Needle Oscillation Leads to Reduced Stress Response and More Humane Blood Sampling

GentleSharp™

A More Humane Blood Sampling System

GentleSharp™ Benefits

The benefits of GentleSharp are derived from micro-oscillation of the needle tip and its interaction with tissue during insertion (*see Figure 1*). The needle oscillates backward and forward (i.e., axially) with an electrically controlled displacement and frequency.

During insertion, the oscillation causes the needle tip to cut through tissue in short, repetitive, high velocity bursts (>200 mm/s peak velocity). These momentary increases in the needle insertion velocity during the forward cutting phase leads to significant reduction in insertion force and tissue deformation due to the viscoelastic properties of soft biological tissues.[1-3] Reducing tissue compression, deformation, and damage may play a contributing role in reducing pain from needle insertion.[4,5]

Vibration, Soft Tissue, and Insertion Force Reduction

Prior research has demonstrated that vibrating needles during insertion leads to reductions in both puncture and friction forces.[6-12] This phenomenon is utilized in nature by mosquitos when they vibrate their proboscis to penetrate the skin of their host.[7,8,13-16] The increased needle velocity from oscillation results in decreased tissue deformation, energy absorbed, penetration force, and tissue damage.[1-3] These effects are partly due to the viscoelastic properties of the biological tissue and can be understood through a modified non-linear Kelvin model that captures the force-deformation response of soft tissue.[2,3] Since internal tissue deformation for viscoelastic bodies is dependent on velocity[17], increasing the needle insertion speed results in less tissue deformation. From fracture mechanics theory, the reduced tissue deformation prior to crack extension increases the rate at which energy is released from the crack, and ultimately reduces the force of rupture.[2,17] The reduction in force and tissue deformation from the increased rate of needle insertion is especially significant in tissues with high water content such as soft biological tissue.[18] In addition to reducing the forces associated with cutting into tissue, research has also shown that needle oscillation during insertion reduces the frictional forces between the needle and surrounding tissues.[10]

The Gate Control Theory of Pain

Research has shown that tissue penetration with lower insertion forces results in reduced pain.[4,19,20] In addition, the mechanical vibration itself can produce an anesthetic effect as explained by the Gate Control Theory of Pain.[21-23] The vibration produced by the oscillating needle may stimulate non-nociceptive Aβ fibers and inhibit perception of pain and alleviate the sensation of pain at the spinal cord level.[6,21-26] A significant number of devices have been developed that employ a vibrating sharp to improve outcomes,[7,27] including dental surgery tools,[28,29] dental scalers,[30,31] sinus surgery tools,[32,33] and the ultrasonic scalpel.[34-37]

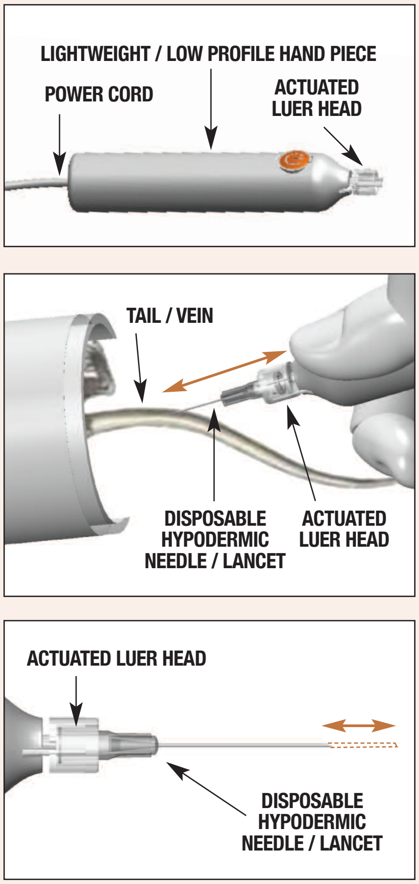

Figure 1: *GentleSharp device for small volume blood sampling. Orange arrow shows the minute oscillation backward and forward.* **NOTE: Movement is exaggerated for purpose of illustration (i.e., not to scale).**

Learn more at GentleSharp.com

GentleSharp Research

In 2009, National Institutes of Health, National Institute on Aging (NIH/NIA) released a Small Business Innovation Research (SBIR) Omnibus Solicitation. NIH/NIA was seeking proposals to develop minimally-perturbing techniques for collecting blood from mice, rats, and other animals several times a day in sufficient quantities for measurement of hormone levels and other circulating factors. Actuated Medical, Inc. was funded by NIH/NIA to develop this technique. As a result, a device designed to use the force reducing and anesthetic effects of vibration, GentleSharp, was developed.

