the discharge assessment on a numerical scale of 0 to 10 (none to severe). They were asked to rate the compression experience on a scale of 1 to 5 (great-1, good, OK, fair and poor-5). Physical-exam results, including any evidence of a new lump, bruise or skin tear were recorded. If a new lump/possible hematoma was detected, and not noted on the post-biopsy mammogram, a targeted ultrasound was performed to evaluate for and then, if present, measure all hematomas. Technologists with 4, 18 and 19 years of SGBB experience were asked to evaluate perceived changes to work flow using the device on a numerical scale of -5 to plus 5 (extreme degradation to extreme enhancement) and estimate the net time saved or lost (in minutes) relative to standard manual compression (assuming they would have been responsible for performing the compression).

All adverse events including, but not limited to, excessive bleeding, bruising, pain and clinically significant hematomas were recorded.

For this study, clinically significant hematomas were defined as hematomas requiring surgical consultation for large or expanding hematoma, requirement for transfusion, admission for observation or surgical control and hematomas resulting in a delay of required follow-on surgery including excisional biopsy or lumpectomy.

Any treatments required for complications of biopsies were recorded and any complications felt to be possibly related to use of the compression device were to be specifically noted.

Patients were called within 24 hours (72 hours if biopsy was performed on a Friday) and at 7 days after biopsies. At both points of contact, patients were again asked to assess pain on a scale from 0 to 10 (none to severe) and satisfaction on a scale from 1 to 5 (great-1 to poor-5). Per protocol, all patients with a new lump, significant or increasing pain, signs or symptoms of an infection or bruising greater than a "half dollar"/30 mm were asked to return for assessment, including a targeted sonogram at the time of scheduled contact or at any time during the week follow long follow-up period. In assessing for delayed hematoma, it was felt that patients without a lump or significant ecchymosis were unlikely to have a hematoma as noted by Harlow et al.[1]**.** Patients were informed that there would be no additional charges to them, or their insurance companies, for any additional evaluation and imaging if required.

Results

Stereotactic-guided biopsies were performed for evaluation of 120 lesions in 118 women averaging 57 years of age (34 to 79) between 3/4/2015 and 11/4/2015. Two patients had one lesion sampled in each breast.

All biopsies were performed on a dedicated prone biopsy table utilizing a 9-gauge vacuum-assisted biopsy system with most antithrombotic agents discontinued per protocol, including three patients on coumadin, two on clopidogrel, one on rivaroxaban and two on high-dose ASA. 7.6% (9/118) of patients were on low-dose ASA at the time of the procedures. No patients were on NSAIDS at the time of biopsy.

Biopsies targeted clusters of calcifications in 80 cases and small (<1.5 cm) masses or densities in 40.

The average number of cores obtained was 9.9 (range 6-24 cores).

Hematomas greater than 0.52 cm^3 (spherical hematoma 1 cm diameter) were detected in 9 (7.5%) of 120 biopsies, with an average volume of 4.4 cm^3 (spherical hematoma measuring ~2.0 cm diameter) ranging from 1 cm^3 to 12.1 cm^3 (spherical hematomas ~ 1.3 cm to 2.9 cm in diameter). The immediate post-biopsy hematomas were detected on mammograms in 8 patients and on sonography in one patient. An average of 8.6 cores was obtained in the patients with observed hematomas.

Primary Safety Endpoint

The observed rate of hematoma using the mechanical compression device(s) was non-inferior relative to manual compression using a historical-control rate of 25.4% ($p<0.0001$), as detailed below. Per our stated definition, no clinically significant hematomas were observed in the study population.

The primary safety endpoint was defined as mammogram- or sonogram-detected hematomas for 120 observations, where each observation was independent and from the same single-device arm.

A non-inferiority test was performed using the BINOMIAL option in PROC FREQ (SAS® v9.3, Cary, North Carolina). The analysis was performed by testing for a larger proportion experiencing no adverse effects, 1-p. The null proportion of the test was $1\text{-}p_0=1 - 0.1946 = 0.8054$, where 19.46% equaled the maximum proportion of adverse events. A margin of 10% was used, as a rate within 10% of the target, was not deemed to be clinically important.

A total of 9/120 (7.5%) patients were reported as “yes” for hematoma seen on mammogram or ultrasound (Table 2).

