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Establishing the reference interval for pulse oxygen saturation in neonates at high altitudes: protocol for a multicentre, open, cross-sectional study

Bo Wang [1], Chongde Liu,[2] Yanli Yao,[3] Zhihui Lu,[4] Rong Yu,[5] Zhuoma CaiRen,[6] Zhixiu Wang,[7] Runwu Liu,[2] Yazhen Wu,[8] Zhangbin Yu[9]

For numbered affiliations see end of article.

Correspondence to
Zhangbin Yu;
yuzhangbin@126.com

ABSTRACT

Introduction Establishing the reference interval for pulse oxygen saturation (SpO_2) is essential for sensitively identifying neonatal hypoxaemia due to various causes. However, the reference interval for high altitudes has not yet been established, and existing studies have many limitations. This study will aim to establish the reference interval for various high altitudes and determine whether preductal and postductal measurements at the same altitude vary.

Methods and analysis This is a multicentre, open, cross-sectional study, which will begin in February 2022. Approximately 2000 healthy full-term singleton neonates will be recruited from six hospitals (altitude ≥2000 m) in Qinghai Province, China. The participating hospitals will use a uniform pulse oximeter type. The measurements will be performed between 24 hours after birth and discharge. During the measurement, the neonate will be awake and quiet. Preductal and postductal measurements will be performed. The measurement time, site and results will be recorded and input, along with the collected basic information, into the perinatal cloud database. We will carry out strict quality control for basic information collection, measurement and data filing. We will perform descriptive statistics on the distribution range of the collected data, determine the lower limit value of the reference interval for each hospital and the corresponding altitude, perform curve fitting for the lower limit value, use the altitude as a covariate for the function corresponding to the fitted curve, establish the prediction equation and ultimately determine the reference intervals of each high altitude location.

Ethics and dissemination Our protocol has been approved by the Medical Ethics Committee of all participating hospitals. We will publish our study results in academic conferences and peer-reviewed public journals.

Trial registration number NCT05115721.

Strengths and limitations of this study

► This study will ensure the accuracy of the data by using the same type of measuring instruments, conducting uniformed training, deploying dedicated operators and implementing three-level quality control.
► This study will verify the differences between the measurement results obtained at different sites at the same altitude, which will help to establish a more accurate reference interval.
► The curve fitting method will be used to predict the reference interval for pulse oxygen saturation that changes constantly with the increase of altitude.
► The accuracy of the study result is limited by the number of altitude distribution points participating in the study.

and medical costs and improve the quality of nursing.[2 3]

The now widely used SpO_2 reference interval for neonates 24 hours after birth has been developed based on data from low altitudes.[4] It is not suitable for neonates at high altitudes because many studies have shown a downward trend in the mean SpO_2 of neonates with the increase in altitude.[5–11] Unfortunately, no reference interval has been established for high altitudes, and the existing studies on the topic have many limitations.

Obtaining accurate data from a suitable reference population is essential in determining reference intervals, requiring strict criteria to match the reference population characteristics to a normal or healthy population.[12] However, previous studies were deficient in the selection of the reference populations. For example, a study conducted by Guo et al[11] on neonates born at high altitudes found that the thresholds should be adjusted. However, their study population included premature infants. Another study, performed on a population at an altitude

INTRODUCTION

Establishing the reference interval of neonatal pulse oxygen saturation (SpO_2) is conducive to more sensitive identification of hypoxaemia due to sepsis, congenital heart disease and other causes.[1] It could reduce the number of arterial blood gas samples

of 1371 to 2484m, found a difference in SpO_2 between preterm and full-term infants with no clinical symptoms and signs.[13]

Differences in measurement sites might contribute to differences in the results, an aspect many previous studies did not focus on.[14 15] A multicentre large sample study from Yunnan, China, found significant differences between preductal and postductal measurements.[11] However, the highest altitude in that study was only 2202m. How the measurement site affects the results at higher altitudes needs further study.

Our previous study found only a few reports on the SpO_2 of neonates 24 hours after birth in areas above 2000m. We also noted that while these previous studies used the mean±SD to describe the results, their mean+2 SD exceeded the theoretical maximum of 100%, indicating that their results were not normally distributed.[16] IQRs should have been used so that reliable reference intervals could be derived. Furthermore, previous studies were often limited to a specific altitude. However, the SpO_2 decreases with the increase in altitude,[16] so the results of these studies can be applied to the specific altitude studied, while they cannot be generalised and applied to other altitudes.

