Assessing the safety and efficacy of a novel intra-nasal high flow cannula for brain cooling

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Method Article

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Abstract

Targeted temperature management plays an important role in the treatment of myriad critical illnesses. Invasive therapies such as ECMO and cooled intravenous fluid are available but are invasive and not without risk. Noninvasive therapies are also available such as ice packs and cooling blankets but like the invasive options these do not provide isolated brain cooling. This off-target cooling likely has hemodynamic, coagulopathic and other effects which may not be desired.

Non-invasive, quick-onset and portable options for control of brain temperature remain lacking. Here, we are testing a non-invasive intra-nasal cooling system which provides cooled air to facilitate brain cooling. The goal of this study is to assess the efficacy and short- and medium-term safety of a novel, intranasal high flow cooled air device on a large animal model system.

Introduction

There are several clinical scenarios in which cerebral and systemic targeted temperature control is necessary: from cardiac surgery to after neurologic injury to post-hypothermic management. There are numerous extant modalities for warming and cooling and some that can do either, depending on how they are employed. However, the options available for cooling are some combination of invasive, non-portable, or provide only systemic cooling.

In some clinical scenarios, systemic cooling is needed. This can be accomplished with a collection of adjuncts (e.g., ice packs, cooling blankets, cooled IVF). When needed urgently these adjuncts are used often used together. However, sometimes only isolated, single organ system cooling is needed, such as for the management of cerebral edema and fever after acute neurologic insult. This motivated the development of a novel intra-nasal cooling system to provide chilled air via a nasal cannula to specifically cool the brain. A device of this design could theoretically be used in isolation to cool the brain – by cooling the facial veins which drain into the cavernous sinus thereby cooling the ICA via countercurrent heat exchange – or used with other adjuncts as mentioned to speed up systemic cooling when that is needed. This system could be made portable also and therefore would also be useful in a forward military or resource limited scenario. This unmet need led the development of the Intranasal Cooler for Encephalopathy Prevention in Combat Casualties (ICEPICC).

The goal of this study is to test the safety and efficacy of this novel cooling device that uses high flow cooled air via intranasal cannula. We aim to assess the temperature in multiple anatomic locations in the head and elsewhere both with and without the device, and to examine, using a two-pronged strategy (survival and non-survival arm) for safety using CT imaging of the head and snout, CT perfusion scanning of the brain and histology of the brain immediately post-use as well as in a delayed arm in the survival arm.

Reagents

· Telazol (5 mg/kg)

· Xylazine (2 mg/kg)

· Heparin Sodium 10,000 Units/10cc vial

· Formalin (Sigma-Aldrich, SKU HT501128-4L)

· Isoflurane

Equipment

ICEPICC Intra-nasal cooling device: https://www.vivonics.com/technologies/icepicc

Access:

· 5 Fr micro-puncture access kit (Cook Medical, Bloomington, USA) - MPIS-502-NT-U-SST

· 10 cm 7 Fr sheath (Terumo, Elkton, NJ) - REF/Product Code RM*RS7F10PA

Pressure Catheters and temperature probes:

· Pressure Catheter (5 F, Dual, Straight, 3 cm, 120 cm, PU/WD) - SPR-751S or SPR-751

· At least 6 Temperature probes (ADInstruments, Large Animal Rectal Probe (RET-1))

· Powerlab set up, also from ADInstruments or equivalent for data recording

Imaging:

· C-arm for fluoroscopy (OEC 9800, General Electric, Boston, USA)

· Medrads Mark V power injector

· Omnipaque contrast (1264910 | GE Healthcare - Y546)

· Bedside US system, such as Phillips Lumify App and US Probes (Phillips, NV, USA) (available: https://www.usa.philips.com/healthcare/sites/lumify/lumify-android-app)

· OmniTom Computed Tomography Scanner (Neurologica, Danvers, MA, USA)

Labs:

· iSTAT 1 (Abbott Labs; available: https://www.pointofcare.abbott/us/en/offerings/istat/istat-handheld#specs)

· iSTAT test cartridges for Lactate, Chemistry (Abbott Labs; available: https://www.pointofcare.abbott/us/en/offerings/istat/istat-test-cartridges)

· Blood Gas Analyzer with appropriate solutions for functioning (ABL-800 Flex, Radiometer, Copenhagen, Denmark)

Other:

· Endotracheal Tube 28 French 7.0mm 10/bx Endotrol (SAM Medical: 026351)

· 0.9% Normal Saline, IL bags

· Infusion Tubing (BD: SKU 10013365)

· Prefilled 10 cc 0.9% Saline Syringes (BD-9104 BD PosiFlush Saline Syringe) or syringes which may be manually filled

· Blood gas analyzer with rinse solution, or access to a lab with laboratory support

· Fogarty Balloon Catheter

· Surgical tools necessary for swine burr holes:

o Dremmel

o Dremmel tips

o Bovie electrocautery setup

o 11 blade scalpel

o Surgical instruments including 2 cokers, 2 debakey's, a periosteal elevator, boe wax, pituitary instruments of varying sizes

Procedure

Animal Husbandry:

The study utilizes castrated male Yorkshire swine (weighing 45–70 kg). Swine are all subject to an acclimatization period under the care of licensed veterinary staff for at least 48 hours prior to proceduralization. During to this time, animals have free access to food and water until the night before surgery when they were fasted overnight.

