World as it is

Equipoise: an important ethical consideration when contemplating participation in a randomised controlled trial of hyperbaric oxygen treatment in necrotising soft tissue infections

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Abstract

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A proposal for a large, multi-centre, randomised controlled trial investigating the role of hyperbaric oxygen treatment (HBOT) in necrotising soft tissue infections (NSTI) has led to much discussion locally and internationally about whether participation is ethical for a centre where stakeholders already consider HBOT standard practice. This article systematically addresses the concept of clinical equipoise specific to the role of HBOT in NSTI, and presents a series of considerations to be taken into account by key stakeholders at potential participating sites.

Introduction

Highly regarded and widely published Danish colleagues are in the advanced phases of planning a multinational randomised controlled trial (RCT) investigating the use of hyperbaric oxygen treatment (HBOT) for necrotising soft tissue infections (NSTI). The trial involves patients with NSTI being randomised to receive either standard care (surgical debridement, antibiotics, intensive care support) or standard care plus HBOT.

Some Australian hospitals have used HBOT as part of the treatment for NSTI for many years, based on early work in clostridial infections, clinical experience and several retrospective and prospective studies that indicate HBOT may provide a mortality benefit.[1–3]

There has not previously been an RCT addressing this. Challenges in planning an RCT are imposed by the rarity of NSTI (requiring a multicentre, international study to achieve adequate power), the practical issues and considerations for the management of severely ill patients, as well as uncertainty amongst stakeholders regarding the presence or absence of equipoise for the role of HBOT in the treatment of NSTI.

Equipoise is a state of genuine uncertainty regarding the role of a treatment modality or the superiority of one treatment over another. It is a fundamental requirement of ethical clinical research, seeking to first do no harm. Equipoise may exist in an individual clinician who is indifferent to the treatment modalities ('individual equipoise') or amongst the expert medical community where 'honest professional disagreement' exists regarding the role of a treatment, or regarding which treatment modality is best ('clinical equipoise').[4,5] A reliance on individual equipoise of all clinician investigators in a trial, presents potentially insurmountable obstacles to the commencement or completion of a controlled trial, and the impact of such a scenario on an RCT for HBOT in NSTI will be discussed below. In contrast, clinical equipoise considers the entire range of expert medical opinion as *a priori* equally valuable; essentially constituting a 'fair bet' procedure – and as such RCTs in areas of clinical equipoise are considered to not present a risk of harm to trial participants.[6]

In this article I will endeavour to systematically address the concept of clinical equipoise specific to the role of HBOT in NSTI.

Commentary

The critical question is 'is it ethical for centres which already utilise HBOT as an adjunct to standard treatment for NSTI, to be involved in a study where fifty percent of patients will be randomised to not receive HBOT? The answer involves another question (a few, actually):

IS HBOT STANDARD TREATMENT FOR NSTI?

My health service treats more cases of NSTI with HBOT per year than all other Australian and New Zealand centres combined, so this question requires particular consideration.[7] To adequately answer the question, we need to review whether the provision of HBOT for NSTI is considered standard practice at the individual clinician level, Health Service level, State level, national level, and also at an international level.

IS TREATMENT OF NSTI WITH HBOT CONSISTENTLY OFFERED BY ALL CLINICIANS AT YOUR HEALTH SERVICE?

Or does the provision of HBOT depend on specific clinicians being present, rostered on, and aware of an NSTI case in your centre (e.g., an anaesthetist who is also a hyperbaric physician being made aware of the case in theatre, hyperbaric doctors 'finding' cases, or a 'believer' specialty doctor making a referral to the Hyperbaric Service)?

In centres where there is variability between clinicians, patients with NSTI are essentially already receiving 'random' care (e.g., receiving HBOT or not, based on factors independent of any evidence). In this case, it is roster allocations or plain chance that determine the treatment pathway the patient is allocated to, without the advantages of an RCT to advance the level of evidence for (or against) this practice. Participating in an RCT simply changes the mode of allocation of treatment that is already occurring in many centres (amongst numerous other advantages).