Reduced Insertion and Extraction Force

To quantify the performance of the GentleSharp device in lowering insertion force, bench-top force measurement experiments were carried out measuring needle insertion and extraction forces in cadaver rat tails. Prepared rat tail segments were placed in a test fixture incorporating a force gauge that measured forces parallel to the tail axis during needle insertion. Hypodermic needles (25 G Becton Dickinson Precision Glide) were attached to GentleSharp and manually inserted into the rat tail at approximately a 15° angle to the skin surface with GentleSharp either ON (oscillating at 150 Hz with ~0.5 mm peak-peak displacement) or OFF (non-oscillating) during the insertion.

Analysis of the insertion force profiles showed that oscillating needles had a significant reduction in the peak insertion force as compared to non-oscillated needles (see **Figure 2** for example). It can also be seen in this example that the extraction forces (negative peaks) were smaller with oscillation, indicating that the oscillation also reduced the friction force between tissue and needle.

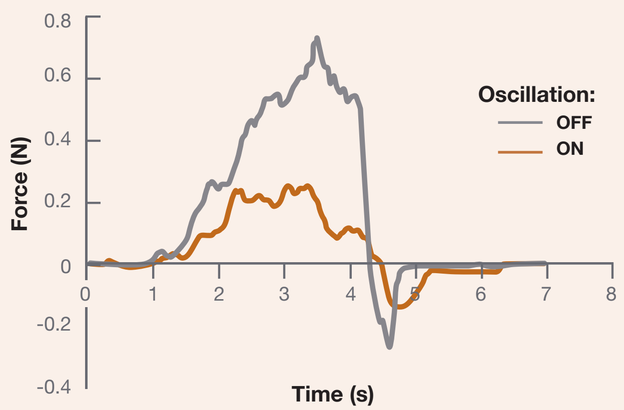

Figure 2: *Example of force vs. time plots for 25G needle insertions into rat tail with oscillation (orange) and without oscillation (gray). Insertions performed on opposite sides of same tail segment.*

In repeated trials, needle oscillation with GentleSharp consistently reduced both the peak insertion force (puncture) and the force required to extract the needle after the puncture event (see **Figure 3**). Three different tail locations were studied (see **Figure 3A**), though the results across locations did not vary significantly. Needle oscillation significantly reduced the average insertion force by 72.6% ($p=1.3x10^{-9}$) and average extraction force by 63.0% ($p=1.4x10^{-7}$) when compared to non-oscillated insertion (see **Figure 3B**). The variation in both insertion and extraction forces across trials was also greatly reduced with needle oscillation provided by GentleSharp.

GentleSharp Highlights

- *GentleSharp used low frequency oscillations (<150Hz, <500 µm displacement) directly applied to the needle to reduce insertion force into cadaver rat tails by up to 72.6%.*
- *Stress hormone development and behavioral response in a rat model showed significant reduction with GentleSharp compared to a static needle.*
- *No increased risk of injury (e.g., temperature rise, bruising) was observed with needle oscillation during insertion into rat tails.*
- *Focus Group of potential end-users all agreed very strongly that the oscillated needles were easier to insert.*
- *Focus Group of potential end-users agreed that reducing animal discomfort and stress during blood sampling was important and believed that the device has value.*

