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A comparison of a new automated method with the traditional manual method of managing blood oxygen saturation in infants receiving respiratory support in the intensive care unit

Submission date
15/03/2013

Recruitment status
No longer recruiting

Registration date
03/04/2013

Overall study status
Completed

Last Edited
07/07/2015

Condition category
Pregnancy and Childbirth

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Most premature babies need to breathe extra oxygen in order to have a normal level of oxygen in the blood. Many babies need the extra oxygen for several days or weeks. Because too much or too little oxygen are not good for the baby's health, the level of oxygen in the baby's blood is closely monitored. Depending on the reading of the monitor, nurses or respiratory therapists change the amount of oxygen given to the baby to breathe. If the level of oxygen in the baby's blood is below normal, nurses and respiratory therapists give the baby more oxygen to breathe or vice-versa. However, nurses and therapists cannot be at the baby's bedside to change the amount of oxygen given to the baby at all times. This study evaluates a new function that is part of a ventilator (machine that helps the baby breathe) that can automatically change the amount of oxygen given to babies to breathe according to what the baby needs at all times. The purpose of the study is to find out if this new function is better at keeping the level of oxygen in the baby's blood inside a normal range over a 2-day period (one day each of automated and routine care) Because the range that is considered normal by the baby's doctors is wide, the study will also find out if the oxygen level in the baby's blood can be kept inside one of two slightly different ranges (both considered normal) equally well by the nurses or respiratory therapists and the automatic function.

Who can participate?
Born with a gestational age between 23 and 32 weeks
Weight at study entry between 0.4 to 4 kilograms
Receiving invasive mechanical ventilation or non-invasive respiratory support (NCPAP or NIPPV)
Receiving supplemental oxygen at the time of enrollment and for at least 18 hours during the previous 24 hours

What does the study involve?
The baby will be in the study for 48 hours. During the study period one of the two oxygen ranges will be assigned. During one half of the 48 hours oxygen will be controlled automatically, and in the other half manually by the clinical staff.

What are the possible benefits and risks of participating?
There is no direct benefit for the baby participating in the study. In some babies the automatic method may avoid giving too much oxygen to the baby or prevent long periods with low oxygen in the blood. The study duration is short (2 days) compared to the entire time these babies receive extra oxygen (weeks) and therefore it is difficult to determine if this study will benefit the baby. The study may be helpful in finding how to better maintain the level of oxygen in the blood at the normal range. It is also possible that the automated method will result in proving inadequate or excessive amounts of oxygen.

Where is the study run from?
The study will be conducted at about 10 newborn Intensive care units in different countries.

When is the study starting and how long is it expected to run for?
The study starts in March of 2013 at four centers (City Hospital, Ruda Slaska, Poland; University of Amsterdam/Academic Medical Center, Amsterdam, The Netherlands; Center Medical Post Graduate Education, Warsaw, Poland, Vittore Buzzi Children's Hospital, Milano, Italy) others will be added in the Spring. The study will include up to 100 babies and is expected to be complete in December 2013.

Who is funding the study?
Investigators and CareFusion (USA) - manufacturer of the AVEA ventilator.

Who is the main contact?
Tom Bachman
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
IMCS-r1

Study information

Scientific Title
International Multicenter Study of Saturation Targeting by Automatic vs. Manual Adjustment of Inspired Oxygen in Neonates

Study objectives
The primary null hypothesis of this study is that there will be no difference between the manual and automatic Fraction of inspired oxygen (FiO2) adjustment periods in the primary outcome variable defined as the proportion of time with oxygen saturation (SpO2) within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21.

The rationale for selecting this as the primary outcome variable is based on the defined primary purpose of automatic FiO2 adjustment to increase the time the infant's arterial oxygen saturation is within the clinician's desired target range while the infant receives supplemental oxygen. Arterial oxygen saturation levels above the target range are acceptable when the infant is not receiving supplemental oxygen.

This is the effectiveness hypothesis. It will be tested using the statistical model described below. A $p < 0.05$ will be sufficient to rule out the null hypothesis and indicate superiority of either manual or automatic FiO2 adjustment.

The safety null hypotheses of this study are that there will be no difference between the manual and automatic FiO2 adjustment periods in the proportion of time in a) hypoxemia defined as SpO2 < 80% and b) hyperoxemia defined as SpO2 > 98% while FiO2 > 0.21.