IS THERE A CONSENSUS AMONGST CLINICIANS AT YOUR HEALTH SERVICE ABOUT THE ROLE OF HBOT FOR NSTI?

In Melbourne, we treat more cases of NSTI with HBOT than any other centre in Australia or New Zealand.[7] Despite this, there is still a lack of consensus about the role of HBOT for NSTI.

Indeed, we evaluated this specific question and published our findings in ANZ Journal of Surgery in 2021.[8] We surveyed experts at our centre on their beliefs about the role of HBOT in the treatment of NSTI. Whilst some clinicians felt strongly (n = 4, 6% strongly disagreed that HBOT has a role in the treatment of NSTI and n = 8, 12% strongly agreed), the most common response (n = 31, 45%) was not being sure if HBOT has a role in the treatment of NSTI. We concluded that there is clinical equipoise at our centre regarding the role of HBOT in the treatment of NSTI, that an RCT should be considered ethical, and that further work towards increasing the level of evidence is highly necessary.

ARE PATIENTS WITH NSTI ROUTINELY OFFERED HBOT IN YOUR STATE?

In Victoria, Australia, they are not. Results from a (currently unpublished) project in which data from the Victorian admitted episodes dataset (VAED) and the Australia and New Zealand Intensive Care Society (ANZICS) adult patient database (APD) were linked by the Centre of Victorian Data Linkage (CVDL), indicate that less than one third of NSTI patients admitted to intensive care units in Victoria receive HBOT. That means that over two-thirds of Victorians who develop NSTI are not currently being referred for or receiving HBOT. Of interest, no statistically significant difference was found in APACHE III score or predicted risk of death in the groups who went on to receive, or not receive, HBOT.

WHAT ABOUT ON A REGIONAL LEVEL? IS HBOT FOR NSTI CONSIDERED STANDARD ACROSS AUSTRALIA AND NEW ZEALAND?

It is not. Table 1 contains the number of cases of NSTI who received HBOT as reported by each Hyperbaric facility around Australasia in the 2022–2023 financial year; if the Alfred's case numbers reflect less than one third of the Victorian NSTI case load, these statistics indicate that only a very small fraction of patients from around Australasia are currently receiving HBOT for NSTI. Assuming that disease incidence is similar across Australia and New Zealand, these data indicate a greater than ten-fold variation in the use of HBOT between regions.[9,10]

WHAT ABOUT ON AN INTERNATIONAL LEVEL? IS HBOT STANDARD PRACTICE FOR NSTI INTERNATIONALLY?

It is not. The use of HBOT for NSTI varies markedly between countries.

In July 2018 the NHS England published their *Clinical Commissioning Policy: Hyperbaric Oxygen Therapy for necrotising soft tissue infections (all ages).*[11] They concluded that there is not enough evidence to make the treatment available at this time, and funding was removed for the use of HBOT for NSTI from 1 April 2019. Likewise in the USA, only ~1% of NSTI cases are treated with HBOT.[12]

In contrast, more than one third of patients with NSTI in Denmark receive HBOT.[3]

Table 1

Cases of necrotising soft tissue infections treated with hyperbaric oxygen in Australia and New Zealand (NZ) (data are from 2022-23 financial year); ACT – Australian Capital Territory; NSW – New South Wales; NT – Northern Territory; pop – population; QLD – Queensland; SA – South Australia; TAS – Tasmania; VIC – Victoria; WA – Western Australia

Institution	The Alfred Hospital (VIC)	Fiona Stanley Hospital (WA)	Royal Hobart Hospital (TAS)	Royal Adelaide Hospital (SA)	Prince of Wales Hospital (NSW, ACT)	Royal Brisbane & Women's Hospital (QLD)	Wesley Hospital (QLD)	Townsville University Hospital (QLD)	Royal Darwin Hospital (NT)	North Shore Hospital Auckland (NZ)	Christchurch Hospital (NZ)
Cases treated[4]	27	5	3	1	6	1	0	1	0	2	0
Population[6,7]	6,766,600	2,855,600	572,700	1,844,600	8,758,600	5,418,500			251,700	5,223,100	
Cases treated per 10^6 pop	3.99	1.75	5.24	0.54	0.69	0.37			0.00	0.38	

DO INTERNATIONAL SCIENTIFIC SOCIETIES UNIVERSALLY RECOMMEND HBOT FOR NSTI?