The non-inferiority test indicated that the hematoma rate from the mechanical compression device (7.5%) was not substantially inferior to the historical manual compression target rate of 19.46% ($p<0.0001$; Table 3). The significance of the test is verified by the lower limit of the 90% confidence interval (0.8566) being greater than the non-inferiority limit (0.7054 = 0.8054 -0.1). The observed rate of hematoma using the mechanical compression device (7.5%) was found to be non-inferior relative to the manual compression historical target rate of 19.46%.

Table 2. Frequency of ‘HEMATOMA Mammogram/Ultrasound outcome

Outcome*	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	111	92.50	111	92.50

1	9	7.50	120	100.00

*0 = “no” and 1 = “yes”

Table 3. Noninferiority Analysis.

Noninferiority Analysis						
H0: P - p0 <= -Margin Ha: P - p0 > -Margin						
p0 = 0.8054 Margin = 0.1						
Proportion	**ASE under H0**	**Z**	**Pr > Z**	**Noninferiority Limit**	**90% Confidence Limits**	
0.925	0.0416	5.277	<.0001	0.7054	0.8566	0.9934

Secondary Safety and Efficiency Endpoint Results

Compression:

Patients were in compression for an average of 10.8 minutes, with a range of ten to twenty minutes. Twenty patients (16%) were in compression greater than ten minutes, with fourteen (11.6%) in compression for 15 to 20 minutes. Three of the nine patients (33%) with hematomas were in compression for 15 to 20 minutes because the radiologist or technologists noted significant intra-procedural bleeding indicated by bloody lavage, bloody return in the biopsy needle sheath or a hematoma on immediate post-clip placement small field imaging.

Patients reported average pain scores of 2 (0 to 10, none to severe) during the biopsy with 6.7% reporting a score of seven to ten. Patients reported an average pain score of 0.9 during compression, with two patients (1.7%) reporting a score of seven to ten. Pain reported prior to discharge averaged 0.3.

The patients' satisfaction was rated on a scale from 1 to 5, (great, good, OK, fair, poor) for the compression experience. This averaged 1.35 (range 1 to 3) with 97% of patients rating the compression as good (27%) or great (70%).

Intervention-suite staff estimated average net time saved at 10.5 minutes per case, closely mirroring the average time patients were in compression (10.8 minutes), with the average effect on work flow compared to standard manual compression rated at 4.9 (negative 5 to positive 5 scale, extreme degradation to extreme enhancement).

Post-Biopsy Follow-Up:

96% of patients were reached for 24-hour follow-up and 94% were reached at seven days (multiple documented calls were made to the non-responders).

At close interval follow-up, delayed hematomas greater than 0.52 cm^3 were detected in 3.3% (4/120) patients. (Detected on days 2, 5, and 2 on day 7). Delayed hematomas, all measured on sonograms, had an average volume of 9 cm^3 (range 1.1cm^3 to 30.5 cm^3). Two additional patients reported bruising greater than 30 mm but declined to return for evaluation.

Average pain score reported post biopsy was 0.7 at 24 hours (0 to 10 /none to severe) with two patients reporting a score of greater than 4 (6 and 9) but without lump or bruising. Both declined to return for evaluation. Patients' satisfaction scores at 24 hours averaged 1.3 (1 to 5, great, good, OK, fair, poor).

At seven days, the patients reached reported an average pain score of 0.4 (0 to 10) and satisfaction of 1.2 (1 to 5, great, good, OK, fair, poor). Four patients reported pain of 4 or greater. One of the patients declined evaluation, with three returning for assessment. Sonography demonstrated a small hematoma (1.8 cm^3) in one patient and no hematoma in another. The third patient returned for evaluation and was noted not to have a lump or any bruising on physical exam. Per protocol, she should have had a sonogram assessment but none was performed.

All available delayed imaging performed for localization at the time of lumpectomy or surgical biopsy of high-risk lesions was reviewed for thirty patients in the study population. The average time of follow-up imaging (2-view mammogram) was 4 weeks post biopsy (range 2 to 11 weeks). No new hematomas were detected. One previously detected hematoma, noted on immediate post-biopsy imaging, persisted and was partially resolved at 2 weeks post biopsy.

Other:

Clip-deployment failure/inadequate position was noted in 2 patients requiring a second clip.

No deep or superficial breast infections or skin irritations other than bruising were observed in the study population.