The rationale for selecting a) SpO2 < 80% and b) SpO2 > 98% while FiO2 > 0.21 as the Safety endpoints is based on common clinical recommendations to minimize exposure to both extreme ranges of arterial oxygen saturation that can be associated with insufficient or excessive oxygen supplementation.They will be tested using the statistical model described below. A $p < 0.025$ will be sufficient to rule out the null hypothesis and indicate superiority of either manual or automatic FiO2 adjustment.

Statistical comparisons of the continuous variables to evaluate the primary and safety hypotheses, that is within-subject differences between the manual and automatic FiO2 adjustment periods and between groups (two target ranges) will be conducted using the Generalized Linear Model Repeated Measures Analysis method (ANOVA Repeated Measures).

Updated 26/02/2014: The trial was completed on 06/02/2014 with enrollment of 80 infants as planned (previous anticipated end date: 31/12/2013)

Ethics approval required
Old ethics approval format

Ethics approval(s)
This study plan requires the approval of each of the participating sites Research Ethics Committee. The status of each is listed below.
1. Klinik für Kinder und Jugendmedizin/Universitätsklinikum Ulm, Ulm, Germany, approved July 2013.
2. James Cook University Hospital/University of Durham, Middlesbrough, United Kingdom, approved June 2013.

3. City Hospital, Ruda Slaska, Poland. Approved as #KNW/0022/KB1/175/12/13, 8 January 2013 by Komisja Bioetyczna Slaskiegi Uniwerstetu Medycznego w Katowicach.
4. Leiden University Medical Center, Leiden, The Netherlands, approved August 2013.
5. University of Amsterdam/Academic Medical Center, Amsterdam, The Netherlands. Approved as #2012_365#B2013190a, 18 January 2013 by Academisch Medisch Centrum Medisch Ethische Toetsingscommisie
6. Center Medical Post Graduate Education, Warsaw, Poland. Approved as #392, 5 December 2012 by Centrum Medyczne Kszalcenia Podyplomowego Komisja Bioetyczna
7. University Hospital North Tees, Stockton-Cleveland, United Kingdom, approved June 2013.
8. Alberta Children´s Hospital, Calgary, Canada, June 2013.
9. Vittore Buzzi Childrens Hospital, Milano, Italy. Approved as #82/PB/2012, 13 November 2012 by Comitato Etico: Azienda Ospedaliera-Insituti Clinici de Perferionamento-Milano

Primary study design
Interventional

Study design
Multicenter unblinded randomized crossover study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neonatal pulmonary insufficiency requiring respiratory support and supplemental oxygen

Interventions
Intervention
The intervention in this study is an automated FiO2 control system tied to a pulse oximeter. This is embodied as the CLiO2 option of the Avea Ventilator (CareFusion Yorba Linda, CA USA). It has been in commercial distribution (CE mark) for nearly 3 years.

The control is the usual and customary care, that is manual adjustment of FiO2 in response to pulse oximetry monitor display and alarms.

For both intervention and control one of two SpO2 target ranges (89-93% and 91-95%) will be randomly assigned.

Joint Scientific Contact:
Tom Bachman
The Clinical Monitor and Study Manager
Lake Arrowhead
California, U.S.A.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)

1. The proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21.
2. The proportion of time in hypoxemia defined as SpO2 < 80%
3. The proportion of time in hyperoxemia defined as SpO2 > 98% while FiO2 > 0.21

Key secondary outcome(s)

Secondary Effectiveness End Points:
1. Time Within Assigned Range: To compare the proportion of time within the assigned target range of SpO2 between the periods of manual and automatic FiO2 adjustment.
2. SpO2 Distribution:
To compare the distribution of SpO2 between the periods of manual and automatic adjustment of FiO2. This will specifically include the comparisons of the 5th, 25th, 50th, 75th, and 95th percentiles.
3. Fraction of Inspired Oxygen: To compare the fraction of inspired oxygen between the periods of manual and automatic adjustment of FiO2. For this, the mean, standard deviation, median interquartile and hourly-median FiO2 will be calculated over each recording period.
4. Time with FiO2 at 0.21:
To compare the proportion of time with FiO2 at 0.21 between the periods of manual and automatic adjustment of FiO2.
5. SpO2 variability:
To compare the variability of SpO2 between periods of manual and automatic FiO2 adjustment. This will specifically include the coefficient of variation (Standard deviation divided by the mean) of SpO2 over each recording period.
6. Assessment of Staff Effort:
To compare the effort of the clinical staff involved in manually adjusting FiO2 between the periods of manual and automatic FiO2 adjustment. This will specifically include a count of the number of manual changes in FiO2 during each period.
7. Adherence to Guidelines for FiO2 adjustment:
To characterize the adherence of the clinical staff to the guidelines for manual FiO2 adjustment during the 24-hour manual period. This will be determined by calculating the proportion of episodes with SpO2 outside the target range in which the clinical staff responded within the time and with a step size of FiO2 adjustment in concordance with these guidelines.

