Original Contribution

The Gel Box – a Testing Device for the Characterization of Cryo- and Radiofrequency Lesions Employed in Interventional Pain Therapy

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Free full manuscript: www.painphysicianjournal.com **Background:** Radiofrequency (RF) and cryolesioning are established methods for the therapeutic interruption of sensory nerve supply to facet joints and other painful musculoskeletal structures. The varying clinical success rates of these treatments have – among other technical issues – been attributed to the small size of these lesions combined with the limited precision in placing them. Since there are 2 different physical methods for lesioning and a wide range of probes and lesion generators available, it is likely that the lesions generated by them may be of different size.

Objectives: We sought to devise an experimental setup that would allow for the reproducible and comparable evaluation of the size of cryo and RF lesions as they are being used in interventional pain therapy.

Methods: A wide range of potential media was evaluated for this purpose. Based on technical specifications, as well as on preliminary testing, a specific agar agar gel with a gel point of between 32°C and 35°C and a melting point of between 80°C and 85°C was selected for these experiments. Two different testing containers were constructed from transparent acrylic: one with a volume of 1,500 mL and the other with a volume of 12 mL. Each of them allows for the introduction of a cryo or a RF probe and 2 bundles of thermoelements into the gel volume. A water bath was used to maintain the gels at 37°C and bundled, ultrafine NiCr-Ni thermoelements type K were used for measuring the isotherms. A series of RF and cryolesions were performed within these experimental setups to evaluate their suitability for the comparative testing of cryo and RF probes and generators.

Results: Both testing setups generated reproducible results and proved to be suitable for measuring RF as well as cryolesions. Visual observation of the lesions was better with the small testing container and rewarming / recooling after performing a cryo / RF lesion was more rapid with the smaller gel volume.

Limitations: Our setup allows for the comparative measurement of RF and cryolesions, but it cannot simulate the realities within living tissue. While convection as a confounding factor was excluded by use of a gel, capillary perfusion and the specific characteristics of different tissues cannot be simulated.

Conclusions: The testing setup described in this manuscript can serve for the comparative and reproducible study of RF and cryolesions that are commonly used in interventional pain therapy.

Key words: Radiofrequency lesioning, cryolesioning, interventional pain therapy, experimental study, agar agar gel, thermoelement.

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here is increasing evidence supporting the efficacy of medial branch denervation in the treatment of facet joint pain (1-8) and while the best randomized-controlled trials have been performed using RF (9-14), trials of lesser quality using cryodenervation show similar therapeutic effects (15-17). The scientific groundwork for therapeutic cryolesioning was laid between 30 and 40 years ago and while the primary target of this technology was the treatment of tumors, it has successfully been employed in the treatment of a wide range of peripheral pain syndromes (15-18).

Radiofrequency lesioning also has a very long history in interventional pain therapy and was first used for facet joint pain in the 1970s (19,20). Lesion size has been recognized as a factor in the efficacy of denervation procedures and there have been attempts to improve the positioning of RF probes by using special radio-opaque, markers or to use more than one RF needle for RF lesioning (21-23). There are a number of studies investigating the cryolesions used for the ablation of tumors in various tissues in vivo (24), ex vivo with life tissues (25), as well as in vitro in various media with or without cells (25-29). In addition, a number of mathematical and finite element simulations have been done for the application of cryosurgery to tumor tissue ablation (30-34).

Other important factors influencing the effectiveness of cryolesioning as well as of radiofrequency lesioning are the shape and isotherms of the lesions generated. For obvious reasons, such lesions cannot be studied in real patients and even real-time temperature measurements in the tissues of experimental animals have clear limitations. Such measurements would have to be obtained with open surgical access, which in turn distorts the conditions from what they would be in a real therapeutic situation where perfused, uninterrupted tissues surround the area of treatment.

Surprisingly, there are only few studies investigating the character and the size of the lesions generated by the typical cryoprobes / cryogenerators currently in use for interventional pain therapy in an in vitro setup (35-37).

Having extensive clinical experience with the cryodenervation of lumbar facet joints (16,38), we became interested in the underlying issues outlined above and sought an investigational method that would allow us to better understand the character of such lesions. It was our goal to devise a setup that would allow for the testing of cryo and radiofrequency probes and for the objective comparison of the lesions generated by such probes and generators in order to better understand the effects (or lack thereof) of such lesions in interventional pain therapy.

