Towards interventional trials on the use of oxygen during and after cardiac arrest

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2016

Skrifvars , M B 2016 , ' Towards interventional trials on the use of oxygen during and after þÿcardiac arrest ' , Resuscitation , vol. 101 , pp. A3 A4 . https://doi.org

http://hdl.handle.net/10138/223926
https://doi.org/10.1016/j.resuscitation.2016.01.030

publishedVersion

Resuscitation 101 (2016) A3–A4

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Editorial

Towards interventional trials on the use of oxygen during and after cardiac arrest

Supplemental oxygen is likely to be the most used medical drug in modern intensive care.[1] Until the twenty-first century its use was commonly liberal and even included in the so-called "Three Golden Rules of Anesthesia" i.e., "trust no one", "assume nothing" and "give oxygen" (Michael Parr and Malcolm Fisher, personal communication). During cardiopulmonary resuscitation (CPR), the guidelines have recommended ventilation with 100% oxygen.[2] This would seem intuitive, since lack of oxygen is the main cause of anoxic brain injury. Nonetheless, the medical community has not been blind to the possible toxic effects of oxygen.[1] The toxic effects of hyperoxia during the resuscitation of newborns and during the intensive care of neonates have been acknowledged for several years.[3] During the care of patients with myocardial infarction, the requirement of supplemental oxygen has been debated, clinical trials have been undertaken and several more are underway.[4,5] For the scientific community interested in CPR and ICU management of adult patients after cardiac arrest, the study by Kilgannon and colleagues in 2010 turned out to be some form of a wakeup call.[6] Kilgannon and colleagues analyzed data from an US ICU registry and found that hyperoxia, defined as the first arterial oxygen level exceeding 300 mmHg (40 kPa), was associated with lower survival when controlling for ICU severity of illness. The study has been replicated in various settings with conflicting results; some studies show that strict normoxia is related to better outcome, whilst others suggest that moderate hyperoxia may be of benefit.[7–9]

In this issue of Resuscitation, Eastwood and colleagues report the results of a pilot trial studying the feasibility of a more stringent approach to oxygen use in mechanically ventilated cardiac arrest patients.[10] As a part of a larger cohort study, the authors report the results of a subset of patients treated following cardiac arrest. With a before and after design, the authors show with 50 patients in the conventional (control group, the before group) group and 50 in the conservative (intervention group, the after group) group that titrating the inspired oxygen fraction to target a Sp02 of 88–92% results in an increase in the amount of measured normoxic values and reduces documented hyperoxia. The difference in used fraction of oxygen was around 10% between groups during the first 24 h. The study suggests first and foremost that stringent titration of oxygen is possible and safe. Several aspects of the study warrant further debate. The study does not report whether the target of Sp02 of 88–92% was successfully achieved. Based on the reported pa02 values, it is likely that this was not the case; without lung pathology, this is likely not even possible in all patients, since a Fi02 of 21% was used in 38% of the patients in the intervention group. In addition, studies on oxygen use in neonates have shown that during a trial, oxygen levels are often higher than the set target.[11] The study also reports differences in the amount of patients on a spontaneous ventilation mode throughout the study and a shorter length of ICU stay. The authors suggest that an oxygen titration strategy might trigger earlier attempts to spontaneous ventilation because of a "lack of an oxygenation problem" perceived by clinicians, and also by stimulating the patients' intrinsic respiratory drive. These findings should be interpreted with caution since there were important differences between patient samples, such as a more frequent use of targeted temperature management in the liberal (control) oxygen period.

The neurological injury that develops after cardiac arrest is likely to be multifactorial. Not surprisingly, the most marked exposure of the brain to hyperoxia is likely to be right after return of spontaneous circulation when the brain is perfused with arterial blood with a very high oxygen content, which is due to intra-arrest ventilation with 100% oxygen. In an elegant case report from 2003, oxygen values during CPR were measured in an invasively monitored neurosurgical patient who had an iatrogenic cardiac arrest.[12] This case suggests that during CPR, oxygen measured in parenchyma of the brain is related mainly to perfusion pressure and less so to arterial oxygen content. Perfusion pressure during CPR can only be achieved with high-quality chest compressions. After ROSC, brain oxygen levels increases rapidly due to the combined effect of high content of oxygen in the blood and high perfusion pressure. In addition, clinical studies have shown that a clear majority of cardiac arrest patients are indeed exposed to hyperoxia prior to ICU admission.[13] Thus, if we think that hyperoxia is harmful to the brain after ROSC, it is likely that we should start titrating its use early, perhaps already during CPR? This has been tried by the same group from Australia in the "Hot or Not" trial published in Resuscitation in 2012.[14] This study attempted to titrate oxygen use by monitoring the peripheral oxygen saturation immediately after CPR. The study was prematurely stopped because of inherent difficulty in achieving the planned SaO_2 target. Rather than trying to titrate oxygen during or immediately after CPR, we might need to study whether using a fixed oxygen fraction of, for example, 50% during CPR is feasible and safe, and whether it results in less hyperoxia after ROSC. Ideally, such a study should focus on cardiac arrests of a cardiac origin (myocardial infarction or arrhythmia) rather than those of a respiratory origin (drowning, suffocation or pulmonary embolism). There is no doubt that we desperately need large trials on the use

http://dx.doi.org/10.1016/j.resuscitation.2016.01.030

of oxygen during and after cardiac arrest. Eastwood and colleagues should be commended for providing important data that will be needed when designing and conducting such trials, hopefully, in the very near future.

Conflicts of interest

Lecture fee from Covidien.

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