Secondary Safety End Points:
1. Extended episodes with SpO2 below or above the target range: To compare the incidence of extended episodes with SpO2 outside the target range between periods of manual and automatic FiO2 adjustment. This will specifically include the frequency of episodes lasting longer than 1 and 2 and 3 minutes with a) SpO2 < 80% and b) SpO2 > 98% while FiO2 > 0.21.
2. Incidence of Episodes with SpO2 below the target range: To compare frequency and duration of episodes with SpO2 below the target range between periods of manual and automatic FiO2 adjustment. This will specifically include the frequency and duration of episodes with SpO2 below the target range, SpO2 < 80%, SpO2 < 70%, SpO2 between 80-86%, and SpO2 between 80 % and the lower limit of the assigned target range.
3. Time with SpO2 below the target range: To compare the proportion of time with SpO2 below the target range between periods of manual and automatic FiO2 adjustment. This will specifically include the proportion of time with SpO2 below the target range, SpO2 < 80%, SpO2 < 70%, SpO2 between 80-86%, and
SpO2 between 80 % and the lower limit of the assigned target range.
4. Incidence of Episodes with SpO2 above the target range: To compare the frequency and duration of episodes with SpO2 above the target range between periods of manual and automatic FiO2 adjustment. This will specifically include the frequency and duration of episodes

with SpO2 above the target range, SpO2 > 95%, SpO2 > 98% and SpO2 between the target range and 98%. These will include only episodes while FiO2 > 0.21.
5. Time with SpO2 above the target range: To compare the proportion of time with SpO2 above the target range while FiO2 > 0.21 between periods of manual and automatic FiO2 adjustment. This will specifically include the proportion of time with SpO2 above the target range, SpO2 > 95%, SpO2 > 98% and SpO2 between the target range and 98%. These will include only episodes while FiO2 > 0.21.
6. Assessment of response to SpO2 signal loss: To compare the oxygen saturation status following pulse oximeter signal drop-out between periods of manual and automatic FiO2 adjustment. The oxygen saturation status will be defined as SpO2 within, above or below the assigned target range for at least 10 seconds within the first minute after drop-out ends (i.e. Initial status) and at least 60 seconds over the first two minutes after the drop-out ends (i.e. Persistent status).
7. Assessment of overshoot:
To compare the rate of overshoot status following episodes when SpO2 decreased below the target range between periods of manual and automatic FiO2 adjustment. This will be defined as SpO2 above the target range for at least 10 seconds over the first minute following recovery from an episode of SpO2 below the target range (Initial overshoot status) and as SpO2 above the target range for at least 60 seconds over the first two minutes following recovery from an episode of SpO2 below the target range (Persistent overshoot status).

Secondary Comparisons Within and Between Groups of Assigned Target Range of SpO2:
These assessments will be used to characterize and provide an insight into the performance of manual and automatic FiO2 adjustment within and between the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%). These are not intended to provide evidence to support or detract from the primary claim.
1. To compare the variable defined as the proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21 between the manual and automatic FiO2 adjustment periods within each of the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).
2. To compare the mean and median Manual-Automatic differences in the variable defined as the proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21 between the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).
3. To compare the variables defined as the proportion of time with a) SpO2 < 80% and b) SpO2 > 98% while FiO2 > 0.21 between the manual and automatic FiO2 adjustment periods within each of the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).
4. To compare the mean and median Manual-Automatic differences in the variables defined as the proportion of time with a) SpO2 < 80% and b) SpO2 > 98% while FiO2 > 0.21 between the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).
5. To compare the manual and automatic FiO2 adjustment periods in the variables described above in the Secondary Effectiveness End Points section within each of the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).
6. To compare the manual and automatic FiO2 adjustment periods in the variables described above in the Secondary Safety End Points section within each of the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).
7. To compare mean and median Manual-Automatic period differences in the variables described above in the Secondary Effectiveness End Points section between the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).

8. To compare mean and median Manual-Automatic period differences in the variables described above in the Secondary Safety End Points section between the two groups of infants according to their assigned target range of SpO2 (89-93% or 91-95%).

