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High-Flow Nasal Cannula vs CPAP in Acutely Ill Children by P. Ramnarayan

In this World Shared Practice Forum Podcast, Dr. Padmanabhan Ramnarayan discusses the findings of his clinical trial comparing high-flow nasal cannula (HFNC) therapy to continuous positive airway pressure (CPAP) therapy in pediatric critical care. The trial, which was published in JAMA, explores the effectiveness of HFNC as a non-inferior alternative to CPAP for respiratory support in acutely ill children. Dr. Ramnarayan reviews the trial's design, key outcomes, and implications for clinical practice, providing valuable insights for healthcare professionals involved in pediatric respiratory care.

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Sarah Marcley *00:04*
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Jeff Burns *00:18*
Welcome to the World Shared Practice Forum Podcast on OPENPediatrics. I'm Jeff Burns from Boston Children's Hospital and Harvard Medical School. We're here today with Dr. Padmanabhan Ramnarayan from the St Mary's Hospital in London and the Imperial College also in London. I should also add that Dr. Ramnarayan is the chair of the pediatric critical care study group research network in the UK. Ram, welcome to OPENPediatrics.

Padmanabhan Ramnarayan *00:46*
Thanks, Jeff. And it's a great pleasure to be here, particularly talking to you about a favorite topic of mine, noninvasive breathing support.

Jeff Burns *00:54*
Yes. And Ram, I've asked you to the podcast today because we were very interested to talk to you about your publication as the senior author and first author in JAMA, now, almost three years ago, entitled "Effect of High-Flow Nasal Cannula Therapy vs Continuous Positive Airway Pressure Therapy on Liberation From Respiratory Support in Acutely Ill Children Admitted to Pediatric Critical Care Units: A Randomized Clinical Trial", and our interest was twofold. The first was, you know, in PubMed, this has been cited over 50 times, and yet there has been no clinical trial comparing the relative effectiveness of high flow versus CPAP in this context, since your clinical trial. And so, we were interested to talk to you about that and where you see the field now and then, secondly, you used a non-inferiority analytic plan here, and this could also be considered, really one of the paradigmatic examples of a non-inferiority trial. And so, we were interested to speak to you about both. But I wonder if we could begin by asking in your study, what was the question that you were attempting to ask?

Padmanabhan Ramnarayan *02:17*
The study question was to compare two commonly used modes of noninvasive respiratory support, CPAP and high flow nasal cannula, and test the hypothesis that high flow nasal cannula was non inferior to CPAP in terms of time to liberation from all forms of respiratory support. So, that essentially means the time it takes for the child to start breathing unaided, without any respiratory support, that was the primary question. And the population that we chose to answer this question in was deliberately chosen to be a broad and pragmatic population of children with all diagnoses who needed noninvasive support, so that could include respiratory, cardiac and other reasons for respiratory support.

Jeff Burns *03:10*

Ram in the introduction, I noted that this might be a paradigmatic example of a non-inferiority trial in the current era in our field of pediatric critical care. Why did you choose to use a non-inferiority analytic plan?

Padmanabhan Ramnarayan *03:27*
So, Jeff, we know that high flow nasal cannula has several advantages compared to CPAP, in terms of better tolerability, less discomfort for children and possibly greater ease of use and familiarity for staff to put the interface on. So, what we wanted to test in this trial was not so much whether high flow was superior to CPAP, because we didn't think that that would be a legitimate question to ask. What we wanted to ask really was whether high flow was unacceptably worse compared to CPAP, and obviously we would give ourselves a margin of non-inferiority that corresponded to what clinicians thought was an acceptable level of superiority or inferiority that we would judge. And as part of the trial preparation and design, we had several discussions in the trial team, but also with parent and other consumer stakeholders within our research team to identify what that margin should be for the trial and we decided that hazard ratio of 0.75 would be our non-inferiority margin, which, in plain English, translated to from our pilot study, about 16 hours of time on respiratory support. So, effectively what we were testing was whether high flow was unacceptably worse to CPAP by 16 hours of respiratory support time.

Jeff Burns *05:04*
So to feed that back to you, as you well, just said you weren't looking to prove that high flow nasal cannula was better than CPAP, but rather whether it was not unacceptably worse than CPAP, and that the so called non-inferiority margin that you were looking for was that it didn't increase the risk of unfavorable outcomes in the high flow group compared to the CPAP group by more than 25%. Is that another way of saying what you just said?

Padmanabhan Ramnarayan *05:38*
That's right. That's right. Exactly.

Jeff Burns *05:40*
What are the advantages of a non-inferiority trial as compared to the typical randomized, controlled clinical trial comparing efficacy?

