Blisters on the Anterior Shin in 3 Research Subjects After a 1-MHz, 1.5-W/cm², Continuous Ultrasound Treatment: A Case Series

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Context: Clinicians should consider multiple factors when estimating tissue-heating rates.

Objective: To report 3 separate occurrences of blisters during an ultrasound treatment experiment.

Background: While we were conducting a research experiment comparing the measurement capabilities of 2 different intramuscular temperature devices, 3 female participants (age = 26.33 ± 3.79 years, height = 169.34 ± 3.89 cm, mass = 63.39 ± 3.81 kg) out of 16 healthy volunteers (7 men: age = 22.83 ± 1.17 years, height = 170.61 ± 7.77 cm, mass = 74.62 ± 19.24 kg; 9 women: age = 24.22 ± 2.73 years, height = 171.88 ± 6.35 cm, mass = 73.99 ± 18.55 kg) developed blisters on the anterior shin after a 1-MHz, 1.5-W/cm² continuous ultrasound treatment delivered to the triceps surae muscle.

Differential Diagnosis: Allergies; chemical reaction with cleaning agents; sunburn; negative interaction between the temperature measurement instruments and the ultrasound field; the ultrasound transducer not being calibrated properly, producing a nonuniform field and creating a hot spot or heating differently when compared with other ultrasound devices; the smaller anatomy of our female subjects; or a confounding interaction among these factors.

Treatment: Participants were given standard minor burn care by a physician.

Uniqueness: (1) The development of blisters on the anterior aspect of the shin as a result of an ultrasound treatment to the posterior aspect of the triceps surae muscle and (2) muscle tissue heating rates ranging from 0.19°C to 1.1°C/min, when ultrasound researchers have suggested tissue heating in the range of 0.3°C/min with these settings.

Conclusions: These adverse events raise important questions regarding treatment application and potential differences in heating and quality control among different ultrasound devices from different manufacturers.

Key Words: muscle heating, burn, spatial average intensity, beam nonuniformity ratio, therapeutic modalities

During a research experiment comparing the tissue-temperature measurement capabilities of 2 intramuscular temperature devices, the thermocouple (thermocouple microbe IT-23; Physitemp Instruments, Inc, Clifton, NJ) and the thermistor (thermistor microprobe-23/5; Physitemp Instruments, Inc, Clifton, NJ), 3 adverse events were noted. Three female volunteers experienced cutaneous blisters on the anterior shin as a result of an ultrasound treatment delivered to the posterior triceps surae muscle. To our knowledge, no similar events have been reported previously in the ultrasound literature. Therefore, our purpose is to report these observations and to discuss why they may have occurred.

CASE SERIES

Personal Data

Sixteen healthy volunteers (7 men: age = 22.83 ± 1.17 years, height = 170.61 ± 7.77 cm, mass = 74.62 ± 19.24 kg; and 9 women: age = 24.22 ± 2.73 years, height = 171.88 ± 6.35 cm, mass = 73.99 ± 18.55 kg) enrolled in this study. Unexpectedly, 3 of the female volunteers (subjects 9, 15, and 16 [age = 26.33 ± 3.79 years, height = 169.34 ± 3.89 cm, mass = 63.39 ± 3.81 kg]) developed blisters on the anterior shin after the ultrasound treatment.

Chief Complaint

These women developed blisters on the anterior shin approximately 18 to 24 hours after ultrasound treatment to the triceps surae muscle group.

History of Present Complaint

A sterilized thermocouple and thermistor were inserted at a depth of 5 cm into the medial aspect of the subject’s triceps surae muscle group. The thermocouple and thermistor were inserted parallel to each other, separated by 3 cm.

Instrument Insertion Methods. Subjects lay prone on a standard treatment table. The leg was measured for the area of greatest girth. A carpenter square was placed flush to the medial aspect of the calf and was leveled. The insertion sites were marked 5 cm inferior to the carpenter square, so that the temperature recordings were taken at a depth of 5 cm. Two markings were placed 3 cm apart on the medial aspect of the calf to mark the insertion sites for the thermocouple and thermistor. The insertion area was cleaned thoroughly with a...
povidone-iodine scrub, and a physician then injected 1 mL of 1% lidocaine into each injection site.