We designed this multicentre, open, cross-sectional study to solve the many limitations of existing studies and establish the SpO_2 reference interval for healthy neonates 24 hours after birth at several high altitudes. This study will provide the basis for neonatal care and medical decision making at high altitudes.

OBJECTIVE

The primary objective of this study is to establish the reference interval of SpO_2 for healthy neonates 24 hours after birth at high altitudes.

The secondary objective of this study is to observe whether there are statistical differences between preductal and postductal measurements at the same altitude.

METHODS AND ANALYSIS
Study design

This is a multicentre, open, cross-sectional study, which will begin in February 2022. More than 2000 healthy neonates delivered consecutively will be recruited from six participating hospitals in Qinghai, China. This study protocol has been approved by the Medical Ethics Committee of all participating hospitals. All participating hospitals will be required to conduct the study in strict accordance with the established rules. Figure 1 presents a summary of the study process.

Jinan University designed and initiated the study, which is the affiliation body of the promoter (ZY). Qinghai Women and Children's Hospital is the coordinating centre, the training centre and the affiliation body of the main verification person (CL). This is an open study. We welcome additional eligible hospitals to join this study.
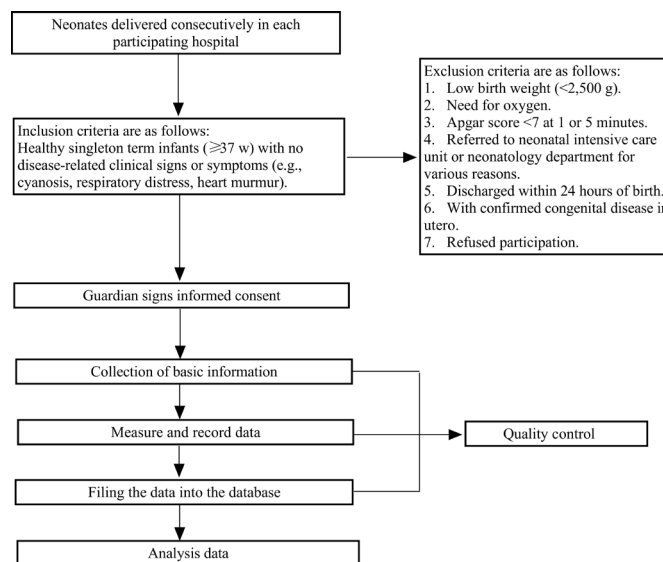

Figure 1 A flow chart showing the study plan.

The protocol was drafted in accordance with the recommended statement for standardised study protocol items: Recommendations for Observational Studies statement (online supplemental file 1).

Patient and public involvement

The guardians of the neonates and the public were not involved in the study and/or protocol design. Participation in this study will be entirely voluntary. The findings will be disseminated to the guardians and the public through popular science education, health brochures and academic conferences.

Participants

The six participating hospitals from Qinghai Province, China, form the Qinghai Plateau neonatal multicentre collaborative research group. Basic information of the participating hospitals is shown in table 1. This study is planned to begin on 1 February 2022. Healthy neonates who meet the requirements will be consecutively recruited at the six participating hospitals and will undergo SpO_2 measurements. The recruitment will be stopped when the sample size requirements are met at each altitude point. We expect the study will be completed within a year. The infants clinical management will not be affected by whether their guardians decided to participate, refused participation or withdrew from the study.

Inclusion and exclusion criteria

Inclusion criteria are as follows:

Healthy singleton term infants (≥37 weeks) with no disease-related clinical signs or symptoms (eg, cyanosis, respiratory distress and heart murmur).

Exclusion criteria are as follows:
1. Low birth weight (<2500 g).
2. Need for oxygen.
3. Apgar score <7 at 1 or 5 min.
4. Referred to neonatal intensive care unit or neonatology department for various reasons.