Padmanabhan Ramnarayan *05:49*
I think there are several advantages. I think in this particular situation, the clinical question aligned with a non-inferiority hypothesis. Clinicians were not using high flow because they thought it was better than or superior to CPAP. They were using it because it was an acceptable alternative to CPAP. So, we really mirrored that clinical impression by asking a non-inferiority question. So, I suppose the advantage then is that what we said at the end and what we came up with from the trial would be consistent with the mental model that clinicians already had about the use of high flow and CPAP. We were also able to use the non-inferiority hypothesis in both the step up, which is the acutely ill patients and the step down, so post extubation support patients. So, that's a separate trial. So, there were two different trials. They were paired together under a master protocol, so we could align these two questions very clearly in that there are a couple of disadvantages. One is that the sample size does go up a little bit when you do a non-inferiority trial compared to a superiority trial. So, that's one disadvantage, and the second, I wouldn't say disadvantage, but feature of non-inferiority trials is that you have to demonstrate alignment

of the findings in both the intention to treat and the per protocol analysis in the same direction to be able to conclusively determine non-inferiority. So, for example, we if we had seen a discordance between the intention retreat and the per protocol analysis in terms of non-inferiority, that would have been difficult, whereas a consistent signal from both the intention to treat and the per protocol population would help you to conclude non-inferiority much more strongly.

Jeff Burns *07:46*
Well, Ram, before we go to the salient findings of your study, can we talk a little bit about the protocol itself? Where did you set the initial high flow settings? And I noticed, noted that you had a table for high flow based on weight, but roughly where did you set the initial settings for high flow, and what were the initial settings for CPAP, and what were the thresholds that indicated that the patient was escalating and not succeeding on that particular mode of therapy?

Padmanabhan Ramnarayan *08:19*
Yeah, the high flow dose that we recommended at starting dose was equivalent to two liters per kilo per minute gas flow for all children who weighed under 10 kilos. We then had a weight banded flow rate, just to make it easier for clinicians to follow between 10 and 50 kilos, or over 50 kilos. And so that just went up in a not in exactly a two liter per kilo fashion, but it approached about one liter per kilo per minute when you got up to 50 kilos. So, you would gradually go up on the flow rate. For the CPAP, we recommended, based on what little physiological and experimental evidence we have that a pressure of seven to eight was the most efficacious starting pressure for CPAP, so we recommended that that would be the starting pressure for the for the trial. In terms of determining failure, we had clear criteria for failure, determination of failure of that first line treatment, there were three concepts. One was based on oxygenation, one was based on respiratory distress, and the third was based on agitation or patient discomfort. So, you could fail one of the treatments for one or more of these reasons, and so your FiO2 increasing beyond 60% was an oxygenation failure criterion. Your respiratory distress moving up from where you started or unchanged, would be a treatment failure criterion. And your patient intolerance, which we didn't set an objective measure to but mainly based on clinical assessment of patient tolerance or discomfort, was used as the third criterion for treatment failure.

Jeff Burns *10:12*
Can we also talk about the protocols weaning criteria?

Padmanabhan Ramnarayan *10:15*
So, we recommended that the high flow was weaned when the patient reached a FiO2 of 40% or below, and the recommended weaning step was to halve the flow rate from the initial starting flow rate. So, for example, a two liters per kilo per minute flow rate would be halved to one liter per kilo per minute. And for CPAP, we recommended that the pressure come down from seven to eight to five. And again, the same criterion applied, if your FiO2 was under 40% you could wean. We had a minimum recommendation of twice daily assessments whether the patient was fit to wean. And this we introduced to make sure that there was no delay in assessing patients for weaning, which might introduce some bias in terms of the time to liberation between the two, two interventions. So, in both groups, we wanted clinicians to assess on a twice daily basis. Is the patient ready to wean? Have they hit the criteria? Can I start weaning at this point?

Jeff Burns *11:20*

And now can we move into your findings, in particular, the primary outcome. What was your primary outcome? And what did you find?

Padmanabhan Ramnarayan *11:28*
The primary outcome was the time to liberation from all forms of respiratory support. And in this definition, we included noninvasive and invasive respiratory support. So, in effect, what this meant was the time that it took for the patient to come off all respiratory support and start breathing without any assistance, so that could include supplemental oxygen, but definitely off respiratory support. And the reason we chose this, as opposed to, say, for example, intubation as an outcome is because feedback from clinicians, as well as from our parent representatives on the research team suggested that sometimes children don't get intubated, even if they are failing the treatment, they are managed on various forms of noninvasive respiratory support, and that just gets prolonged and prolonged. And what the clinical team and the parents wanted to reflect was that both invasive and noninvasive prolongation of support was relevant to this study as a primary outcome. So, we chose that primary outcome, and what we found in the Step Up trial was that high flow was non inferior to CPAP, based on our non-inferiority margin, which we'd set as a hazard ratio of 0.75. The lower confidence interval of our point estimate was 0.8, so it was greater than 0.75, so we could conclude that high flow was non inferior.