Before each injection, the temperature instruments were sterilized in Cidex Plus 3.4% glutaraldehyde solution (Johnson & Johnson Medical, Arlington, TX) for at least 10 hours as deemed necessary by the manufacturer for sterility. The thermocouple was handled with sterile gloves, wiped with sterile gauze, and marked 10 cm from the tip of the thermocouple. This marking provided a landmark that remained outside the leg to assess how far the thermocouple was inserted into the muscle after injection. Once the area was anesthetized, the physician injected a leveled 21-gauge 5.7-cm (2¼-in) intramuscular catheter needle into the medial triceps surae muscle group. After the catheter needle was removed, the thermocouple was pushed through the catheter until no additional length of the thermocouple could be advanced due to resistance met by the muscle. The catheter was then carefully withdrawn over the thermocouple. The thermocouple was inserted 5 cm into the muscle tissue. (After the thermocouple was inserted, the investigator measured the distance from the insertion site to the spot marked on the thermocouple. The thermocouple was backed out of the muscle tissue, if needed, to ensure that it was inserted 5 cm into the muscle tissue.) The thermocouple was secured to the skin with tape to prevent accidental withdrawal of the thermocouple from the muscle. The thermistor then was inserted into the second injection site. A level was again used to ensure the thermistor was inserted levelly. A sterilized hemostat was used to grip the sterilized thermistor approximately 1 cm proximal to the distal tip to prevent bending of the thermistor as increasing pressure was applied until it penetrated the skin. The thermistor was inserted 4.5 cm into the muscle. After the temperature instruments were inserted, they were interfaced to the Data Logger (Cole-Parmer Instrument Co, Vernon Hills, IL). Baseline temperatures were recorded for 2 minutes, and temperatures were taken every 30 seconds for the duration of the experiment.

Ultrasound Treatment. The investigator performed a standard ultrasound treatment (1-MHz, 1.5-W/cm² continuously for a maximum of 10 minutes) perpendicular to the thermocouple and thermistor. A 10-cm (effective radiating area [ERA] of 8.5 cm²) transducer attached to a Chattanooga Intelect Combination Unit (Intelect Legend Combination unit 4C; Chattanooga Group, Inc, Hixson, TN) was used for the ultrasound treatment. Treatment area was controlled for each subject with a template to trace an area twice the ERA. A premeasured amount (5 mL) of Aquasonic 100 Transmission Gel (Parker Laboratories, Inc, Orange, NJ) at room temperature acted as the coupling agent for all treatments. A metronome set at 40 beats per minute standardized the speed at which the ultrasound head was moved. The ultrasound treatments were performed until the intramuscular temperature increased by 4.0°C, the subject complained of pain, or a treatment time of 10 minutes was reached. The investigator encouraged the volunteer to be honest about the sensations and to avoid attempting to “tough out” the treatment if it became uncomfortable.

Blister Formation. Treatments were stopped in 3 subjects because the tissue temperature had increased at least 4.0°C from baseline and 2 of the subjects noted the sudden onset of intense pain on the anterior shin. Baseline and final muscle temperatures and heating rates for the 3 subjects, respectively, were 35.5°C/min, 40.5°C/min, and 1.1°C/min over a 4.5-minute treatment for subject 9; 37.7°C/min, 40.9°C/min, and 0.8°C/min over a 4.0-minute treatment for subject 15; and 36.4°C/min, 40.4°C/min, and 0.4°C/min over a 10-minute treatment for subject 16. Subject 16 also reported a feeling of slight warmth on the anterior shin during the ninth minute of treatment, but she did not feel the treatment needed to be terminated because it was merely a mild warming sensation.