Pathology revealed 10 cases of invasive cancer, 6 cases of DCIS, 14 cases of atypia, 5 papilloma and 3 findings of radial scar.

Upgrade at surgery (underestimation of pathology on VABB biopsy) was noted in two patients, with atypia upgraded to invasive in one (1/14) and DCIS upgraded to micro invasive cancer in another (1/6) patients.

Discussion:

The reported rates of hematoma formation significantly increases from ultrasound through stereotactic- and MRI-guided MIBB. (Summarized table 1) Typical of the literature, Chetlen et al. noted rates of hematoma formation of 3.2% with 14–gauge core USGBB, 10% with larger 12-gauge VABB systems used in USGBB, to 25.5% for stereotactic-guided procedures using 9–gauge VABB needles and 43 % for their MRI-guided biopsy cohorts also using a 9-gauge ATEC VABB needle system.

This increase in the rate of hematomas may reflect a number of factors, including the almost exclusive use of larger, 8- and 9-gauge VABB needle systems in stereotactic- and MRI-guided biopsies versus the

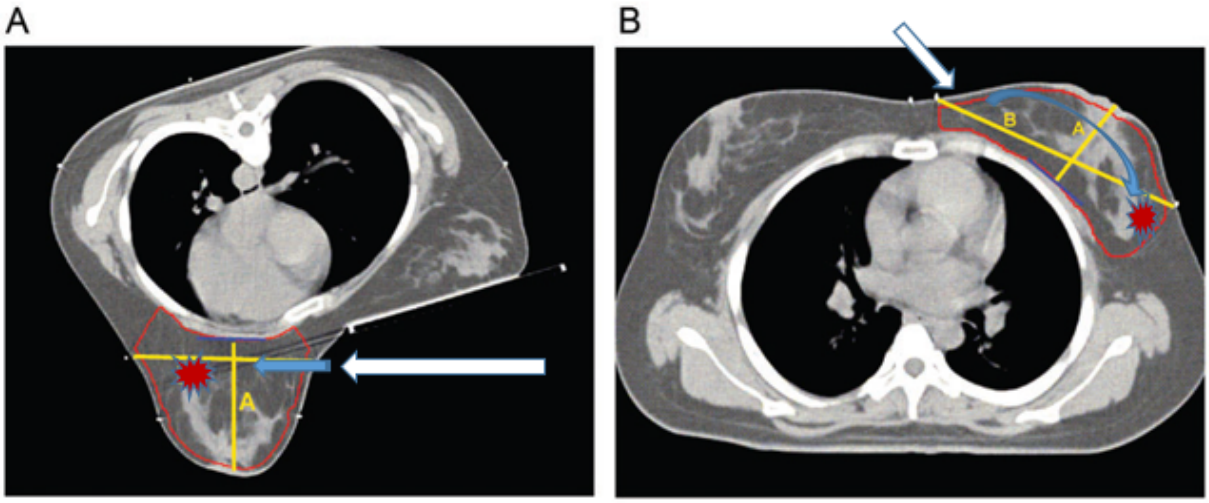
14-gauge core needles commonly used in ultrasound-guided biopsies, as well as an increase in the average number of cores from 5 or less in USGBB to 12 or more cores obtained in SGBB but other factors affecting rate of hematoma formation may be equally important. During USGBB constant direct pressure can be applied with the ultrasound transducer directly on the target lesion during the biopsy. Additionally, if active bleeding is noted during real-time imaging, compression may be increased immediately and significantly. Furthermore, as the biopsy site is precisely located directly beneath the transducer, and patients are rarely moved after ultrasound-guided biopsy, accurate and immediate manual compression is easily applied to the biopsy site with excellent compression ergonomics as the medical staff, standing above their supine patients, may easily exert downward pressure on the biopsy site.

In contrast, stereotactic-guided breast biopsy has several less favorable factors to consider. In the practice of performing stereotactic-guided breast biopsy, compression of the breast by the biopsy paddle/guide is firm but compression is necessarily peripheral to the target site. Unlike ultrasound-guided procedures, there is an absence of real-time visualization of the biopsy site during the stereotaxic- guided procedures and consequently patients may bleed significantly without detection during the course of the typically more lengthy biopsy procedure prior to compression.