Jeff Burns *13:02*
Ram, what I find very interesting about your study and the primary outcomes is, first, it wasn't solely defined by the investigators. You asked first your colleagues, what would be a meaningful outcome here, and then you included family, parents. And so not only is this truly a pragmatic trial design, but that has faced validity for me, the way you defined the primary outcome as including all respiratory support, and not merely, you know, failure to intubation, for example, as you noted. So, I salute you for that. You also had seven secondary outcomes. And of course, most clinical trials aren't powered to fully assess all the secondary outcomes. But what were some of the salient findings from your secondary outcome analysis?

Padmanabhan Ramnarayan *13:57*
The main secondary outcomes we were interested, of course, were intubation, which was not different between the two groups. About 15% of patients got intubated in both, the both the intervention and control groups. But what was different was the proportion of children who got sedation as part of their respiratory support management, about 35% received sedation for on CPAP and about 25% on high flow. So, 10% clear, 10% difference in the amount of sedatives given to children to be on respiratory support. We know this from practice. We expected some of this, but we had no clear idea of how different this practice would be in the trial. We also obviously looked at length of stay, both in the hospital and in the critical care unit, and we did see some difference. Of course, this is not statistically powered to detect any differences, but there was a difference in the number of days that the child stayed in the critical care unit and in the hospital between high flow and CPAP, a bit longer for CPAP compared to high flow. Of course, we also looked at mortality and quality of life in in a secondary health economic evaluation, and those weren't that different between the two groups.

Jeff Burns *15:17*
Well, Ram, you know, as I've searched the literature, including up to this morning, no one has replicated a clinical trial comparing high flow nasal cannula versus CPAP in the pediatric, critically ill patient, as you did now three years ago, whether as a superiority trial or as a non-inferiority trial. Of

note, however, is a manuscript that appeared in JAMA within the last several months entitled "High-Flow Nasal Oxygen vs Noninvasive Ventilation in Patients With Acute Respiratory Failure: The RENOVATE Randomized Clinical Trial" in adults, and they also used a non-inferiority analytic plan here, and found that, compared with noninvasive ventilation, high flow nasal oxygen met pre specified criteria for non-inferior inferiority for the outcome of endotracheal intubation or death within seven days, in again, patients who are adults with all forms of acute respiratory failure. So, not the same trial design, but somewhat similar results as yours. Your thoughts on that?

Padmanabhan Ramnarayan *16:35*
Yes, I think, I think, firstly, I suppose it's very sad that no one has done a clinical trial in children, and I think it's very much needed in pediatrics. From the RENOVATE trial point of view, I think there were, of course, a few differences. It's adult critical care patients rather than pediatric critical care patients. They also used a Bayesian statistical model to assess their, their results, which was different from our first AVC trial, but I think it fits into the overall narrative of or supports the overall narrative that high flow is non inferior, or seen to be non-inferior to noninvasive ventilation, CPAP being the most commonly used form of NIV in children. And I think they obviously also use a very useful mortality outcome, or re intubation outcome, intubation outcome in adults, which we wouldn't be able to replicate in children, because it's a very infrequent outcome in our population compared to adults. So, I think there are some good, strong signals from adult population that suggest that high flow is not unacceptably worse than NIV in the adult critical care population. And so that resonates with our findings, but there are obviously key differences that we have to recognize.

Jeff Burns *17:44*
Ram, another manuscript that I want to discuss with you is pediatric related, although they did not do a clinical trial. And I'm referring to the article by Pelletier and colleagues that appeared in the May 2024 issue of JAMA and JAMA Open Network entitled "Respiratory Support Practices for Bronchiolitis in the Pediatric Intensive Care Unit", and this was a retrospective review across 27 PICUs of patients admitted, and they utilized the VPS, virtual pediatric network database, and really found that the use of high flow nasal cannula and noninvasive ventilation is associated with an increase in PICU admissions for bronchiolitis. Almost a four to five fold increase in PICU admissions over the study period, which again was a retrospective study from 2013 to 2022 What are your thoughts on that? Does that resonate with you? Are you seeing the same thing at St Mary's and beyond that, the wider London population, but throughout the UK?

Padmanabhan Ramnarayan *19:12*
It does. It does. And I think there's evidence, not just from the US, UK, Canada, now Australia, that shows in bronchiolitis, noninvasive respiratory support usage has increased significantly. In the UK, practice has evolved over the last, say, five to seven years, where high flow nasal cannula therapy is no longer started in the ICU, it started in the general wards and emergency departments. So, high flow nasal cannula therapy patients don't now come to PICUs. Previously they did. So, I think we've decompressed some of the problem by keeping them on the on the pediatric wards. However, it doesn't mean that. It does mean, of course, that more patients are being put on high flow nasal cannula therapy. And so, there are more patients on the wards on high flow, nasal cannula therapy at varying levels of severity and physiological disturbance. Some are quite sick, even though they are on high flow, and some are not so sick. So, we've introduced a new therapy, which we are, at least in the UK, promoting to be used on the wards with not that much critical care level monitoring. So, there's a

concern around this. But yes, you're absolutely right that the usage of high flow has, has gone up quite significantly.