At treatment completion, the investigator noted that subjects 15 and 16 exhibited mild redness on the anterior shin directly opposite where the ultrasound had been applied. Within 24 hours of treatment, subjects 9 and 15 reported a small (approximately 1 cm [0.39 in] in diameter) blister on the anterior aspect of the shin (Figure 1), whereas subject 16 reported 10 to 12 very small blisters (Figure 2; approximately 1 mm [0.4 in] in diameter). Although the blisters were pain free and the subjects had no other complaints, they contacted the investigators the next day with concern and to report the blister formation. However, the women first noticed the blister formation the night after treatment (approximately 6 hours later). All blisters were located on the anterior shin directly opposite where the ultrasound treatment had been delivered, a distance of approximately 10 cm. Subjects had no altered physical function and reported no adverse reactions to previous ultrasound treatments, abnormal skin conditions, or known allergies.

Upon notification of the first adverse event (subject 9), which occurred on day 6 of data collection, we halted the study for 2 days to assess probable causes of the blister formation. Because we found no similar reaction to ultrasound treatments in the literature and our treatment protocol used commonly accepted clinical guidelines,1,2 we reconvened the study. Five additional subjects completed the study over the next few days without complications. Subjects 15 and 16 developed blisters and, therefore, the study was terminated. The post hoc analysis of the final change in tissue temperature was a mean increase of 3.83°C for the 13 subjects who did not develop blisters, whereas the mean temperature increase was 4.03°C in the subjects who developed blisters.

Results of Physical Examinations

Upon report of the blisters, a physician immediately examined each subject. Subjects’ vital signs were within normal limits with no signs of infection or physical impairment. No laboratory tests were performed. Subjects 9 and 15 reported a single blister on the anterior shin (Figure 1), whereas subject 16 reported multiple tiny blisters on the anterior shin, in addition to a distinct erythemic ring that surrounded the middle and distal portions of the tibia (Figure 2).

Medical Histories

Investigators thoroughly questioned all 3 subjects regarding their medical histories to identify any previous reactions to therapeutic ultrasound treatments, any known allergies (eg, to detergents, cleaning solvents), previous sun exposure, and any accidents that might have caused the blister formation (eg, accidental burns). None of the subjects had a previous history that would predispose them to the blisters.

Diagnosis

Because the subjects had no histories that led to the explanation of blister formation, we suspected that the blisters were
related directly to the ultrasound treatment and were likely a result of overheating or unstable cavitation. Ultrasound has thermal and nonthermal cavitation effects on tissue. Ultrasonically induced pressure changes cause gas-filled bubbles to form within the tissue that expand and contract. These rhythmic pressure fluctuations are deemed beneficial, as long as they remain stable and do not implode and collapse (ie, unstable cavitation). Unstable cavitation is believed to cause tissue damage and to be the result of low frequencies and high intensities.\(^3,4\) Unstable cavitation may have occurred due to a higher-than-expected spatial average intensity (SAI), hot spots within the ultrasound beam, and their combined effects with patient-specific characteristics (ie, depth of triceps surae muscle).

**Treatment and Clinical Course**

Subjects were given standard minor burn care. The physicians instructed subjects to keep their blisters clean, to avoid puncturing the blisters, and to report any further complications. All subjects were seen by the physicians for follow-up 2 weeks after the blisters appeared. All subjects’ skin had healed normally, and they stated that they had no further adverse effects from the study.

**Deviation From Expected**

We report 2 unique observations while using continuous 1-MHz, 1.5-W/cm\(^2\) ultrasound: (1) the development of blisters on the anterior shin as a result of an ultrasound treatment to the triceps surae muscle and (2) an atypically wide rate and range of muscle heating (from 0.19°C to 1.1°C per minute). Other researchers using other ultrasound devices produced a narrower, more uniform range of heating using similar settings.\(^1,5-9\)

**DISCUSSION**

To explore all possibilities, we developed various hypotheses: (1) that subjects were reacting to something other than the ultrasound; (2) the ultrasound field was interacting negatively with the 2 temperature measurement instruments inserted into the triceps surae muscle; (3) the ultrasound machine was not calibrated properly; (4) the SAI or beam nonuniformity ratio (BNR) of the ultrasound device caused irregular heating; (5) the ultrasound machine was heating at a higher rate, more deeply than anticipated, or both; (6) ultrasound may heat more deeply than originally theorized; (7) the smaller anatomy of our female subjects was problematic; or (8) a confounding interaction among these factors.