Table 1	Participating hospitals basic information	
Hospital name	Altitude (m)	Number of infants delivered in 2020
Qinghai University Affiliated Hospital	2261	1356
Qinghai Red Cross Hospital	2261	8725
Qinghai Women and Children's Hospital	2261	1471
Geermu People's Hospital	2808	1274
Yushu Prefecture People's Hospital	3680	2278
Guoluo Tibetan Autonomous Prefecture People's Hospital	4200	1403

5. Discharged within 24 hours of birth.
6. With confirmed congenital disease in utero.
7. Refused participation.

Informed consent

This study follows a completely voluntary principle. If consented, a written informed consent form will be signed by the subject's guardian. The study complies with the Declaration of Helsinki. For details of the informed consent form, please refer to online supplemental file 2.

Collection of basic information

Information of the subject's mother will include name, age, hospitalisation number, hospitalisation date, home address, telephone number and ethnicity.

Information on the infant will include name, date of birth, gestational age, sex, mode of delivery, birth weight and Apgar scores (1 and 5 min).

Definition standardisation

1. High altitude: at present, there is no unified standard classification of high altitude.[14] Stanton *et al* defined high altitude as altitude greater than 1400 m,[17] while Moore[18] defined it as altitude greater than 2500 m. In this study, an altitude ≥2000 m is defined as high altitude.
2. Twenty-four hours after birth: ≥24 hours.
3. Measuring site: preductal SpO_2 is the value measured on the right hand. Postductal SpO_2 is the value measured on any foot.
4. The reference interval of SpO_2 for neonates 24 hours after birth is defined as the lower limit value $<SpO_2 \leq 100\%$. If the data do not conform to a normal distribution, the lower limit value will be defined as the value corresponding to the 2.5th percentile of the SpO_2 distribution range in healthy neonates 24 hours after birth in the corresponding altitude. If the data are normally distributed, the lower limit value will correspond to the –2 SD value.[11 19]

Method of measurement

The neonate should be awake and quiet during the measurement, rather than crying or breast feeding. The measurement environment shall be a well-ventilated quiet room without strong light or electromagnetic field interference. The measurement will be performed between 24 hours after birth and discharge. When measuring, the probe will not be placed on the limbs that have just been used or are presently used to measure blood pressure. The surveyor will first clean the skin at the measuring site and keep it dry. The pulse oximeter's special probe (sensor) will be wrapped around the neonate's right hand and any foot. The measurement data of the two sites and the measurement time will be recorded after the SpO_2 value and the signal waveform of the pulse oximeter were stable for at least 10 s.

Standardised management of the operation

All participating hospitals will use the COVIDIEN 10005941SG pulse oximeter (Covidien Company, USA) with a reusable probe to measure SpO_2. Each hospital shall select at least two full-time measuring operators. The coordination centre shall carry out standardised training for all measuring operators on 15 January 2022. Assessment will be conducted after training, and qualification will only be obtained after passing this assessment. The coordination centre will also provide standardised videos to all participating hospitals to facilitate repeated learning.

Each hospital will designate at least one high-level physician as the quality control person, who will conduct on-site operational inspections of the measuring personnel at least once a week in their respective hospitals. If the inspection finds that the operator was unqualified, the operator will be trained again. The coordination centre will conduct on-site inspections at least once a month in all hospitals to check whether the operation process and quality control were qualified.

Data collection

The data collected in this study will be divided into two parts, basic information data and measurement data. These data will be uploaded into the perinatal cloud database (https://www.perinatalcloud.com/) developed by the promoter (ZY). This database can be accessed to upload data from a computer or mobile phone at any time. See online supplemental file 3 for details of data collection.

Standardised management of data

The perinatal cloud database will be managed and operated by Jinan University to ensure data security. Each hospital has its independent account, and operators will only be able to browse and fill in their hospital's data once logged in. Each subject will be given a unique number that will appear when analysing the data and issuing reports to protect the information of the subjects.

We established a data monitoring committee composed of research group chairpersons from the participating hospitals and the promoter. It has the authority to browse all the data and is responsible for monitoring the progress of the study to ensure compliance with the study plan. It will also recommend stopping further recruitment when the enrolment of a sufficient number of participants at a specific altitude has been met. The committee will hold regular quality control and analysis meetings to evaluate the study progress and whether there are any deviations from the protocol. The committee is also responsible for the overall sampling quality control, recruiting other participating hospitals, organising training, providing training materials, checking, collating and analysing the data and publishing the study results. If the study design needs to be changed, the committee should apply to the Medical Ethics Committee of Qinghai Women and Children's Hospital for approval. The ethics committee is independent of sponsors, the promoter or any other entity that might influence their decisions. It is responsible for performing the annual audit of the study.