In consequence, we researched a wide range of potential media for simulating tissues, tested a range of these media for their physical properties, and developed two alternative testing setups.

METHODS

Preconditions

While a laboratory testing setup can never simulate the realities of living tissue, we formulated several preconditions, which we consider important. For one, the setup should be transparent, so that the thawing and freezing cycles of cryolesions could be visually observed and documented. Second, the baseline temperature needs to be well controlled at 37°C. Third, fluid convection on a macroscopic scale needs to be avoided. While convection occurs even within living tissues at a cellular level and / or in the interstitial space, these effects are expected to be at a microscopic level. Were we to use a fluid medium for our experiments, however, convection would take place on a large scale around the cryo or RF lesion and would be expected to substantially alter the temperatures around the probes and hence the size of the lesions created. In consequence, the medium surrounding the probe tip cannot be liquid.

Fourth, this medium should have a melting point of above 37°C in order to avoid convection in all situations during freezing from and thawing to normal body temperature. Ideally, the melting point should be at 80°C or higher in order to allow for the identical setup to be used for the testing of radiofrequency probes. Fifth, the medium should ideally contain ions at a concentration comparable to living tissues for the same reason.

Test Medium

Resulting from the above preconditions, the natural choice for a non-liquid transparent medium for our application would be a gel of some sort, the main constraints being transparency and melting point as outlined above.

As secondary parameters, temperature storage capacity and temperature conductivity would be of importance, since the medium would have to be maintained at 37°C by an external heat source and after the application of cold or heat, the zone of the immediate cryolesion would need to be re-warmed to 37°C prior

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to the next test cycle. The reverse would be required for the measuring of radiofrequency lesions.

There are 3 major categories of gels available for a host of scientific applications as well as for use in the food industry: Gelatin-based substances, agar agar in its varieties, and alginate-based gels. While scientific-grade gelatins can possess high transparency, they invariably have melting points of around or only slightly above 37°C. The agar agar group contains products whose properties are extremely widespread, but most are not highly transparent.

The alginate-based gels, in contrast, do have higher melting points, good transparency, but are not widely available. They are more expensive than either of the other products and the choices available are more limited.

After casting a number of preliminary trial gels with various concentrations of the different base components, we found one agar agar gel which best matched our demands. The "05038" agar (manufactured by Fluka BioChemika, supplied by Sigma Aldrich Germany, product number 05038, CAS number 9002-18-0) is a (C12H18O9)n - polymer for special microbiology applications. It has a gel point between 32°C and 35°C and is highly transparent. Its melting point is between 80°C and 85°C and the gel is well suited for immunoelectrophoresis, which also indicates its potential usefulness for the testing of radiofrequency probes. However, there were no data available from the manufacturer as to the temperature storage capacity and the temperature conductivity of the gel. For the experiments, gels were prepared at the recommended concentration of 1.5 g/100 mL saline 0.9%.

Container

Based on the preconditions outlined above, we chose transparent acrylic with a 3 mm wall strength. As mentioned above, there were no pre-existing data on how the gel would perform with regards to temperature storage capacity and temperature conductivity. So we could not decide from the outset whether a large gel mass would be of advantage in maintaining the core temperature steady or whether this would render the temperature in the center of the gel uncontrollable.

We therefore built 2 different designs of testing containers: one with a large gel volume (1500 mL) and one with a very small gel volume (12 mL). The 2 designs, as well as their specifications, are displayed in Figs. 1 and 2. A thermostat-controlled water bath with an automatic circulator pump was chosen as a heat source in order to maintain the gel at 37°C.

The thermo elements were positioned into the center of the container through 2 canals opposite and

Fig. 2. View of the small-volume testing container. Surrounding the container is the water bath. The cryoprobe enters from the left and the 2 bundles of thermoelements from the top and from the right, each through waterproof acrylic tubes. The thermoelement bundles are mounted on micrometer drives for fine adjustment. The lid of the testing container is held by rubber bands. The gel volume is approximately 12 mL and the visibility through the gel is excellent. On the right-hand wall of

the water bath, the water inlet and outlet can be seen.







perpendicular to the entry point of the cryoprobe / radiofrequency probe in the large volume container.