**Interactions Unrelated to the Ultrasound Treatment?**

Subjects were questioned regarding dermatologic history. They reported no allergic reactions or any previous problems with skin irritation due to laundry detergents, soaps, or contact with cleaning solvents. Some thought was given to the cleaning solvents used on the treatment table. However, none of these 3 subjects or the remaining 13 developed any skin irritations on any other areas of skin that came in contact with the table. The blisters only developed on the anterior shin directly in line with the ultrasound-treatment area. The subjects also were questioned regarding their activities after their ultrasound treatment. None reported abnormal sun exposure that might have caused blisters or any noted activity that would have caused these blisters to form (eg, burns, bites, clothing irritation, abnormal friction to the area, exposure to poison ivy or oak).

In this study, the instruments were inserted into the muscle in a similar manner to previous studies\(^1,10-12\) and were sterilized before use with Cidex for at least 10 hours, as recommended by the manufacturer for sterility. Additionally, the instruments were handled using sterilized gloves and were wiped with sterile gauze before insertion.

**Interaction Between the Thermocouple and Thermistor?**

Although we cannot prove that an interaction was not the cause, it seems improbable because a number of ultrasound researchers have used implanted temperature measuring devices\(^1,5-11,13-21\) with no reported adverse reactions. The thermocouples and thermistors were unlikely to have caused a problem because they do not produce a thermocouple effect: that is, the thermocouple heats up but the surrounding tissue does
not. This is evident because the temperature decay was slow, not rapid.\textsuperscript{21} Therefore, we do not believe that the thermocouple or thermistor negatively interacted with the ultrasound and have no viable reason to believe they interacted with each other.

**Improper Ultrasound Calibration?**

The Chattanooga Intellect ultrasound unit we used here was calibrated by the manufacturer before this study. Immediately after the study ended, the calibration of the ultrasound machine was reassessed and the transducer was found to be within the acceptable Food and Drug Administration range\textsuperscript{22} for total power (±20\% of digital display) at both the 1-MHz and 3-MHz frequencies. Therefore, we have no reason to believe that the ultrasound device was calibrated improperly.

**Spatial Average Intensity and Beam Nonuniformity Ratio of the Ultrasound Device**

Chattanooga and several other manufacturers use computer software to determine the SAI that is displayed on the digital output in W/cm\textsuperscript{2}. This method uses mean ERA and predetermined watt measurements to calculate SAI. Chattanooga reported an ERA of 8.5 cm\textsuperscript{2} and a BNR of less than 6:1 for the 10-cm\textsuperscript{2} transducer we used.\textsuperscript{24} After the study ended, we set the machine’s digital display to 1.5 W/cm\textsuperscript{2} (12.8 total W/8.5 cm\textsuperscript{2}) and measured 15.3 total watts with a wattmeter (UPMDT-10; Netech Corp, Easton, MD; ±20\% of the digital display), which demonstrated that the unit was calibrated within Food and Drug Administration standards\textsuperscript{22} (watts ± 20\% of digital display). The ERA of the ultrasound transducer then was scanned via the hydrophone method and was measured at an ERA of 8.12 cm\textsuperscript{2}. The calculated SAI was 27\% higher than the digital display (1.5 W/cm\textsuperscript{2} versus 1.9 W/cm\textsuperscript{2}). Although most clinicians use SAI to guide treatment protocols, the Food and Drug Administration does not regulate the accuracy of SAI. The BNR was determined to be 4.75:1, which suggests that the most intense area within the beam was in the range of 9 W/cm\textsuperscript{2}. Further analysis showed that a 0.005-cm\textsuperscript{2} high-intensity area (8.9 W/cm\textsuperscript{2}) did exist but was likely too small to result in blister formation. When we expanded the area to closely match the size of the blisters, areas measuring 0.03 cm\textsuperscript{2} (6.8 W/cm\textsuperscript{2}) and 0.2 cm\textsuperscript{2} (4.4 W/cm\textsuperscript{2}) were identified near the center of the beam.

We believe that a 27\% increase in SAI was a contributing factor to the higher heating rates and blister formation; yet, if that had been the only factor, we would predict that a larger number of the subjects would have presented with blisters.