All collected data will be entered into the online database. See online supplemental file 4 for the specific login and filing steps. The data entry will be completed by the data entry personnel designated at each hospital. These personnel will be trained by the coordination centre and pass an examination before taking up their posts. We have adopted a three-level quality control method to ensure data input accuracy. Each hospital shall designate at least one first-class data quality controller responsible for checking each data entry. The coordination centre shall appoint secondary data quality controllers, one for each hospital. These will sample and inspect weekly at least 30% of the input data during that week. The third quality control level will be assumed by the data committee, which will sample and inspect monthly at least 10% of the input data. We have also established a WeChat group (an instant messaging application) in each hospital to disseminate timely feedback on the inspection results for rectification.

Missing data or withdrawal from the trial
We will apply strict quality control procedures during the data collection and filing process to ensure that no data will be missing from the database.

If a subject's guardian requested to withdraw during or after the trial, we will fully respect this wish, withdraw the informed consent form, remove the information from the database and proceed to recruit new subjects.

Sample size estimation
The main statistical goal of this study is to establish reliable reference intervals. A large enough sample will be needed to generate precision estimates of extreme percentiles (such as the 2.5th percentile); however, there is no standard method for defining 'precision'.[20] Theoretically, the SpO_2 should show normal distribution when the sample size of such a cross-sectional study is large enough. We set

the precision of this study, that is, the allowable error D, to 0.1 SD, using two-sided tests with α at 0.05. The required sample at each altitude was estimated by PASS V.15 at 387 infants. Moreover, we increased the sample size by 30% to reduce sampling errors and account for possible subject withdrawals, resulting in a sample size of 503 infants at each altitude. There is no need to expand the sample size by measuring site subgroups because preductal and postductal measurements will be performed on the same neonate. Because of the different volumes of infants delivered at each of the participating hospitals in 2020, we anticipate that the end of study at each altitude will occur at different time points. We expect this project will be completed within a year.

Statistical analysis
First, a normality test will be performed on the SpO_2 data at each altitude. If the data show normal distribution, the mean±SD will be used to describe the distribution of SpO_2. Paired-samples t-test will test for differences between the preductal and postductal data. If the two are statistically similar, the preductal and postductal data for each subject will be averaged, and then the lower limit value for the reference interval of each altitude will be determined. If the two measurements differ statistically, the lower limit value of the reference interval will be determined separately for preductal and postductal at each altitude. If the data are not normally distributed, the median (IQR) will be used to describe SpO_2 distribution, and Wilcoxon signed-rank test will test for differences between the preductal and postductal measurements. The same principle will determine the lower limit value for the reference interval of each altitude.

After determining each lower limit value, we will visualise it using the altitude as the abscissa and SpO_2 as the ordinate to generate a curve fitting the data points. This will allow us to establish the function corresponding to a fitted curve that uses altitude as a covariate and the prediction equation for the reference interval lower limit value. The prediction equation will output the reference interval lower limit value by inputting the corresponding altitude. If the preductal and postductal will differ statistically, the prediction equation will be established separately for each.

Considering the Guoluo Tibetan Autonomous Prefecture People's Hospital is located at a significantly higher altitude (4200m) than other hospitals, we expect that the lower limit value of the reference interval at this location will be much lower, which may affect the fitting curve. Therefore, we will perform a subgroup analysis by excluding the data points obtained at this altitude. Finally, we will compare both analyses (ie, the one including and the one excluding this altitude) and select an appropriate curve to determine the optimal prediction equation.

All statistical tests will be two tailed, and p<0.05 will be considered significant. Statistical analysis will be performed using Stata V.16 and Python V.3.8.