Furthermore, for a number of reasons affected by workflow patterns, compression after the biopsy is variable in terms of its immediacy, accuracy and consistency. For interventional suites that choose to compress patients while they remain on the biopsy table, the compression of the biopsy site is immediate and accuracy is maintained as the biopsy site and needle tract remain directly deep to the skin incision. Unfortunately, forceful consistent compression is difficult to apply and maintain as most commonly used prone-table designs require the physician or technologist to apply manual digital compression off axis to their body with their hand above their shoulder. (**Image 5**) The awkward ergonomics may result in variable and suboptimal application of force for a standard ten minutes of compression following biopsy and may be extremely difficult to maintain in cases of prolonged bleeding requiring 15 to 20 minutes, or more, of manual compression.

Some centers, using prone tables, routinely move their patients to a stretcher for all or a portion of the post-biopsy compression due to the difficult ergonomics associated with compression on the biopsy table. Movement of patients from the biopsy table to a stretcher may result in a potentially significant delay in the initial application of post-biopsy compression. This workflow pattern also diminishes the accuracy of post-biopsy compression as breast rotation, attendant moving patients from a prone to a supine position, necessarily destroys the linear alignment of all the possible sites of SGBB-related bleeding from the skin incision and needle tack through to the breast-biopsy site. As the 180-degree breast rotation makes the biopsy skin incision a poor guide to determining the location of the biopsy site deep within often voluminous breast tissue targeting of the biopsy site for manual compression becomes, in effect, an educated guess. (**Art. 1**) Supporting the likelihood that these multiple factors are important additional determinants of hematoma formation, consider that the highest hematoma rates are routinely reported with MRI-guided breast biopsy (MRBB)[3] where in order to maintain lesion enhancement and visualization, there is necessarily minimal peripheral compression of the biopsy site during often lengthy biopsy procedures. Additionally, if patients are moved off the MRI table for post-biopsy compression in the supine position, similar problems of delay and reduced accuracy of post-biopsy compression described for stereotactic-guided biopsy would apply as well.

Image 5. Challenging ergonomics of standard manual compression with compressing hand of technologist held above the shoulder and off axis to her body during compression.



Art 1.

A) Collinear straight-line arrangement of all possible bleeding sites, including incision, needle tract and biopsy cavity, is preserved with maintenance of prone positioning post biopsy.

B) Loss of collinearity with breast rotation from prone to supine position. Note that after rotation, the needle tract follows a 3-dimensional twisting arc. The location of the biopsy cavity for targeted compression must be roughly estimated based on a woman's breast size, the estimated depth of the biopsy cavity and intra-procedural compression thickness of the breast, among other factors. After patient rotation, the biopsy skin incision now offers minimal guidance for targeted manual compression.

Art Key: The yellow lines are reference lines between metallic markers placed on the skin (white) used for supine to prone radiation therapy planning.

Red Star: biopsy cavity site

Blue Arrow: biopsy needle tract

White Arrow: biopsy needle and incision site

While not considered clinically significant by commonly reported definitions, MIBB-related hematomas may, nonetheless, be the cause of signifiant post-procedural pain, create management dilemmas, and cause significant patient dissatisfaction. Dershaw et al. [17] reported that 33 of 100 patients experienced pain following SGBB, in some cases lasting up to 2 weeks, with 15 patients requiring analgesics. Post-biopsy pain was noted by 69% of patients as reported by Jackman et al. [19]. Even a brief perusal of patient-centered internet blogs describing stereotactic-breast biopsy often finds very unflattering descriptions of SGBB- related bruising and painful hematomas. Patients frequently state that they are told in effect, "Hematomas are just part of the procedure" or relate "They didn't compress long enough and now my entire breast is black and blue." Our often used definitions of "clinically significant" may not be applicable from the patient's perspective.

Although most reported MIBB-related hematomas do not delay surgery, even a moderate hematoma, in a small breast, may be problematic, resulting in a "treatment dilemmas"[2] or cause a clinically significant delay in the "time to surgery" (TTS) following diagnosis. Delays in TTS, regardless of the causes, were recently demonstrated to diminish overall and disease-specific survival.[28]

Poor residual tumor-site visualization and clip displacement in association with hematoma may require excessive tissue removal, thus reducing post-surgical cosmesis. Displacement of clips by hematomas, movement of clips within the needle track due to loss of compression ,"accordion effect", and both early and delayed migration combined to produce clip malposition relative to the biopsy site of 20 mm or more in 14% to 21.5%, as reported by Rosen et al. and Kass et al.[2,8,9]

