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Journal club

Does high-flow oxygen reduce escalation of care in infants with hypoxaemic bronchiolitis?

Commentary on:

Franklin D, *et al*. A randomised trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018; 378:1121–1131.

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Context

Bronchiolitis is an acute, lower respiratory tract disease of viral aetiology that affects infants below 2 years of age [1]. Bronchiolitis is common. One in five children have at least one healthcare visit related to bronchiolitis during infancy and it is a major cause of hospitalisation, accounting for 18% of all hospitalisations in the USA in children younger than 1 year [2]. The diagnosis is clinical and based on viral respiratory infection symptoms and signs such as tachypnoea, wheeze, crackles, rhonchi and respiratory distress [3]. There are no effective medical therapies for bronchiolitis so treatment is based on hydration and respiratory supportive care when necessary [3]. The use of high-flow oxygen through nasal cannula as respiratory support in infants with bronchiolitis has increased in recent years [4]. It provides a high flow of humidified air warmed to body temperature with an adjustable fraction of oxygen, and is usually well tolerated by infants. It may improve oxygenation and breathing effort by producing a positive pressure at the end of the expiration [5]. Franklin *et al*. [6] examined treatment failure resulting in escalation of care in infants with bronchiolitis and hypoxaemia who were treated in emergency departments or general paediatric wards with either high-flow oxygen or standard therapy with supplemental oxygen through a nasal cannula.

Methods

This multicentre randomised controlled trial was conducted in 17 Australian and New Zealand hospitals; eight of the hospitals had an on-site intensive care unit (ICU). Infants younger than 12 months presenting with signs of bronchiolitis and needing supplemental oxygen to keep oxygen saturation above 92% or 94%, depending upon institutional practice, were included. Infants who needed oxygen therapy for any reason other than suspected bronchiolitis were excluded. Eligible infants were randomised to receive either standard-therapy oxygen through a nasal cannula up to a maximum flow of 2 L·min^{-1}, or high-flow therapy with humidified air with variable oxygen through a nasal cannula at a rate of 2 L·min^{-1} per kilogram bodyweight. In the standard-therapy group, flow rate was adjusted, while in the high-flow group the inspiratory oxygen fraction (FIO_2) was varied. In both groups this was done to maintain oxygen saturation in the range of 92–98% (six hospitals) or 94–98% (11 hospitals). Children were randomised using a

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Treatment failure leading to escalation of care occurred less often in infants with hypoxaemic bronchiolitis treated with high-flow oxygen than with standard oxygen therapy, but there were no differences in the proportion needing ICU transfer or intubation http://bit.ly/2F3rSi1

computer-generated randomisation sequence with a block size of 10, stratified by hospital. Allocation was concealed but treatment was not blinded. The primary outcome was treatment failure resulting in an escalation of care. A conclusion of treatment failure was reached by a clinician if at least three of four criteria were met: 1) heart rate remained unchanged or increased since admission; 2) respiratory rate remained unchanged or increased since admission; 3) oxygen requirement in the high-flow group exceeded a F_{IO_2} of at least 0.4 to maintain an oxygen-saturation level of at least 92% or 94%, depending on hospital threshold, or the requirement for supplemental oxygen in the standard-therapy group exceeded 2 $L \cdot min^{-1}$ to achieve the same oxygen-saturation threshold; 4) the hospital internal early-warning tool (a standardised set of physiological and clinical factors) indicated medical review and escalation of care. Clinicians could also escalate care if they considered it appropriate for other clinical reasons apart from the four explicit criteria. Escalation of treatment was defined as an increase in respiratory support. Infants in the standard-therapy group who required escalation of care were changed to high-flow oxygen therapy and infants in the high-flow group were transferred to an ICU. Secondary outcomes included the proportion of children transferred to an ICU; intubation; durations of hospital stay, ICU stay and oxygen therapy; and adverse events.

