Editorial

Intravenous oxygen administration: Fact or fiction?

Sri Lanka Journal of Child Health, 2022; **51**(3): 335-337
DOI: http://dx.doi.org/10.4038/sljch.v51i3.10234
(Key words: Intravenous oxygen administration, Fact, Fiction)

It is an axiom of life that all humans need oxygen for survival. Under normal circumstances, oxygen enters the bloodstream through the lungs and then it is delivered to all tissues where it works as the terminal electron acceptor during oxidative phosphorylation. Hypoxaemia with a reduction in the amount of oxygen carried in the blood, has drastic consequences and when extreme, has the potential to even kill humans. There are many causes for hypoxaemia but the ultimate result of a lack of an adequate amount of oxygen being supplied to tissues is that it leads to widespread damage and multi-organ failure. Given the potentially severe effects of hypoxaemia on all tissues and multiple organ systems, it is a standard therapeutic principle that rapid and urgent action is compulsorily needed to counter any degree of hypoxaemia.

Administration of oxygen is the therapeutic manoeuvre that is resorted to in all forms of hypoxaemia. This can be done by increasing the fraction of inhaled oxygen (FiO_2) by using nasal cannulae or masks, by mechanical ventilation with higher concentrations of inspired oxygen or by extracorporeal membrane oxygenation (ECMO) where blood is removed from the circulation, oxygenated and carbon dioxide removed from the blood through an external device, and then returned to the circulation. All these manoeuvres can alleviate the effects of hypoxaemia but they are not without their problems and disadvantages. These undesirable effects have a confounding effect on the potential benefits, and by themselves these drawbacks could even threaten lives. In such a context, it is of considerable interest that some entirely different and innovative initiatives have come into the scenario where oxygen could be directly delivered through the intravenous route.

One way in which this could be accomplished is by artificially increasing the amount of dissolved oxygen in the blood[1]. In their publication in the Expert Review of Respiratory Medicine 2017, Jonathan A. Gehlbach and co-workers provide a discourse on intravenous oxygen (IVO_2), a novel method to improve oxygen delivery that involves the intravenous administration of a physiologic solution containing dissolved oxygen at hyperbaric concentrations. They also summarize the current evidence surrounding IVO_2[1]. However, experts agree that while not yet at the stage of clinical testing in the United States and Europe, the procedure has been used safely in Asia and that initial laboratory data have been encouraging. These suggest that IVO_2 may have a role in the management of patients with hypoxaemic respiratory failure in the future. Yet for all that, more work needs to be undertaken, including clear evidence that such a therapy is safe, before it can be advocated for general use for hypoxaemic respiratory failure[1].

A more recent development is the use of nanotechnology to administer intravenous oxygen. The initial published work on this procedure goes as far back as 2012[2]. Those investigators developed an injectable foam suspension containing self-assembling, lipid-based microparticles encapsulating a core of pure oxygen gas for intravenous injection. When mixed with human blood *in vitro*, oxygen transfer from 70 volume per cent microparticles was complete within 4 seconds. When the microparticles were infused by intravenous injection into hypoxaemic rabbits, arterial oxygen saturations increased within seconds to near-normal levels, only to be followed by a decrease in oxygen tensions after stopping the infusion. The particles were also infused into rabbits undergoing 15 minutes of complete tracheal occlusion. Oxygen microparticles significantly decreased the degree of hypoxaemia in these rabbits, and the incidence of cardiac arrest and organ injury was reduced, when compared to controls. The investigators postulated that administering oxygen directly to the bloodstream could represent a technique for the short-term rescue of profoundly hypoxaemic patients.

More recently, scientists at the USA Boston Children's Hospital, in a report published in 2022, claim to have perfected a device that can inject oxygen directly into the bloodstream through the intravenous route[3]. There are risks of directly injecting oxygen into the bloodstream as it has the potential to create air bubbles that can block blood vessels. This can often even be fatal.

The new technology claims to overcome this with an entirely new procedure using a new device. To prepare the oxygen to be injected into the bloodstream, the researchers have put it into the device along with a fluid containing phospholipid, a type of fat that is found in the linings of human cells. The gas and fluid are then made to move through nozzles of decreasing size to create tiny nano-

bubbles of oxygen with a phospholipid coating, all smaller than a single red blood cell. These bubbles are coated with the phospholipid 'membrane' similar to that in every cell in the body. This prevents them from merging with other bubbles to create larger ones and provides a path for oxygen to diffuse out and into the blood while minimizing the likelihood of material-related toxicities. The phospholipid packaging and tiny size of the bubbles are critical for providing safety to the entire manoeuvre[4].