It is hoped that use of this, or other mechanical compression devices, will encourage further study and, if shown to be safe and efficacious, increase the acceptance of MIBB in the setting of diminished clotting parameters when the risks of discontinuing antithrombotic therapy are significant. Patients on coumadin and various antiplatelet drugs for coronary artery stents face relatively uncommon but potentially devastating clinical risks, including stroke, peripheral arterial embolization, myocardial infarction and death if anticoagulation and antiplatelet therapy is discontinued for even short intervals.[21,22,23] Bridge therapy, conversion from oral anti-coagulation and antiplatelet therapy to IV heparin and back, is expensive and has significant risks (primarily bleeding) that are similar to continuous therapy for patients with atrial fibrillation, as reported by Douketis et al.[22] For patients with recently placed bare-metal or, more problematic, drug-eluting coronary artery stents requiring uninterrupted antiplatelet and antithrombotic therapy, the decision is more complex, as reported by Nuttall et al. and S. Savonitto et al.[23,24] While stopping blood thinners may be absolutely necessary for many major surgical procedures, where massive blood loss might occur, the female breast is a closed space without continuity to the chest and abdominal body cavities, thus altering the risk-benefit ratio. Multiple studies examining the continuation of low-dose ASA and NSAIDS are supportive of MIBB in that setting, based on a documented lack of "clinically relevant" hematomas in those cohorts, but acknowledge a significant difference in rate and size of non-clinically significant hematomas.[3,4,11] Additionally, the decision to continue coumadin therapy within the therapeutic range for patients with atrial fibrillation during MIBB has support in the radiologic literature, but large data sets evaluating the use of ribaroxaban and antiplatelet drugs, including clopridogrel, and multiple newer agents is lacking.[3,4,11]

The risk-benefit discussion, often primarily between a patient and her cardiologist, regarding withdrawal of anticoagulant and antiplatelet therapy for procedures, may be complex. Consideration of many factors, such as whether or not a stoke occurred with atrial fibrillation, the time interval from recently placed drug-eluting and less problematic bare-metal stents and which specific antiplatelet drug is being used, among other factors, play into that calculation.

Complicating this decision, for the radiologist and patient, is a fear that prolonged manual compression may be required for control of bleeding in a patient who may choose to continue anticoagulant and or antiplatelet therapy. Understandably, this concern may alter a breast interventionist's willingness to proceed with MIBB in patients who might prefer to continue therapy. Patients, cardiologists and radiologists are thus forced into an asymmetric assessment of risk and benefit that hinges on weighing the small risk of a potentially devastating complication attendant withdrawal of blood thinners versus the risks of managing a potentially difficult problem of bleeding after a biopsy. We believe that potentially making that an easier choice, if possible, warrants continued study of this or similar devices.

Given the low rate of clinically significant bleeding complications reported in the literature, a large double- blinded multi-institutional study would be optimal and necessary to provide proper power and guidance for evaluation of the safety and efficacy of MIBB with mechanical compression in the face of ongoing antiplatelet and anticoagulant therapy.

CLINICAL PRACTICE POINTS

Bleeding and hematoma formation are the most common complications of stereotactic-guided breast biopsy. Large hematomas following stereotactic-guided biopsy may displace marker clips, delay and alter optimal surgical planning, diminish cosmesis and pose other treatment dilemmas. Biopsy related hematomas diminish patient satisfaction and we believe that it should be acknowledged that our commonly reported low rates of narrowly defined "clinically significant bleeding and hematoma formation" offer little comfort to a large number of patients with extensive bruising or large post biopsy hematomas.

Observed rates of hematoma formation following MIBB may be related to a number of factors, including the size and number of core specimens obtained, but also may be significantly influenced by whether compression was applied directly on, or peripheral to, the biopsy site during the biopsy as well as by the immediacy, accuracy and sustainability of forceful post-biopsy breast compression.

The medical device studied addressed a number of the limitations of standard manual compression following SGBB by providing immediate, accurate and consistent post biopsy breast mechanical compression. Use of the device was shown to be non-inferior to standard manual compression ($p<0.0001$) reducing the rate of hematomas by 70% and the size of hematomas by 52% relative to historical controls.

