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Expert Panel Discussion

CNS Injury and Temperature Management

Moderator: Patrick Kochanek, MD, FCCM¹

Participants: Ryan S. Kitagawa, MD², Peter Batchelor, MD³, Marianne Thoresen, MD, PhD⁴

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During the 2016 Therapeutic Hypothermia and Temperature Management Meeting in Miami, state-of-the-art lectures were presented on current advances in the use of therapeutic hypothermia. Experts in the field discussed the use of therapeutic hypothermia and temperature management in different clinical settings including traumatic brain injury, spinal cord injury and moderate to severe neonatal hypoxic-ischemic encephalopathy. Dr. Ryan Kitagawa from the Department of Neurosurgery at the University of Texas, provided an overview of the use of therapeutic hypothermia targeting severe traumatic brain injury (TBI). Although supported preclinical and clinical data suggest that therapeutic hypothermia is beneficial after severe TBI targeting neuroprotective and intracranial pressure (ICP) elevations, recent multicenter trials have failed to show efficacy. Dr. Kitagawa presented the rationale and updates on the HOPES trial that is targeting patients undergoing decompression surgery with therapeutic hypothermia on board. Dr. Peter Batchelor, Department of Medicine at the University of Melbourne, Australia presented his work on the use of hypothermia in spinal cord injury. Various groups have now reported in both preclinical and clinical models that induced hypothermia after severe SCI can be neuroprotective and prolong the beneficial effects of decompression surgery. Thus, therapeutic hypothermia is now being tested in a multicenter spinal cord injury (SCI) trial to evaluate safety and efficacy. Dr. Marianne Thoresen Professor of Physiology at the University of Oslo in Oslo, Norway presented an update on the use of Xenon and hypothermia in neonates. Although hypothermia has been used to target the detrimental effects of neonatal encephalopathy with a significant degree of success, after more severe insults, hypothermia in combination with additional treatment strategies including Xenon may be most beneficial. Dr. Patrick Kochanek, Department of Critical Care Medicine, University of Pittsburgh moderated the expert panel discussion and helped lead an informative and interesting discussion.

Question: *I would ask each of you in turn to think about or to help me understand the role of the anti-shivering regimen that each of you are using. You have all described your trials in terms of hypothermia vs normothermia, but of course it is not just hypothermia but hypothermia plus a panoply of anti-shivering agents, some of which might be neuroprotective or beneficial some of which might be harmful and all of which might have side effects, especially since each of you are cooling your patients so long, I wonder if you could address both the toxicity and potential confounding benefit of anti-shivering agents.*

Dr. Ryan Kitagawa: It is a challenging problem all around and as we have talked about in the first session every patient is very different and it is an interesting thing to see that some patients will not shiver at all and with others it gets to the point you could nearly not control them. I think it is a confounding part of really any study when you do hypothermia you are obviously adding Buspirone, surface warming in addition to the catheter cooling that we are doing sometimes, other medications all the way up to sometimes to neuromuscular paralytics if it is really severe. I think that also is a confounding factor because each patient much like many other medications will respond very differently to different medications that you are doing. At the bedside in the clinical side it is sort of an individualized treatment that we have to do to for each and every one of them in the research center I don't think we have a really good answer for that as of yet.

Dr. Peter Batchelor: Yes, it is a vexing issue, I guess we are introducing paramedic cooling and it is another line of problems there. We were going to suggest to them focal counter warming of the head and neck, maybe a bit of fentanyl, but they do have a limited range of drugs in the paramedic setting. Obviously, once they get to the hospital the patients are intubated. As far as toxicity goes, in your neuromuscular agents toxicity is well known, Meperidine and the IP agents, we actually had a girl when I was part of the stroke lab who look in a stroke model the difference between giving Meperidine and not giving Meperidine and she could not find any toxicity. It does not look like there is a lot of data out there on toxicity.