Procedure:

The animal protocol begins with animal preparation and instrumentation. This is followed by a baseline period where control values are collected followed by the experimental portion of the protocol, see Figure 1. Then we perform cooling with the ICEPICC device while continuing to monitor the animal 6 hours, followed by 2 hours of monitoring; lastly the animal is either awakened, or sacrificed and histology is sampled (shown in Figure 1).

Study periods:

I. Animal Preparation and Instrumentation:

1. anesthetize the animal with telazol (5mg/kg) and xylazine (2mg/kg) at appropriate doses.

2. transport the animal to the procedure area, with oxygen saturation monitoring and baseline temperature assessment.

3. place the animal under isoflurane targeting 1.0 MAC by facemask.

4. place the animal in sternal recumbency and intubate the animal with a 7.0 endotracheal tube. Transition to generally 10 ccs/kg TV, RR of 12-14 initially but to target a pCO_2 of 30-45 and an FiO_2 of 40% but adjusted appropriately as needed for the remainder of the cases.

5. make the animal supine and restrain.

6. Place all intravascular catheters using a percutaneous, ultrasound-guided, modified-Seldinger technique. Placement of the pressure catheters/angiographic catheters within the introducer sheaths is performed under direct fluoroscopic guidance. For this study, this consists of at least one 7 Fr. Catheter in a femoral artery through which we place an intra-aortic solid state pressure catheter for blood pressure monitoring, a 5-7 fr intravenous (femoral vein) catheter for IVF and medications as needed. A 7 Fr. Brachial access was obtained for intra-aortic contrast injection for CT perfusion studies. Due to anatomical considerations, the right brachial artery was preferentially cannulated over the left (Edwards et al., 2021).

7. Perform a lower abdominal laparotomy for cystostomy (place a foley catheter into the bladder) to facilitate bladder drainage.

8. Animals enrolled in the non-survival arm had a burr hole drilled and placed, those enrolled in the survival arm did not. Here, once animals are in sternal recumbency, a burr hole is drilled to allow placement of an intracranial temperature probe, laser doppler flowmetry probe, and an ICP probe; this was done in a standard fashion under CT guidance as previously described by our group

- Drill 2 burr holes with the Dremmel ~ 2 cm anterior to the posterior ridge, 1 cm to either side of midline. A third burr hole is made on the right anterior portion of the skull.

- Incise the dura underlying each burr hole with a scalpel. Place the Fogarty balloon into the anterior burr hole, ~ 1 cm deep, ensuring the balloon portion is within the skull. Place a 5Fr pressure catheter through the right posterior burr hole. Seal all burr holes around their respective probes/catheters with bone wax to ensure that there is no leakage of blood or CSF through the burr holes.

- Perform an additional helical CT scan to ensure proper placement of the intracranial instrumentation. Ensure that data is being recorded properly.

9. Perform a TIMEOUT. Confirm all line placements, confirm all sheaths work (drawback and flush), confirm fluids are ready, that the timer is ready and reset, that data is being transduced through LabChart through appropriately labeled channels and saved. Confirm ventilatory settings.

10. Confirm placement of all temperature probes and that they are functioning correctly: rectal, intracranial, middle ear, nasal.

10. Confirm fluoroscopically that all catheters and devices are appropriately positioned.

1. Heparinize the animal with 10k units of heparin

II. Begin Baseline normalization period: (60 min)

1. Once everything is confirmed then start the one hour baseline time period and collect temperature data throughout.

2. Perform baseline CT perfusion. This is a pre-determined protocol. Briefly, it is a 60 second scan that captures the same slice every second. It records the transit of contrast. As such, a power injector is utilized (2.5ml/sec for 7.5ml total) to inject contrast through the angiographic catheter in the proximal aorta. Ensure that contrast is observed transiting through the brain during the scan.

Throughout baseline and observation periods use the following guidelines:

- Treat glucose < 65 with D50

- for pH < 7.2 give on ampule of bicarbonate

- treat pCO_2 as necessary with MV changes

II. Cool

In this phase we apply the ICEPICC intranasal cooler system and continuously monitor the animals for 4 hours, see figure 1. Throughout this period we monitor the parameters noted above. Subjects that are randomized to the cooling group then had the ICEPICC turned on, while those randomized to the control group will not. This period ends at the end of the 4 hour mark.