**Our Ultrasound Unit Heated at a Higher Rate Than Expected**

Some authors have studied the rate of heating during ultrasound treatments using different machines. Although units from several different manufacturers have been tested,\textsuperscript{8–12} most studies have been performed with an Omnisound device (Omnisound 3000; Physio Technology Inc, Reno, NV).\textsuperscript{5,7–9,16,23,25–30} This research was performed originally in 1995\textsuperscript{1} and has been replicated several times with different Omnisound machines. From this research, it has been reported that (on average) 1-MHz ultrasound heats at a rate of 0.2°C/min per W/cm\textsuperscript{2}, whereas 3-MHz ultrasound heats at a rate of 0.6°C/min per W/cm\textsuperscript{2}. These early studies laid a foundation for clinicians and researchers to think about ultrasound dosing with respect to tissue heating rates. Recently, scientists\textsuperscript{8,9} have reported differences in heating rates among transducers from different manufacturers and have described field characteristics that may provide more insight into why heating variability exists.\textsuperscript{31,32} Here we report that 2 of the 3 subjects with blisters had tissue heating rates of 0.8°C/min and 1.1°C/min when treated with a 10-cm\textsuperscript{2} transducer from Chattanooga, heating rates and ranges of more than twice those of the heating rates established for 5-cm\textsuperscript{2} transducers from Omnisound. Additionally, the third subject who developed multiple blisters had a heating rate of 0.4°C/min, which is considered normal. The average heating rate for our 3 subjects was 0.59°C/min ± 0.23°C/min. However, the heating rates for all subjects ranged from 0.19°C to 1.1°C/min.

Our observations here raise important clinical questions. Are there large differences in heating rates among individuals? Do differences exist in heating rates among ultrasound machines at 1 MHz? The latter seems reasonable, because previous reports already have established that transducers from other manufacturers heat at different rates during 3-MHz treatments.\textsuperscript{8,9} Do different-size ultrasound transducers (2 cm\textsuperscript{2} versus 5 cm\textsuperscript{2} versus 10 cm\textsuperscript{2}) heat differently? This is also likely because a larger soundhead produces a more focused or collimated beam of energy, as may be the case with the 10-cm\textsuperscript{2} soundhead. A smaller soundhead, such as the 5-cm\textsuperscript{2} head, produces a more divergent or spread-out beam.\textsuperscript{4} The larger soundhead is likely to apply more focused heating during application. Additionally, because the 10-cm\textsuperscript{2} soundhead is simply larger, the near zone (Frenzel zone) of the ultrasound beam will be larger. Further, the energy contained within the near zone has a constantly fluctuating strength.\textsuperscript{4} At the end of the near zone, the ultrasound energy becomes aligned and indistinguishable, creating a point of maximum acoustic intensity. This point of maximum acoustic intensity is likely to occur deeper in the tissue when using a larger sound head.

**Ultrasound May Heat More Deeply Than Theorized**

From the results of therapeutic ultrasound research, we can infer that the anterior tibia is out of range of the ultrasound beam treating the triceps surae muscle group. Investigators\textsuperscript{1,33} reported that 1-MHz and 3-MHz ultrasound treatments produced the greatest level of heating between 3 and 5 cm and near 1.6 cm of tissue depth, respectively. A recent group\textsuperscript{10} demonstrated that 3-MHz ultrasound produced vigorous heating (an increase of 4.0°C from the baseline tissue temperature) with a continuous 3-MHz, 1.5-W/cm\textsuperscript{2} treatment at a depth of 2.5 cm. Muscle temperature was measured only at 2.5 cm; therefore, we do not know the extent to which tissue heating occurred deeper than 2.5 cm. Because subjects receiving ultrasound treatment on their triceps surae muscle developed cutaneous burns on the anterior shin, our case series suggests that this unit at 1 MHz likely produced nonuniform heating, leading to overheating of some of the tissues at a greater depth than expected.