Dr. Marianne Thoresen: With neonatal, neonates don't shiver, a lot of these babies are conscious and being cold is very unpleasant. If you are at 33.5 and you are awake it is like hell I think so you have to sedate them. Their blood pressure goes up and I use heart rate drop during hypothermia as a proxy marker of level of oxidation, it does not go down, I think they have not been sedated properly. We have not found and experimentally that morphine or fentanyl increases apoptosis in the animal models, but we don't know for babies. We did do a study with pigs which were randomized between sedating them and not sedating them, the pigs were very unhappy not being sedated. And I had absolutely no neuroprotection, this was published in pediatric research. In that study there was if anything more injury in the cool group, in all regions of the brain. They had no heart rate drop in response to hypothermia and they were 24 hours. There is a big discussion in the neonatal field now, some people do not incubate the cool babies, and they have to give them morphine because they are not happy about being sedated. They get so much more about being intubated on day 2.

Question: *I have a question that applies to probably all of you. The question has to do with when you consider multicenter trials and you have examined the results which reveal no difference between outcomes and groups. I often wonder when you enroll a patient in a study, the nurse who is taking care of that patient do they have one patient, do they have two patients, do they have three patients. What is their competency specifically with respect to hypothermia, are they reactive in their decisions or are they proactive? No one has ever factored that in to determine the quality of a trial No one has specifically examined what is the skill level of the nurse who is standing there 12 hours in his or her shift. I know there is learning curve, it takes probably 10-12 patients for a center and for a nurse to really achieve confidence. These are the most skilled nurses who are usually given these assignments, at least in my facility. I am curious whether or not to is that is controlled in the studies, the physician is there a few minutes in the*

day and then gone, but much happens during standard care on a clinical shift such as decisions on fluid, on pressers, etc..

Dr. Ryan Kitagawwa: I am not aware of any study that has ever looked at that specific problem and obviously much like everything else in every clinical trial there are so many variables that you really can't control well for at all. That is the difficult part about clinical research. In particular for things for like the HOPES trial and other wise a lot of it is also put on the shoulders of the research coordinators and the research assistants for a lot of these patients that person is nearly at the bedside for most of the day along with the nurses trying to make sure that most things are standardized and I think that having a protocol that is easily able to be followed is also the most important part about that and also having the support to the nurse from the clinical coordinators to say whether they are adhering to that protocol or not. There is never anyone there 24 hrs a day at the bedside all the time, they are there for a good majority of it and lots of times there are people there in the night time because in my particular center, we have such a high traumatic injury population that there is coordinators basically 24 hours a day who are enrolling patients in the other studies so they are available in the middle of the night. But you are right no matter what there are gaps involved.

Dr. Marianne Thoresen: The cool cap trials actually developed in Bristol, we did the first 10 babies, as we got experience I expanded the practical protocol, one thing is the cooling protocol and the other thing is the big document that goes with it, which nurses have to fill in data every hour. That is in a way how I know they check it because they have to fill it in. It is very rigorous actually and it is also advice on all the things that can happen to cool babies at the beginning, if it gets hyperbillirubinemia sometimes they do, if they bleed, if they do this, that etc, what do you do? What is the limit? What are the ranges what does it mean if you don't temperature correct the blood gas machine, so I am pretty neurotic about detail. And when I did the first trials every nursing shift I turned up at and talked to the nurse who was going to on the next shift and absolutely always on the night shift. I think is we are running also educational courses all the time. I think it is an endless education exercise to get good data, but you know this has been my life time so I know that it is good and I think it is an investment, but I think a very detailed protocol. Our Bristol protocol is on the web.

Dr. Peter Batchelor: I do not have a lot to add other than we are building on huge expertise in intensive care trials in Melbourne Trial and hypothermia trials and so on we are using the traumas and they have huge expertise and clinically skilled could not do it. You cannot go from ground zero, you really cannot do it.

Dr. Patrick Kochanek: I would just comment that I think that care needs to be taken to even another level and that is on the physician side. Currently we have a cardiac arrest service, that goes to every Cardiac Arrest at the University of Pittsburg Medical Center system wide. The interns and the residents get this little yellow card, that says "1-800-C-A-R-D-I-A-C-A-R-R-E-S-T" so they have faculty experts to come and help them manage at the physician level every cardiac arrest. It is a valuable service and I think that is also important, the clinical evidence for these types of things, probably the best in my mind is in the ECMO literature. ECMO is a highly technically demanding procedures, and there is a learning curve. It has been documented that it is very substantial for these types of technically demanding interventions. Therapeutic hypothermia is a complex intervention.. Thus, I think it is important in all levels.