The container was then set into a second container that contained the water bath. Since the thermoelements and the probes were completely embedded in gel, there was no direct contact with the water bath.

For the small volume container, the outside dimensions and materials remained identical, but a small internal box with internal dimensions of 20 x 20 x 30 mm made from 2 mm acrylic was added in the center of the container. Only the small box was filled with gel while the surrounding container was filled with the water bath. Acrylic tubes were used to allow for passage of the thermoelements as well as of the probes into the gel container without having direct contact with the water bath.

Thermoelements

NiCr-Ni thermoelements of type K were used in this study, bundled in groups of 4 for measurements perpendicular to the probe and in groups of 3 for measurements longitudinally from the tip of the probe. The NiCr as well as the Ni wires were individually protected by an Inconel (Special Metals Corporation, New Hartford, CN) coating and then jointly protected by a stainless steel tubing (1N4301, external diameter 0.5 mm, internal diameter 0.3 mm), closed at the end by highly accurate laser point welding. At the connector piece, the wires were soldered to a NiCr-Ni equivalence wire.

In order to obtain exact one mm isotherm readings, the thermoelement bundles were precisely aligned and assembled under a laboratory binocular with a 0.1-millimeter scale. To reduce the chance of temperature transmission between neighboring thermoelements, each individual thermoelement was coated with special polyester tubing prior to being bundled. The assembled thermoelement bundles were mounted on a micrometer drive and fitted onto docking rings on either of the boxes. This allowed for the thermoelement bundles being positioned exactly onto the surface of the cryoprobe until contact and then to be withdrawn a fraction of a millimeter. The gel was cast after adjusting the thermoelements.

By using this procedure, the most distally aligned thermoelement was measured in the closest proximity of the cryoprobe without actually making surface contact, while the other thermoelements were automatically set to a distance of one, 2 and 3 millimeters, respectively.

Cryoprobe / Cryogenerator

For our experiments we used a Lloyd Cryostat 2000 generator (Spembly Medical Systems, supplied by inomed GmbH, Teningen, Germany) and the standard probe used for lumbar facet cryodenervation with a diameter of 2 mm. The experimental freezing was performed with the probe fixed in the testing container as described above.

The gas flow was adjusted according to the reading of the thermoelements adjusted at 0 mm distance from the probe, which allowed for a more exact adjustment of the temperature minimum than the visual flow meter that is integrated in the cryogenerator.

Radiofrequency Probe and Generator

For the experimental radiofrequency lesions, we used an ElectroThermal 20S Spine System with the matching unipolar needle electrodes (RF Canula/Needles 10 cm, 5 mm Sharp Straight Tip) for facet joint denervation (Smith & Nephew GmbH, Marl, Germany).

RESULTS

Both testing setups proved to be suited for the experiment and delivered reproducible measurements. While visibility was perfect in the small volume testing container, the gel itself proved sufficiently transparent to allow for visual control and documentation of the experimental lesions even when cast in a large volume (Fig. 3).

It was much easier to control the baseline temperature in the small-volume container than in the large-volume container, already indicating that the temperature conductivity of the 05038 agar agar gel is relatively poor. Due to its gel and melting points, the gel effectively avoided convection at any temperature during the experiments with cryoprobes as well as with radiofrequency probes.

One of our main findings was that the agar agar gel seems to be a relatively poor temperature conductor and a good temperature capacitator. Displayed in Fig. 4 is the cooling and re-warming graph after a typical freezing cycle with the large-volume testing container. It is obvious that while the return to 0° C was reasonably rapid, it took beyond 14 minutes for the gel in the immediate surrounding of the cryoprobe tip to re-warm to 33° C.

The re-warming process, however, was only somewhat faster with the small-volume testing container (Fig. 5), taking around 10 minutes. The temperature



Fig. 3. Close-up view of the tips of the cryoprobe and the thermoelement bundles embedded in the agar agar gel in the large-volume testing container

curves obtained with the small-volume container were smoother than the ones obtained with the large-volume container.