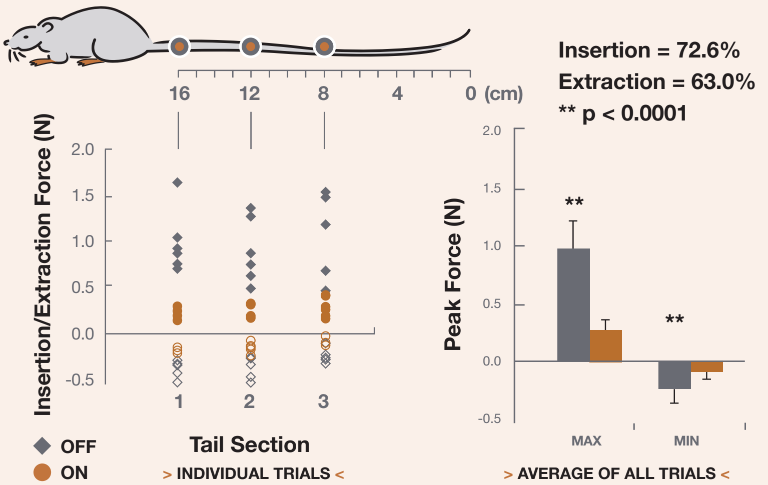

Figure 3: *(A) GentleSharp reduces the insertion and extraction force required for 25G needle penetrations into cadaver rat tails. Plot shows peak insertion force for GentleSharp ON (orange filled circles) and OFF (gray filled diamonds) and peak extraction force (open shapes) for 3 different rat tail locations; N = 6 rat tails. GentleSharp ON also resulted in reduced variability in the peak insertion and extraction forces. (B) Summarized results of peak insertion / extraction forces, combining all locations of rat tail insertions using GentleSharp. With GentleSharp ON during needle insertion (orange bar), the average peak insertion force into rat cadaver tails is reduced by 72.6% compared to OFF condition (gray bar). Likewise, peak extraction force was reduced by 63.0% with GentleSharp ON. Student's T-test, statistical significance of mean difference: **p < 0.0001; N = 18 insertion trials using 6 different rat tails. Error bars = standard deviation.*

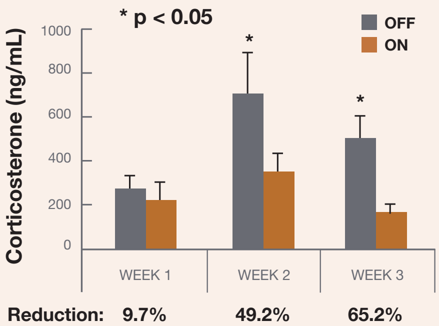

Figure 4: *Mean plasma corticosterone concentrations (CORT) in blood samples obtained with GentleSharp ON (orange bars) or OFF (gray bars) during needle insertion over a three week serial sampling study. Bars represent mean CORT of all samples collected (3 trials / animal / weekly collection day). Repeated Measures Analysis of Variance, statistical significance of mean difference between treatment within week. * p < 0.05; Sample Sizes: ON: N =30 trials with 10 rats; OFF: N = 27 trials with 9 rats). Error bars = standard error of the mean.*

Decreased Stress Hormone and Behavioral Response in Rats

Blood samples obtained with GentleSharp ON (i.e., needle oscillating) during needle insertion yielded lower plasma corticosterone concentrations (CORT). When examined on a week by week basis, the mean CORT was significantly reduced for the ON group as compared to the OFF groups at weeks 2 and 3, 49.2% and 65.2% respectively (see **Figure 4**). Moreover, individual subject variance in CORT over the span of the 3 week serial blood sampling study was reduced by 71% (data not shown).

Consistent with the CORT results, GentleSharp reduced the level of perceived stress exhibited by the animals during the blood sampling procedure. This was evidenced by reductions in both average vocalization and movement scores assigned by multiple, blinded reviewers of the procedure videos (see **Figure 5**).

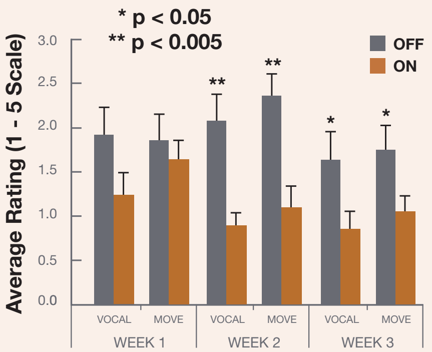

Figure 5: *Average ratings for animal movement and vocalization during serial tail vein blood collection trials (same study as **Figure 4**): venipuncture with GentleSharp ON (orange) vs OFF (gray). Blinded reviewers scored videos of each blood collection trial for animal vocalization (VOCAL) and movement (MOVE) on a 1-5 scale; all reviewer scores averaged to obtain a mean rating per trial. Each bar represents average of mean ratings of all trials for the given week (3 trials / animal / weekly collection day). Statistical significance of within-week mean rating difference between treatments was evaluated by student T-test * p<0.05, ** p<0.005; Sample Sizes: ON: N = 30 trials with 10 rats; OFF: N = 27 trials with 9 rats. Error bars = standard error of the mean.*

