Monitoring targeted oxygen levels in clinical trials – a re-evaluation of HOT-ICU oxygenation levels using time-weighted averages

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Background

Assessment of intervention adherence is essential for interpreting the results of clinical trials. The Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial compared the clinical impact of a lower versus a higher oxygenation target among patients admitted to the intensive care unit (ICU) with acute hypoxemic respiratory failure.¹ Oxygenation levels were targeted through continuous measurement of peripheral oxygen saturation guided by intermittent assessment of the partial pressure of arterial oxygen (PaO₂). Target adherence was reported based on averages of the highest and lowest measurements of PaO₂ in 12-hour intervals. With a mean number of arterial blood gas analyses (ABGs) of 6 per day, all available data were not used. We aimed to evaluate if the original pragmatic registration of daily oxygenation levels was comparable to a time-weighted analysis utilising oxygenation data from all available ABGs conducted in participating Danish ICUs.

Methods

In the HOT-ICU trial, 2928 patients were randomised. Of these, 2332 (79,6%) were included at Danish sites. For each patient enrolled in Denmark, all conducted ABGs were collected, and time-weighted averages (TWAs) were calculated for both PaO₂ and arterial oxygen saturation (SaO₂) during ICU admission in 90-day time frames. Data were compared to the original assessment of adherence to oxygenation targets based on the highest and lowest PaO₂ measurements in bi-daily 12-hour intervals. Statistical comparisons between oxygenation level assessments were conducted using a Wilcoxon matched-pairs signed-rank test. A p-value below 0.05 was considered statistically significant. Further, Bland-Altman plots were used to illustrate data agreement in both intervention groups.

Results

A total of 162.639 ABGs were obtained. In the lower group, the median PaO_2 and SaO_2 of all 90-day TWAs were 9.1 kPa (8.7 – 9.7 kPa) and 92.7% (91.4 – 93.9%), respectively. In the higher group, the median PaO_2 and SaO_2 of all 90-day TWAs were 12.1 kPa (11.4 – 12.8 kPa) and 96.3% (95.2 – 96.9%), respectively. In comparison, the original 90-day assessment reported a median PaO_2 of 9.4 kPa (8.9 – 10.2 kPa) with a concurrent SaO_2 at 92.9% (91.6 – 94.1%) in the lower group, and a median PaO_2 of 12.4 kPa (11.6 – 13.2 kPa) with a concurrent SaO_2 at 96.2% (95.1 – 96.8%) in the higher group. The difference between highest and lowest bi-daily 12-hour assessments and TWA was statistically significant for PaO_2 (p <0.001 in both groups), and for SaO_2 (p <0.001 in the higher group and p=0.002 in the lower group). The Bland-Altman plot is shown in figure 1.

Conclusion

A statistically significant difference in data distributions was found for PaO₂ and SaO₂ in both groups when comparing the two methods, but the absolute differences were clinically negligible. When assessing data agreement in the Bland-Altman plots, the methods were comparable. The original pragmatic assessment of oxygenation levels sufficiently describes the oxygenation levels in the HOT-ICU trial.



1. Schjørring, O. L. *et al.* Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. *N. Engl. J. Med.* 1301–1311 (2021).

Figure 1: Bland-Altman plots depicting agreement between time-weighted averages and averages of the highest and lowest 12-hour measurements for assessment of PaO₂ and SaO₂ in the HOT-ICU trial.

Black line: the mean of the absolute differences between the methods. Dotted lines: limits of agreement corresponding to 1.96 times the standard deviation of the mean. Gray line: reference line at zero absolute difference between methods.

PaO₂: partial pressure of arterial oxygen, SaO₂: arterial oxygen saturation, HighLow: assessments based on averages of the highest and lowest measurements in bi-daily 12-hour intervals, TWA: assessments based on time-weigthed averages, HOT-ICU: handling oxygenation targets in the intensive care unit