**Interaction of Ultrasound Field With Local Anatomy**

The women affected in this study were thin individuals with small calf circumferences (unfortunately, we did not record calf circumference measurements). We estimated a distance of
10 cm from the posterior surface to the anterior surface of the shin. The higher-than-expected heating rate observed here may, in part, be the result of higher tissue heating at the bone-muscle interface when bony structures are present in the ultrasound field. Variations in the amount of muscle mass present or changes in the orientation of an ultrasound transducer on a curved surface like the triceps surae (or both) can introduce ultrasonic energy closer to the bone-muscle interface of both the tibia and fibula. The combined effects of an SAI that is 27% higher than indicated on the digital display, a tissue heating rate and range greater than twice expected, and probable interaction of the ultrasound field with the local anatomy are likely associated with the development of the anterior blisters. It is possible that ultrasonic energy refracted from either the tibia or fibula or reflected from the anterior skin-bone interface. When this happens, the intensity of the energy is increased as the refracted or reflected energy meets the new or continuous energy that is being emitted from the ultrasound head. This is likely to cause the formation of hot spots or standing waves, which can produce tissue damage.

CONCLUSIONS

Degree of Generalizability of Current Therapeutic Ultrasound Treatment Guidelines

Combined reports suggest that some degree of variability in ERA, power, and SAI does exist among ultrasound manufacturers and possibly transducer size, leading to differences in therapeutic dosing. Furthermore, the degree of variance among ultrasound transducers, the possibility that some units may heat more deeply than previously thought, and the variance among individual anatomical structures (eg, adipose tissue, muscle mass, bone structure, leg circumference) add variability to current treatment guidelines that clinicians should consider.

Clinical Considerations

When selecting ultrasound treatment settings to increase tissue temperature, clinicians should be cautious and should take into consideration frequency, bone depth, leg circumference, and patient perception in addition to the current clinical treatment guidelines for therapeutic ultrasound. Through patient education and dialogue, clinicians also should delineate the types of sensations (slight warmth versus moderate warmth) and location of the sensation (within a few centimeters of the surface of the skin in the muscle). In smaller patients, clinicians may choose to use a frequency that does not penetrate as deeply or alternative methods of heating deep tissue (eg, active exercise or pulsed short-wave diathermy).

Ultrasound application is a multifaceted modality with many influential components that can be manipulated. These include treatment considerations such as the rate of ultrasound head movement, size of treatment area, choice of frequency and intensity, and choice of ultrasound head size. Proper management of these application considerations and techniques will help to eliminate harmful ultrasound effects, such as standing waves and hot spots. Clinicians should have proper training in the implications of ultrasound treatment choices in order to make well-informed clinical decisions when applying an ultrasound treatment. For example, the ultrasound head should be moved at a consistent rate in order to avoid excessive heat accumulation in treated tissues. Recommendations have been to move the transducer head at a rate of 4 cm/s over an area that is 2 to 3 times the ultrasound’s ERA. As the BNR of an ultrasound unit increases, this rate may need to be increased to avoid excessive heat accumulation at points in the beam that have higher intensities.

When using ultrasound, the goal is to heat tissues; therefore, some warmth should be felt, although it should not be painful. The ultrasound intensity should be decreased if intense heating is felt, in order to produce an intensity level that remains therapeutic to the patient. Altering the ultrasound frequency will alter the depth of the attenuated ultrasound waves. If the patient describes bone pain during a 1-MHz ultrasound frequency, changing the frequency to 3 MHz will decrease the depth of ultrasound penetration. Further, the intensity may need to be turned down and the treatment time decreased because 3-MHz frequencies have 3 times the heating rates of 1-MHz frequencies. Finally, changing the ultrasound transducer head to a smaller head size in patients who are experiencing pain is another way to decrease the amount of energy emitted into the treatment area. Our opinion is that clinicians should begin ultrasound application using guidelines recommended by ultrasound researchers. We should, however, keep in mind that each patient and individual ultrasound device is different. Therefore, clinicians should be prepared to make treatment alterations in order to create a comfortable, therapeutic ultrasound treatment.

Research Recommendations

A large-scale ultrasound study is warranted to assess heating rates of multiple ultrasound units at multiple tissue depths. This research should also include different ERAs and frequencies. Establishing heating rates under multiple conditions would help clinicians produce safer and more effective heating results.

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