Secondary Comparisons Within Strata of Respiratory Support:
These assessments will be used to characterize and provide an insight into the performance of manual and automatic FiO2 adjustment within each strata of respiratory support (invasive mechanical ventilation and non-invasive respiratory support). These are not intended to provide evidence to support or detract from the primary claim.
1. To compare the manual and automatic FiO2 adjustment periods in the variable defined as the proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21 within each of the two strata of infants according to the type of respiratory support (invasive mechanical ventilation and non-invasive respiratory support).
2. To compare the manual and automatic FiO2 adjustment periods in the variables defined as the proportion of time with a) SpO2 < 80% and b) SpO2 > 98% while FiO2 > 0.21 within each of the two strata of infants according to the type of respiratory support (invasive mechanical ventilation and non-invasive respiratory support).
3. To compare the manual and automatic FiO2 adjustment periods in the variables described above in the Secondary Effectiveness End Points section within each of the two strata of infants according to the type of respiratory support (invasive mechanical ventilation and non-invasive respiratory support).
4. To compare the manual and automatic FiO2 adjustment periods in the variables described above in the Secondary Safety End Points section within each of the two strata of infants according to the type of respiratory support (invasive mechanical ventilation and non-invasive respiratory support).

Assessment of Sequence Effects:
These assessments will be used to characterize sequence effects and provide an insight into the performance of manual and automatic FiO2 adjustment. These findings will not be used to determine exclusion of the data because the study analysis is based on intention to treat. These are not intended to provide evidence to support or detract from the primary claim.
1. To compare the mean and median differences between the manual and automatic FiO2 adjustment periods in the variable defined as the proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21 between groups of infants assigned to the sequence Manual-Automatic or Automatic-Manual.
2. The compare the variable defined as the proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21, calculated from the first 12 hours of each recording period and the remaining 12 hours between groups of infants assigned to the sequence Manual-Automatic or Automatic-Manual.

Assessment of Research Site Differences:
These assessments will be used to characterize the effects within individual sites. Comparisons among sites will be primarily qualitative since per site enrollment limits will not allow for sufficient power for statistical comparisons. These findings will not be used to determine exclusion of the data from any site because the study analysis is based on intention to treat. These are not intended to provide evidence to support or detract from the primary claim. Heterogeneity among the sites is expected to reflect actual differences in neonatal intensive care among institutions and it is in agreement with the purpose of conducting a multicenter study.
1. To compare manual and automatic FiO2 adjustment periods in the variable defined as the

proportion of time with SpO2 within the assigned target range plus time with SpO2 above the assigned target range while FiO2 is set at 0.21 within each site.
2. To compare manual and automatic FIO2 adjustment periods in the variables defined as a) the proportion of time with SpO2 < 80% and b) the proportion of time with SpO2 > 98% while FiO2 > 0.21 within each site.
3. To characterize the adherence of the clinical staff to the guidelines for manual FiO2 adjustment during the 24-hour manual period within each site. This will be determined by calculating the proportion of episodes with SpO2 outside the target range in which the clinical staff responded within the time and with a step size of FiO2 adjustment in concordance with these guidelines.

Completion date
06/02/2014

Eligibility

Key inclusion criteria
1. Born with a gestational age between 23 and 32 weeks
2. Weight at study entry between 0.4 to 4 kilograms
3. Receiving invasive mechanical ventilation or non-invasive respiratory support (NCPAP or NIPPV)
4. Receiving supplemental oxygen at the time of enrollment and for at least 18 hours during the previous 24 hours
5. Expected to complete the 48 hour study period in the current form of respiratory support, i.e. invasive mechanical ventilation or non-invasive respiratory support
6. Written informed parental consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Neonate

Sex
All

Key exclusion criteria
1. Major congenital anomalies
2. Arterial hypotension requiring vasopressor therapy within 48 hours prior to enrollment.
3. Culture proven sepsis within 72 hours prior to enrollment.
4. If the attending physician deems participation in the study is not in the best interest of the infant

Date of first enrolment
01/04/2013

Date of final enrolment

06/02/2014

Locations

Countries of recruitment
United Kingdom

Canada

Germany

Italy

Netherlands

Poland

Study participating centre
AMC
Amsterdam
Netherlands
1105 AZ

Sponsor information

Organisation
Individual Sponsor (USA)

Funder(s)

Funder type
Industry

Funder Name
Investigator initiated and funded

Funder Name
CareFusion (USA) - manufacturer of the AVEA ventilator

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2015		Yes	No