Focus Group

Nine (9) potential end users, including research scientists and veterinarians, whom regularly perform blood sampling in rodents, were surveyed. Each participant was provided a brief background of the development of GentleSharp, a summary of the bench-top testing experimental results, and a brief instruction on how to operate GentleSharp. The participants then proceeded to insert the needle into several models, including a cadaver rat tail, followed by completion of a questionnaire to evaluate their experience with the device. There was significant excitement for GentleSharp and its importance in improving blood sampling procedures by decreasing the stress of animals. All agreed that the oscillation allowed the needle to be inserted with significantly less perceived force.

CITATIONS:

1. van Gerwen DJ, Dankelman J, van den Dobbelsteen JJ. Needle-tissue interaction forces--a survey of experimental data. Med Eng Phys 2012;34:665-80.
2. Mahvash M, Dupont P. Fast needle insertion to minimize tissue deformation and damage. IEEE International Conference on Robotics and Automation 2009:3097-102.
3. Mahvash M, Dupont P. Mechanics of Dynamic Needle Insertion into a Biological Material. IEEE Trans Biomed Eng 2009.
4. Egekvist H, Bjerring P, Arendt-Nielsen L. Pain and mechanical injury of human skin following needle insertions. Eur J Pain 1999;3:41-9.
5. Arendt-Nielsen L, Egekvist H, Bjerring P. Pain following controlled cutaneous insertion of needles with different diameters. Somatosens Mot Res 2006;23:37-43.
6. Marx JA, Greville WL, Granot A, Brown AC. The Effect of Vibration on the Needle Dynamics of Sclerotherapy. Australasian College of Phlebology 12th Annual Scientific Meeting; 2008; Gold Coast, Australia.
7. Muralidharan K. Mechanics of soft tissue penetration by a vibrating needle. Baltimore, MD: University of Maryland Baltimore County; 2007.
8. Yang M, Zahn J. Microneedle insertion force reduction using vibratory actuation. Biomed Microdevices 2004;6:177-82.
9. Begg ND, Slocum AH. Audible frequency vibration of puncture-access medical devices. Med Eng Phys 2014;36:371-7.
10. Khalaji I, Hadavand M, Asadian A, Patel RV, Naish MD. Analysis of needle-tissue friction during vibration-assisted needle insertion. Intelligent Robots and Systems (IROS), 2013 IEEE/RSJ International Conference on; 2013 3-7 Nov. 2013. p. 4099-104.
11. Shin-Ei T, Yuyama K, Ujihira M, Mabuchi K. Reduction of Insertion Force of Medical Devices into Biological Tissues by Vibration. Japanese journal of medical electronics and biological engineering 2001;39:292-6.
12. Huang Y, Tsai M, Lin C. A piezoelectric vibration-based syringe for reducing insertion force. IOP Conference Series: Materials Science and Engineering 2012;42:012020.
13. Kong XQ, Wu CW. Mosquito proboscis: an elegant biomicroelectromechanical system. Phys Rev E Stat Nonlin Soft Matter Phys 2010;82:011910.
14. Cohen D. This won't hurt a bit. New Scientist2002:21.
15. Castelvecchi D. This Bite Won't Hurt A Bit - Science News. Science News2008:11.
16. Ramasubramanian MK, Barham OM, Swaminathan V. Mechanics of a mosquito bite with applications to microneedle design. Raleigh, NC 27695-7910, USA: North Carolina State University; 2008.
17. Atkins AG, Mai YW. Elastic and plastic fracture : metals, polymers, ceramics, composites, biological materials. Chichester, New York: Halsted Press; 1988.
18. Chan KK, Watmough DJ, Hope DT, Moir K, Chan F. The Mode of Action of Surgical Tissue Removing Devices. IEEE 1985 Ultrasonics Symposium; 1985 16-18 Oct. 1985. p. 855-9.