DISCUSSION

SpO_2 is widely used in the field of neonatology. For example, many countries have included it in a routine screening programme for critical congenital heart disease.[21–23] However, a prerequirement for all these applications is to have a reliable reference interval. Rao et al[24] used the standard low altitude interval, that is, 95%, as the threshold, to screen for congenital heart disease in infants at an altitude of 1646 m and found that the false-positive rate was 1.5%, much higher than in the low altitude population. The standard of low altitude is still being used during clinical assessments at high altitudes in China, resulting in misdiagnosing many healthy neonates as having hypoxaemia and the consequent huge waste of medical resources. This is one of the reasons we designed this study. Furthermore, this is the first multicentre investigation of SpO_2 reference interval in healthy neonates 24 hours after birth at high altitudes. We will establish a prediction equation to address the inability to establish a uniform reference interval because of the curvilinear decrease in the lower limit value of the SpO_2 reference interval with the increase in altitude.[16]

This project is a study on the SpO_2 of healthy neonates 24 hours after birth. The SpO_2 level fluctuates and is unstable during the first 24 hours after birth because it is the transition stage from fetal to neonatal circulation.[25] Several studies on the use of SpO_2 to screen congenital heart disease found that the false positive rate of measuring within 24 hours of birth was significantly higher than that 24 hours after birth, confirming that the SpO_2 level within the 24 hours of birth was unstable.[26–28] Besides, we decided to not include multiple measurements after 24 hours of birth in our protocol. This is because: (1) at 24 hours after birth, the neonate has completed the transition from fetal circulation to neonatal circulation; therefore, at 24 hours after the birth of healthy neonates, the SpO_2 should be in a stable state; and (2) a large multicentre study of 41 097 measurements at altitudes ranging from 0 to 2500 m showed no differences in multiple SpO_2 measurements obtained from 24 hours after birth until discharge.[11] Therefore, our protocol focuses on personnel training and quality control to ensure that each SpO_2 measurement is accurate, rather than obtaining multiple measurements.

The measurements in this study will require the neonates to be awake and quiet. It will not consider measurements taken while the infants were asleep. This is because neonates are more prone to apnea or hypoventilation during sleep, resulting in transient periods of hypoxaemia, due to immature control of breathing, and higher compliance of the upper respiratory airway and chest resulting in lower respiratory reserve.[29] While these transient periods of neonatal hypoxaemia might be physiological phenomena, the value of SpO_2 measured in this case might be inaccurate, which is why our protocol excludes sleep periods.

This study hopes to determine the reference interval at high altitudes by formulating a predictive equation.

Theoretically, the precision of the curve fitting to the data points increases with the distribution of the points through various altitudes, resulting in a more accurate predictive equation. The limitation of this study is that thus far, we have recruited only six hospitals at four altitudes, possibly limiting the accuracy of the prediction equation to be generated. We continue to recruit hospitals at other altitudes to address this limitation.

In conclusion, the results of our study will help medical staff identify hypoxaemia in neonates at high altitudes with higher sensitivity, reducing the misdiagnosis rate and medical burden. It will also provide a theoretical basis for determining thresholds to be used when screening for ailments such as congenital heart disease.

ETHICS AND DISSEMINATION

Each participating hospital should be approved by the local Ethics Committee, and the proof of local approval must be sent to the coordinating centre before recruitment can begin at each hospital. Currently, our protocol has been approved by the Medical Ethics Committee of the six participating hospitals. The staff involved will give a detailed explanation to the guardians of all subjects to ensure they have a comprehensive understanding of the study. Written material will also be provided. If they agree to participate, the guardians will sign informed consent forms. Strict confidentiality will be applied to all data collected. The results of this study will be published in academic conferences and peer-reviewed public journals.

Author affiliations
[1]Department of Pediatrics, Suqian First People's Hospital, Suqian, Jiangsu, China
[2]Department of Neonatology, Qinghai Women and Children's Hospital, Xining, Qinghai, China
[3]Department of Neonatology, Qinghai Red Cross Hospital, Xining, Qinghai, China
[4]Department of Obstetrics and Gynecology, Qinghai University Affiliated Hospital, Xining, Qinghai, China
[5]Department of Neonatology, Geermu People's Hospital, Geermu, Qinghai, China
[6]Department of Neonatology, Yushu Prefecture People's Hospital, Yushu Tibetan Autonomous Prefecture, Qinghai, China
[7]Department of Neonatology, Guoluo Tibetan Autonomous Prefecture People's Hospital, Guoluo Tibetan Autonomous Prefecture, Qinghai, China
[8]Department of Neonatology, Qinghai University Affiliated Hospital, Xining, Qinghai, China
[9]Department of Neonatology, Shenzhen People's Hospital, Shenzhen, Guangdong, China

ORCID iD

Bo Wang http://orcid.org/0000-0001-8916-3049

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