DISCUSSION

We were able to devise a simple testing setup that allows for the reproducible and comparable characterization of cryo and RF lesions that are typically used in interventional pain medicine. The use of a gel permits for visual control of the correct setup and the development of the lesions while preventing convection at a macroscopic level.

Our measurements show, that either testing setup may prove useful in the characterization of small cryo or RF lesions. They both allow for a rather precise determination of the isotherms of the RF and cryoprobes



Fig. 4. Temperature measurements obtained with the large-volume testing container. Freezing is begun at 0 seconds and stopped at 420 seconds. "Tip" indicates measurement in the axial extension from the tip of the cryoprobe, "side" indicates measurement perpendicular to the tip of the cryoprobe. 0, 1, 2 and 3 indicate the distance in millimeters.



commonly used for interventional pain therapy. Since these setups are standardized, they also allow for the generation of comparable data and hence for the comparison of the lesion sizes generated by different probes and different devices. As long as a gel with a sufficiently high melting point is used, they also allow for the comparison of the lesion sizes of RF and cryolesions.

Because of the better control of baseline temperature, the smoother temperature curves that we observed and the better visibility, we conclude that the small-volume testing container is preferable over the large-volume container. Using a gel rather than a fluid as medium effectively prevents convection on a macroscopic level and brings the testing setup one step closer to the simulation of tissue. Important limitations remain, however. Capillary perfusion cannot be simulated by using a gel. On a more complex level, the temperature-dependent interruption (during freezing or when capillary vessels are being destroyed by heat) and restoration of capillary perfusion (when thawing from cryolesioning) also can not be simulated.

Our experimental setup cannot account for some specific characteristics of living tissues, namely the microconvection that might occur inside cells and within the interstitial space which may dynamically change during heating or freezing.

A gel – like any homogenous medium – can also not account for the real life situation where an RF probe or a cryoprobe is positioned next to the target nerve with muscle and / or fatty connective tissue cover-



ing the probe from one side and with bone being the neighboring tissue from the other side.

Since any real therapeutic situation is unique regarding its anatomical circumstances, a specific and precise simulation does not appear to make much sense and – more importantly – would not allow for a reliable comparison between different probes, devices and physical modalities. While the use of a gel always represents a compromise, the type of gel used determines what sort of compromise the investigator is willing to make. When visual observation is most important and when only cryolesions are to be studied, a gelatin-based or an alginate-based gel might be the best choice. But when RF lesions are to be compared with cryolesions, the melting point is the primary consideration, because convection needs to be excluded for the cryolesions as well as for the RF lesions.

Most RF lesions are performed using temperatures up to 80°C, which is why we sought a gel with a melting point at or above that temperature. The gel we decided to use for the reasons outlined above proved to be a very good temperature capacitator and a poor temperature conductor. While this does not change the overall results of our experiments, it delays the re-warming or re-cooling process within the test chamber and hence limits the number of measurement cycles that can be performed within a given amount of time. One conclusion could be to make the testing chamber even smaller than the 12 mL that we tested.

However, since the lesions and the thermoelements need to be completely embedded in a homogenous medium, there is a limit to making the testing chamber much smaller than the one we constructed.

There are fundamental limitations to the transfer of our study results into a clinical situation, since we did not realistically simulate a cryo or radiofrequency lesion being generated in living tissue.

Results obtained by in vitro testing with our setup must therefore be interpreted with the necessary degree of caution, since these measurements were not performed within a living body. On the other hand, placing the probes and the very fine and flexible thermoelements inside a perfused tissue volume with the same precision as in our experiment would require direct vision. This could not be achieved without tissue dissection and hence alteration of the tissue's properties.

CONCLUSION

In conclusion, we were able to devise a simple testing setup that allows for the reproducible and comparable in vitro assessment of therapeutic cryolesions and RF lesions.

It will allow for further study on these lesions and may have an impact on the discussion of the varying degrees of success that are being achieved with such techniques in clinical applications. While live tissue testing would be the desirable gold standard, we consider it to be unachievable with the necessary degree of precision. We therefore contend that a testing setup identical or similar to the one outlined in this paper will remain the next best thing to live tissue testing when the comparison of RF and cryolesions generated by different probes and devices is the goal.

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