19. Gill H, Prausnitz M. Does needle size matter? J Diabetes Sci Technol 2007;1:725-9.
20. Hirsch L, Gibney M, Berube J, Manocchio J. Impact of a modified needle tip geometry on penetration force as well as acceptability, preference, and perceived pain in subjects with diabetes. J Diabetes Sci Technol 2012;6:328-35.
21. Gate Control Theory of Pain. www.HowStuffWorks.com, 2007. (Accessed April 23, 2010, at http://health.howstuffworks.com/pain.htm.)
22. Nanitsos E, Vartuli R, Forte A, Dennison P, Peck C. The effect of vibration on pain during local anaesthesia injections. Aust Dent J 2009;54:94-100.
23. Smith K, Comite S, Balasubramanian S, Carver A, Liu J. Vibration anesthesia: a noninvasive method of reducing discomfort prior to dermatologic procedures. Dermatol Online J 2004;10:1.
24. Murray P, Terret K, Lynch E, Hussey D. Efficacy of a vibrating dental syringe attachment on pain levels. 81st General Session of the International Association for Dental Research; 2003; Goteborg, Sweden.
25. Longe SE, Wise R, Bantick S, et al. Counter-stimulatory effects on pain perception and processing are significantly altered by attention: an fMRI study. Neuroreport 2001;12:2021-5.
26. Kandel ER. Principles of neural science. 5th ed. New York: McGraw-Hill; 2013.
27. Feil W. Ultrasonic energy for cutting, coagulating, and dissecting. Stuttgart ; New York: Thieme; 2005.
28. Walmsley A. Applications of ultrasound in dentistry. Ultrasound Med Biol 1988;14:7-14.
29. Bains V, Mohan R, Bains R. Application of ultrasound in periodontics: Part II. J Indian Soc Periodontol 2008;12:55-61.
30. Walmsley A, Laird W, Williams A. Inherent variability of the performance of the ultrasonic descaler. J Dent 1986;14:121-5.
31. Walmsley A. Potential hazards of the dental ultrasonic descaler. Ultrasound Med Biol 1988;14:15-20.
32. Vercellotti T, Pollack A. A new bone surgery device: sinus grafting and periodontal surgery. Compend Contin Educ Dent 2006;27:319-25.
33. Stübinger S, Kuttenberger J, Filippi A, Sader R, Zeilhofer H. Intraoral piezosurgery: preliminary results of a new technique. J Oral Maxillofac Surg 2005;63:1283-7.
34. Lee S, Park K. Ultrasonic energy in endoscopic surgery. Yonsei Med J 1999;40:545-9.
35. Mowry R, Hengerer A. The ultrasonic scalpel in head and neck surgery. Otolaryngol Head Neck Surg 1982;90:305-9.
36. Siperstein A, Berber E, Morkoyun E. The use of the harmonic scalpel vs conventional knot tying for vessel ligation in thyroid surgery. Arch Surg 2002;137:137-42.
37. Wolf R, Ohtsuka T, Flege JJ. Early results of thoracoscopic internal mammary artery harvest using an ultrasonic scalpel. Eur J Cardiothorac Surg 1998;14 Suppl 1:S54-7.

Comments from Participants:

"The RAIL (GentleSharp) has a lot of potential as a refinement for blood collection techniques used for laboratory animals. Potential benefits include: reduced animal pain, reduced stress for the animal and reduced stress for the person using the device."

> *Dr. Jeff W. Dodds, DVM*
Veterinarian-Research Associate
Lab Animal Resource Program, Penn State

"Very smooth. The 25G needle went in on the first poke, saved time and reduced animal handling compared to the standard needle."

> *David Bienus, BS, MM, LAT*
Research Technologist

"It can be a challenge to find effective methods that are humane for the animal. I'm thrilled to see a product that will reduce the animals stress while making it easier for the handler to sample blood. Thank you for your innovative product!"

> *Robyn Graboski,*
Director and Founder
Centre Wildlife Care