Question: My question goes back to the HOPES trial. I think we all appreciate the challenges over the years we have had with hypothermia and brain injury because of the wide variety of injury mechanisms . I am curious about your thoughts on subdural hematoma, which in my mind is often a very heterogeneous population and what directs the decision as to why or when these patients go to craniotomy. Are there objective radiographic data that are being used? subdural width? mass effect, etc.. or is it the physician's choice?

Dr. Ryan Kitagawa: So it is obviously the surgeon's decision whether or not the patient goes to the operating room, it is based on their own experience of these lesions and of course every disease is a heterogeneous disease. The differentiating between whether they go to the operating room or not the decision whether or not the patient is appropriate for the HOPES trial it is the surgical evacuation of the subdural hematoma is the reason why they are going there. If the patient has diffused contusion, epidural, subdural and a skull fracture that patient is not enrolled in the HOPES and that is also that in educating the centers and having all of us have a common vision for what we do has applied to. We want to enroll every patient we can, but at the same time we want the data to be relevant and so yes, those that have polytrauma and an incidental subdural hematoma are not enrolled in the HOPES trail. Those who have the reason that they are going to surgery is the subdural hematoma they may have an incidental lesion or two here and there are the ones that are included.

Dr. Patrick Kochanek: *Marianne I have a question, I have seen some reports published on other inert gasses like argon which may be more plentiful in the atmosphere for instance, so I am wondering your thoughts on xenon versus another inert gas?*

Dr. Marianne Thoresen: Argon is also a neuroprotective much less and it is much cheaper, but it is quite a complicated treatment so if you want to do something as complicated like this, I think it should really work because is a demanding treatment, there are some people who are looking at animal experiments with Argon but it is not at all on the clinical stage yet, so I think we need to wait a bit.

Dr. Patrick Kochanek: And related to xenon, of course it is a more highly dense gas and do you find difficulties in randomizing because a lot of these neonates might have respiratory diseases and their airway pressures could increase substantially when you introduce the xenon and is that an issue?

Dr. Marianne Thoresen: Absolutely and the sickest babies we can't even recruit them, because you are not able to give oxygen, so in a few babies we have actually had to stop because they had to increase the oxygen need. We are allowed to go down 30% transiently, while we are try to sort out the respiratory problem. Because gas is four times heavier than air we were worried that we would have problems with ventilations as such but that actually has not been a problem. If you have for instance an obstructed gut you can't give xenon because you have trapping of gas. There are issues with xenon that makes it more complicated. If you get pneumothorax, we shouldn't talk about money here but then it will be saved. We actually have not had in the two groups had any more problems of any sort related to xenon. Those who need a lot of oxygen, we usually sort them

out quite quickly, this five hour issue makes it difficult for recruitment. We are very good on getting the oxygen down fast.

Dr. Patrick Kochanek: *You showed a very interesting slide that showed that xenon does not induce developmental apoptosis in contrast to isoflurane and many of the commonly used anesthetics for surgery in infants. Has there been any thought since xenon is an anesthetic of taking that kind of approach as a possible strategy for generalized use in the operating room.*

Dr. Marianne Thoresen: Absolutely, and we have a lot going on and we are thinking in particular in vulnerable babies. The neurotoxicity for all the drugs we were just mentioning you do not have them for adults but you certainly have them for premature babies. The more immature the brain the more vulnerable it is. I think, xenon will be a very good anesthetic for them. You can also think about people who have repetitive anesthetic because they had cancer, you go down in 1 ½ minutes with breathing xenon, as soon as you stop inhaling it goes out because it does not bind to anything. It is an anesthetic, it does not sit around in fat. I think if one can sort out the cost, there is some sort of a venture capital, something called neuroprotection using this in adult patients as neuroprotection. I think things will happen.

Comment: Just to comment on the previous question that of the appropriate reminder that nurses are important. I believe Dr. Dave from Paris will be presenting his trial tomorrow and he has actually assessed nursing work load in that trial in adults with cardiac arrest, it may be good to draw on his perspective on this comment.