The new emulsion, a fluid full of tiny bubbles, is then injected into the bloodstream. Once the solution is injected, the material dissolves, leading to the release of the packaged oxygen. *In vitro* experiments on donated human blood have shown that blood oxygen saturation levels could be lifted from 15 per cent to over 95 per cent within just a few minutes. When the study was conducted on live rats, the process increased the oxygen saturation from 20 per cent to 50 per cent quite rapidly. The researchers postulate that these devices allow them to control the dosage of oxygen delivered and the volume of fluid administered. Both of these are vital in the management of critically ill patients.

The researchers have not tested the device on humans as the technology is far from ready to be tested on humans. "If successful, the described technology may help to avoid or decrease the incidence of ventilator-related lung injury from refractory hypoxaemia," the researchers write in their new paper published in the journal *Proceedings of the National Academy of Sciences of the United States of America*[3].

While this is a significant development, we need to consider that there have not been any *in vivo* human studies of this procedure as yet. Injecting oxygen into the body like this can become complicated if it is administered in the wrong way or for doubtful indications or if too much or too little is added. The team has to test their oxygen injection on larger animals before moving on to human trials.

Looking forward, we do hope that this new device can be utilized to keep alive people who cannot breathe properly, by providing them with life-saving oxygen. It can also better prepare the body to be put on ECMO. The study authors are confident that their device could "potentially be integrated into existing ventilators, allowing for seamless integration into existing clinical workflows". They believe that patients who are injected with the solution may regain near-normal blood oxygen levels within seconds. This can drastically reduce the incidence of organ injury and cardiac arrest. Other scientists who studied the paper have opined that the research team needs to make the device more dependable and ensure that it provides at least 10 times more oxygen[4].

If the procedure is found to be efficacious and safe, the initial use for this initiative would be to buy time by its emergency usage in recalcitrant hypoxaemia before other procedures, particularly ECMO, could be instituted as a definitive longer-term management strategy. Intravenous oxygen therapy is unlikely to become a long-term management approach because of clinical limitations imposed by infusion fluid requirements and technical problems in producing the required amounts of packaged oxygen. Such emergency usage of this procedure would be particularly useful in children whenever some bridging time is required before conventional ventilation and even ECMO could be instituted.

Acknowledgement
Professor Sanath P. Lamabadusuriya is hereby appreciated and credited for drawing the attention of the author to this interesting development *via* an electronic mail communication[5].

References

1. Gehlbach JA, Rehder KJ, Gentile MA, Turner DA, Grady DJ, Cheifetz IM. Intravenous oxygen: a novel method of oxygen delivery in hypoxemic respiratory failure? *Expert Review of Respiratory Medicine* 2017; **11**(1): 73-80. https://doi.org/10.1080/17476348.2017.1267568 PMid: 27910706

2. Kheir JN, Scharp LA, Borden MA, Swanson EJ, Loxley A, Reese JH, *et al.* Oxygen gas-filled microparticles provide intravenous oxygen delivery. *Science Translational Medicine* 2012; **4**(140): 140ra88. https://doi.org/10.1126/scitranslmed.3003679 PMid:22745438

3. Vutha AK, Patenaude R, Cole A, Kumar R, Kheir JN, Polizzotti BD. A microfluidic device for real-time on-demand intravenous oxygen delivery. *Proceedings of the National Academy of Sciences of the United States of America* 2022; **119**(13): e2115276119. https://doi.org/10.1073/pnas.2115276119 PMid: 35312360

4. Experimental Device Would Give Oxygen by IV, *Web*MD 2022, Available from: https://www.webmd.com/lung/news/20220322/experimental-device-oxygen. Accessed on 22nd June 2022.

5. A way to inject oxygen directly to the bloodstream. Available from: https://www.ba-bamail.com/science-and-technology/a-way-to-inject-oxygen-directly-to-the-bloodstream/ Accessed 10th June 2022.

B J C Perera orcid.org/0000-0001-7789-8793
Joint Editor

The author declares that there are no conflicts of interest