III. Post cooling and monitoring

1. Turn off the ICEPPICC device and monitor the animals for 2 more hours.

2. Obtain a repeat CT perfusion and CT of the head and snout for evaluation

3. If the animals are going to be survived, then after 2 hours awake and wean the animal.

4. If the animals are non-survival, then we will euthanize and collect histology, and place them in formalin. At a later date these will be collected and taken to a pathologist.

Troubleshooting

Time Taken

Time Taken: estimated 2-hour for instrumentation, one hour of baseline, 4 hours for cooling, and 2 hours of monitoring for an estimated minimum of 8 hour per animal.

Anticipated Results

Anticipated Results:

For each temperature probe, we expect to plot temperature (deg C) versus time (hours), with comparison here between control and experimental animals.

Serial CT images are taken to evaluate for injury to the nose brain and soft tissue. These are evaluated for injury from the cooling device. Similarly, CTP perfusion will evaluate the brain for decreased perfusion. Lastly, we collect histology from the animals to also assess for brain injury.

For survived animals, we will also measure continuous temperature parameters. They will be woken up and 4 days later sacrificed for histology. Histology will be collected and taken to a board-certified pathologist for staining and assessment.

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Figures

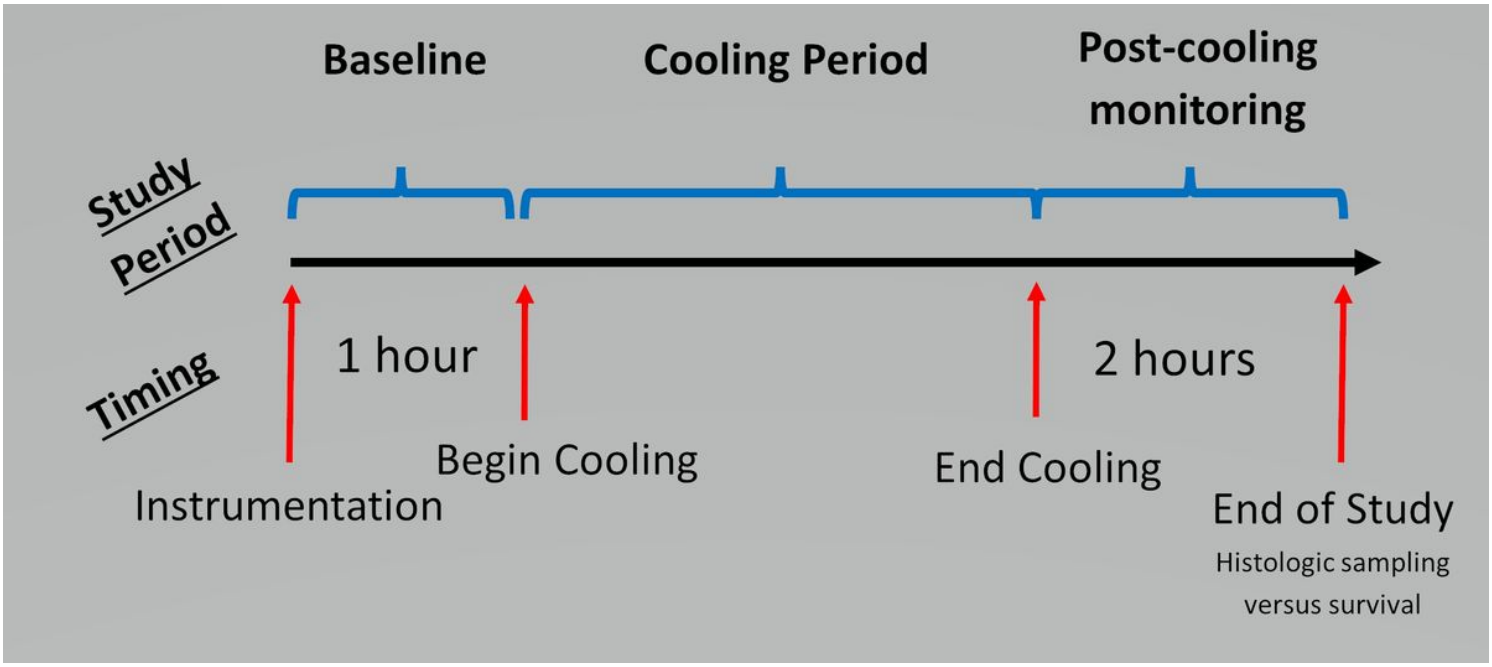

Figure 1

Protocol timeline and overview.