The recommendations from international societies vary; some *do not* recommend HBOT (e.g., The American Infectious Disease Society),[13] some *do* recommend HBOT (e.g., The European and American Societies for diving and hyperbaric medicine),[14,15] and some suggest consideration of HBOT if available and not interfering with standard treatment (e.g., World Society of Emergency Surgery and the Surgical Infection Society Europe).[16]

WHAT DOES COCHRANE SAY?

The authors of a Cochrane review published in 2015 concluded: "*This systematic review failed to locate relevant clinical evidence to support or refute the effectiveness of HBOT in the management of necrotizing fasciitis. Good quality clinical trials are needed to define the role, if any, of HBOT in the treatment of individuals with necrotising fasciitis*".[17]

SO DOES CLINICAL EQUIPOISE EXIST?

Irrefutably, at every level.

Nevertheless, one could argue that with all this uncertainty, maybe it will be simpler to just stay sitting on the fence? Definitely. This trial won't be quick, or easy. However, without a unified effort, the likelihood of completion of this RCT falls. The status quo will remain; ongoing uncertainty amongst experts, ongoing inequity for patients, and ongoing inconsistency in the delivery of care for people with NSTI at hospital, state, national and international levels.

It is critical that such an RCT is planned by experts. If a poorly planned or inadequately powered trial were to be conducted, the outcome would likely be negative and may result in reduced use of HBOT for NSTI at centres which currently utilise HBOT, regardless of the actual impact HBOT has on NSTI. Clinical opinion may also shift away from a state of equipoise, which would reduce the possibility of a future, well conducted trial.

ARE THERE ANY OTHER ETHICAL CONSIDERATIONS WE SHOULD BE THINKING ABOUT?

I think it's important to think about the ethics of not participating in a large, well-designed, multi-national, randomised controlled trial.

Our centre could take the position that HBOT is standard practice that would be unethical to withhold from 14 of the 28 Victorian patients with NSTI we treat on average per year.

However approximately 60 other Victorians are admitted to intensive care units with NSTI each year and are not referred for HBOT, no doubt in part because the current level

of evidence isn't considered adequately robust. There are hundreds of people around Australia who develop NSTI each year who do not receive HBOT, and there will be countless other people, around the world, who will develop NSTI into the future. When deciding whether or not to participate in an RCT, we must consider the large number of people into the future who this choice will impact.

Conclusion

A carefully designed, multi-centre, international randomised controlled trial investigating whether HBOT has a mortality benefit in patients with NSTI, has the potential for profound and lasting impact regardless of the outcome. A negative study may result in reduced workload of hyperbaric units around the world, millions of healthcare dollars saved and the substantial logistics involved with transferring patients with NSTI to hyperbaric services reduced. A positive study may impact the lives of thousands of NSTI sufferers into the future by resulting in increased use of HBOT and increased survival for these patients.

Without clearer answers, health services are unlikely to invest healthcare dollars into improving capacity for hyperbaric treatment of intensive care patients (which may already contribute to the low treatment numbers currently reported in many hyperbaric centres), and many NSTI patients will not be offered HBOT as a result.

If we do nothing, and maintain the status quo, only a small fraction of NSTI cases will receive HBOT at a state, national and international level. If there is a survival benefit from HBOT – which observational data suggest may be the case – remaining at status quo will do more harm than good. Perhaps the real question should be: is it ethical not to participate?

What's your position?

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