Mechanical breast compression was well tolerated by patients and offers a potential welcome improvement to staff workflow, with significant labor savings and reduced blood exposure for medical personnel during compression. Future validation of the device in the setting of active anticoagulation may help bridge a current clinical divide to our patients' benefit.

Limitations of the Study

The study is a single-institution non-blinded study with historical control. The small numbers of patients on low-dose ASA (8) is not sufficient for analysis, but our findings are consistent with many previous studies where the rate of hematoma is increased, but the volume of hematomas is not, relative to patients not currently on ASA or other antithrombotic therapy. [(3)]

Further Study of this device for use in anticoagulated patients is anticipated.

Conflict of Interest. The lead author of this study has secured a U.S. patent on the compression devices with others pending. No other financial or personal interests exist.

Summary of hematoma rates (Table 1)

Guidance used	Needle size/type	Number cores	Hematoma rate	Hematoma volume	Hematoma Diameter (average)	Cohort or study size	Anticoagulants	Compression type	Lead author
US	14-G core	4.6	1.8%	0.52 cm (3)	1.0cm	391	0%	Manual To 15 minutes	Melotti (4)
US	14_G core	5 to 6	3.2%	9.2cm (3) For all patients	2.6 cm (all)	339			Chetlen(3)
US	12-G VAB (ATEC)	NA	10%	9.2cm (3) For all patients	2.6 cm (all)	20	NA		Chetlen (3)
Stereo	14 G Core	5.3	45%	NA	0.6 mm	100	0 %		Melloti (4)
Stereo	14 G VAB	12	30.5%	8.1 cm (3)	2.5cm	108			Liberman(6)
Stereo	11 G VAB	11	45 %	0.4 cm(3)	0.8 cm	171	1% ASA		Melloti (4)
Stereo	9-G VAB (ATEC) 8-G VAB (Mammotome)	24 24	42% 19% 35.5%	NA >1.8 cm(3) NA	All > 1.5 cm All	26 26 31	NA NA	"10 min Manual"	Schaefer (5) Schaefer
Stereo	9-G VAB ATEC	NA	25.5% >0.52 cm (3)	9.2cm (3) For all patients	2.6 cm For all patients	200	11.7% of all patients on ASA	"5 to 10 or more" manual (split on an off table) (PC)	Chetlin (3)
Stereo	9-G VAB ATEC	10	7.5% >0.52 cm(3)	4.1 cm (3)	2.0 cm	120	7.6% low dose ASA	11 min mechanical (10 -20) minutes	Kremers et al. (Current study)
MRI	9- G VAB ATEC	NA	43%	**9.2cm (3)** For all patients	**2.6 cm** For all patients	58	NA	"5 to 10 or more"	Chetlin (3)

Appendix:

Volume of an ellipsoid Eq. (A.1) **(PI**/6) A X B X C, where A, B and C are the diameters of the hematoma.

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Submission Declaration: No conflicts with Elsevier policies for multiple, concurrent or duplicate submissions exist.

Conflict of Interest. The lead author of this study has secured a U.S. patent on the compression device(s) with others pending. The FDA was involved in the study design and consent process through pre submission discussions and is currently evaluating the devices for PMA 510 (K).

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The costs included the contractual hourly employment of a statistician who, in conjunction with the FDA, agreed on initial study design for proper size and statistical power and provide statistical analysis of the results for this paper and for FDA PMA submission.

An oncology nurse was employed on an hourly basis to aid in study design including consent and data collection forms and analysis for local IRB and FDA review and acceptance.

Hourly consultation fees were paid to Mike Maloney (Intertox Corporation) for regulatory guidance and interface with the FDA.

No institutional costs were incurred as our workflows for this study were not materially different than standard departmental work flows. (Follow on post biopsy imaging required for this study for suspected hematomas or abscess is routinely performed and is free of charge at our institution).

A mammography technologist, who was not involved in the study, was paid an hourly wage to compile all imaging studies for review on a Hologic® work station.

All data was obtained and reviewed free of remuneration by all of the, nurses, patient navigators and authors, including summary data by Dr. Judd Goldberg, all of whom, other than Dr. Kremers, have no financial or other disclosable interest.

SecureConsent® software and electronic data storage (IRB approved) was provided free of charge through Enforme Interactive, Frederick, Maryland.

Informed Consent

FDA and IRB approved consent was obtained for all 118 study patients and are available for review.

Consent for patient image(s) are available for review upon request.

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