Jeff Burns *20:37*
Well, Ram, can I ask you your practice at, St Mary's Hospital in London, here you are you did this elegant study that appeared in JAMA in 2022 as we've discussed, no one has repeated a clinical trial comparing the efficacy of high flow nasal cannula and CPAP in this context. But how do you side you know, you have a patient who's got respiratory distress, impending respiratory failure. How do you decide which modality you're going to choose?

Padmanabhan Ramnarayan *21:09*
That's a really good question. I think practice is changing, you know, almost continuously, but at the current time, our practice in our hospital is children who present to emergency department, for example, or to the pediatric wards with respiratory failure, if they have signs of respiratory distress and are needing something more than two liters or three liters per minute of nasal low flow oxygen end up being started on some high flow nasal cannula therapy. I think two to three liters would roughly equate to between 30% and 40% oxygen, if we were to kind of look at it in that in those terms. Those children would get started on the therapy outside the ICU, and the expectation is that the ICU are asked to review them if they haven't made a substantial improvement in one or two hours. And we have guideline that specifies improvement in respiratory rate, improvement in heart rate, improvement in respiratory distress within the first two hours of therapy. And if that hasn't occurred, there is a call put out for pediatric ICU review, and so at that point, we would make a decision whether they should be brought into the ICU and be either managed on the ICU with closer monitoring or escalation to other forms of noninvasive treatment, such as CPAP or BiPAP. That's our current practice, and I think that is increasingly becoming the model by which we are making decisions around admitting children to the to the ICU.

Jeff Burns *22:51*
Ram, I must say your approach at St Mary's is similar to our approach at Boston Children's. Nonetheless, what are the lessons for the wider pediatric critical care community regarding your findings, your study findings?

Padmanabhan Ramnarayan *23:08*
I think the first ABC trial confirms that the first line noninvasive respiratory support mode for most patients could be high flow nasal cannula as a starting first step. We know from the first ABC trial that about 30% of patients started in on high flow as their first step would fail and have the need for escalation. It's one in three patients, and for those patients putting them on CPAP or other forms of noninvasive ventilation such as BiPAP or intubation, would be appropriate, and I think that that model of care provides the best chance of 70% of patients not needing any other treatment and just progressing with high flow nasal cannula therapy and getting weaned off the treatment, and offers the other 30% the option to escalate. I think based on our trial, it's not really easily possible to risk stratify patients at the very at the very beginning or at the very start. And I think a trial of high flow, a time limited trial of high flow to identify failure very quickly, would be the right strategy to go forward.

Jeff Burns *24:27*

Brilliant, brilliant, as I mentioned in the introduction, you are the chair of the pediatric critical care Study Group Research Network in the UK. With that lens, what are the research priorities now in this domain?

Padmanabhan Ramnarayan *24:43*
The first ABC trial was a very inclusive population. I think the next logical step would be to try and replicate these findings in specific populations, for example, bronchiolitis the immunocompromised subgroup of patients where we might expect different results. For cardiac patients, particularly those who have, say, myocarditis or cardiac failure from other causes. And so those would be the natural next steps. We are currently in the UK doing a trial of noninvasive support comparison in bronchiolitis. So, that's one particular subgroup. The other direction of research could be to recruit patients, not just in the ICU, not just in critical care, but also outside the ICU. So, EDs and wards, and we have some collaborations in the UK with those networks, research networks, and those would be ways we could take this forward.

Jeff Burns *25:37*
We've been speaking today with Dr. Ram Ramnarayan from St Mary's Hospital and Imperial College London, regarding his manuscript, "Effect of High-Flow Nasal Cannula Therapy vs Continuous Positive Airway Pressure Therapy on Liberation From Respiratory Support in Acutely Ill Children Admitted to Pediatric Critical Care Units: A Randomized Clinical Trial" that appeared in JAMA now in 2022, nearly three years ago, and it hasn't been repeated since then. Ram, we thank you for this really outstanding clinical trial. It's added to our understanding of how to approach these patients, and we thank you for your expertise as a clinician in sharing how you approach patients and equally, so we thank you for your expertise as a clinical trialist in helping all of us around the world have a better understanding of the evidence in this area. Thanks for being with us on OPENPediatrics today.

Padmanabhan Ramnarayan *26:35*
Thank you. Thank you for the invitation.

Sarah Marcley *26:38*
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