Question: *My question is for the HOPES trial, I was curious about your neurological outcome measures for that study.*

Dr. Ryan Kitagawa: So that is also in the realm of traumatic brain injury and often discussed and debated topic of are the outcome measures too crude as far as that goes, we are following with the convention of nearly all TBI trials and that is mortality and the Glasgow outcome scale extended score at six months as well. That way we will be able to compare to the previous trials that led ultimately to the HOPES trial.

Dr. W. Dalton Dietrich: Any possibility as Peter was telling us, to introduce hypothermia in the emergency vehicle on the way to potentially decrease the time that the surgeon has to wait to bring the temperature down or is that a problem?

Dr. Ryan Kitagawa: So one of the ways that the NABISH two trial allowed for the sort of ultra-fast hypothermia protocols was to do it in route as well with surface cooling and with whatever measures necessary to bring down temperature, the issue with that is that we don't see based on those trials an improvement in outcome of the general population of severe traumatic brain injury. It is very tough to justify inducing hypothermia before you have a diagnosis of subdural hematoma, and that is the main problem with that and it is the whole reason why the decision was made to go with intravascular cooling because from diagnosis to target temperature is a matter of minutes as opposed to hours.

Question: *I have a question for Dr. Batchelor regarding the spinal cord injury hypothermia treatments, I am assuming that most of the spinal cord injury patients are not unconscious, so how much of a big deal is it actually to fully sedate them when they go into the hospital for hypothermia treatment. Or is it standard of care to do decompression?*

Dr. Peter Batchelor: When the patients get to the hospital it is pretty much standard for them to be intubated and sedated the problem is what is going to happen in the ambulance, we don't know. When we looked at the data, a lot of these patients were already hypothermic when they come in. And they don't seem to defend their temperature very well, they are vasodilated, often below the level of injury, they are often hypertensive and we do not know how much of a problem shivering is going to be, obviously the large muscle groups below the neck are going to shiver. I guess we will have to see. Dalton, what is your experience, have you had patients awake and cold with spinal cord injury.

Dr. W. Dalton Dietrich: In our clinical studies, patients are intubated and anesthetized before cooling is initiated. Pat Lyden can probably tell us some of the strategies they are using now where cooling can be initiated in awake stroke patients.

Question: *Because usually we see the patient has no indication for decompression or surgery, we start to cool the patient. But for the patient with spinal injury or with subdural hematoma, we start cooling the patient but suddenly the doctor says the patient has indication for surgery, how we can control surgery for rewarming in that case. Do you have a situation like this?*

Dr. Peter Batchelor: What you are saying is that if the patient made surgery and they are cooled that is a problem? This is a problem we talked about, that the neurosurgeons they really don't like operating in patients in less than 35 degrees and they had options to warm the patients. That is why we have in the protocol the options for the neurosurgeons for the temperature to be raised to 35 degrees.

Dr. Ryan Kitagawa: I find that most of us who are relatively comfortable with hypothermia have no problems operating on patients who are cooled down to 33 degrees. It is very common for us when a patient is in ICP crisis, they have been in the hospital for a day or two, they are sedated, paralyzed and cooled down to 33 degrees and either your reaching for a bottle of Pentobarb or getting ready to take them to surgery. We typically do not rewarm those patients we just take them to surgery and do the surgery and as we get more comfortable with other difficult hemostasis situations. We are becoming more and more comfortable in operating under difficult conditions and obtaining better hemostasis at the end of the case. Most of us who are in major centers have no problem operating on a patient who is 33 degrees.

Question: *I do not make decisions as to whether a patient has an indication for surgery when that occurs so we have to stop cooling the patient so temperature will be increased freely. Often the coded patient will reach 37 very quickly, so in that case for me, I am not happy with that. Do we have to bring the cooling machine to the operating room? That is my question.*

Dr. Ryan Kitagawa: Absolutely, we bring it all downstairs. We transport them with the cooling device, there is a transient period where they are actually being transported that there is an issue

and then we hook it up in the OR and maintain it at that temperature. That is also a big nursing issue. Traditionally we have to have a nurse in the operating room for a good 30 minutes of the case, because the anesthesiologists have no idea how to use these machines and so the transition between all those areas is a challenge.

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