Main results

Between October 2013 and August 2016, 2217 infants were eligible for inclusion, 1638 (74%) underwent randomisation, and 1472 (90% of those randomised) were included in the analysis. Treatment failure leading to escalation of care occurred more often in the standard-therapy group (167 out of 733, 23%) than in the high-flow therapy group (87 out of 739, 12%) with a risk difference of 11% (95% CI 7–15%). Escalation of care was influenced by whether the hospital had an on-site ICU. In hospitals without an on-site ICU, care was escalated in 69 out of 247 infants (28%) in the standard-therapy group and 20 out of 270 (7%) in the high-flow group. In hospitals with an on-site ICU, care was escalated in 98 out of 486 infants (20%) in the standard-therapy group and 67 out of 469 (14%) in the high-flow group. Restricting analysis to children meeting at least three of the four criteria, treatment failure remained lower in the high-flow group, in which 53 out of 739 (7%) infants experienced treatment failure, in comparison with 115 out of 733 (16%) in the standard-therapy group. There was no difference between the high-flow and the standard-therapy group regarding any of the secondary outcomes.

Commentary

This randomised controlled trial showed that treatment failure leading to escalation of care among children admitted for hypoxaemic bronchiolitis was lower among infants treated with high-flow oxygen supplementation than those treated with standard therapy. However, certain aspects of the study suggest that its results should be interpreted with caution. Comparison of the two groups is complicated by different main outcome definitions. In the high-flow oxygen group, the only way to escalate care was to transfer to ICU, whereas escalation of care in the standard-therapy group was to cross over and start high-flow oxygen. Clinicians might perceive switching infants from standard nasal cannula to high-flow oxygen as a smaller escalation step than transferring infants under high-flow oxygen therapy to the ICU, especially if high-flow therapy was already standard practice in their hospital. Were this true, it would increase escalation of care in the standard-therapy group compared to the high-flow group. Infants in the standard-therapy group had a lower respiratory rate at escalation than infants in the high-flow oxygen group, which suggests that perception was, to some extent, present. To address this problem, the authors performed a sensitivity analysis using the sample of patients that strictly met at least three out of four preset criteria for escalation of care. The analysis showed that escalation of care remained higher in the standard-therapy group, indicating that high-flow oxygen might really be better than standard therapy.

Presence or absence of an on-site ICU affected the risk of escalation of care in a different way in each treatment group. The risk difference in escalation of care was greater in hospitals without an on-site ICU than in those with an ICU. Possible reasons for this differ. ICU patient transfer could have been easier in hospitals with an on-site ICU. Also, clinicians might have greater confidence in waiting to escalate care from standard-therapy to high-flow oxygen if an ICU was present on-site. Therefore, it seems that mode of oxygenation did not alone influence escalation of care, but also presence of an on-site ICU. However, further sensitivity analyses including only infants that met at least three out of four preset criteria for escalation of care stratified by presence of an on-site ICU consistently favoured high-flow oxygen over standard therapy. In addition, Franklin *et al*. [6] did not mention whether there were any children who should have been escalated according to these criteria, but were not. Those children were not included in the sensitivity analysis and it is difficult to predict how this would have affected the results.

The comparatively higher cost of high-flow oxygen was not discussed by Franklin *et al*. [6]. Also, most of the infants in the standard-therapy

group did not require escalation of care, which indicates that most would not benefit from initial high-flow oxygen treatment. Additionally, no differences between the two groups were observed in any of the secondary outcomes, such as transfer to the ICU or intubation. In spite of the fact that escalation of care was experienced by fewer infants in the high-flow group, overall the cost–benefit balance would favour initiating treatment with traditional nasal cannula.

Most of the previous evidence for high-flow oxygen treatment of bronchiolitis comes from observational studies [7]. Among the few randomised controlled trials comparing high-flow oxygen to standard, low-flow oxygen therapy in infants with bronchiolitis [8, 9], this study by Franklin *et al*. [6] is the largest, and the most important.

Implications for practice

The escalation of care results of Franklin *et al*. [6] favour high-flow oxygen over standard nasal cannula. In the absence of other large randomised controlled trials, however, aspects of this study's design and interpretation of its results, and the higher costs of high-flow therapy need to be considered before implementing high-flow therapy as initial therapy; previous commentators have also raised these points [10–13]. Further research is needed to establish the best moment to start high-flow oxygen therapy in hypoxaemic infants with bronchiolitis. In the meantime, clinicians should assess the individual situation of each patient before deciding to initiate high-flow oxygen therapy.

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Conflict of interest

None declared.

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