ABSTRACT

Background: Many countries have adopted a mandatory routine pulse oximetry screening of newborn infants to identify babies with otherwise asymptomatic critical congenital heart disease (CCHD).

Objectives: To describe the current status of pulse oximetry CCHD screening in Israel, with a special emphasis on the experience of the Shaare Zedek Medical Center.

Methods: We review the difficulties of the Israeli Medical system with adopting the SaO2 screening, and the preliminary results of the screening at the Shaare Zedek Medical Center, both in terms of protocol compliance and CCHD detection.

Results: Large scale protocol cannot be implemented in one day, and regular quality assessment programs must take place in order to improve protocol compliance and identify the reasons for protocol failures.

Conclusions: Quality control reviews should be conducted soon after implementation of the screening to allow for prompt diagnosis and quick resolution.

KEY WORDS: congenital heart defect, critical congenital heart defect (CCHD), neonatal screening, newborn screening, pulse oximetry

The Saga of Pulse Oximetry Screening for Critical Congenital Heart Disease in Israel: A Historical Perspective

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Pulse oximetry, which has led to the definition of a new vital sign [1], has been used extensively over the past few decades in various clinical conditions such as emergencies [1,2] or monitoring [3]. In the early 2000s a few studies started reporting the efficacy of routine pulse oximetry screening of newborn infants. This practice allows physicians to identify those affected by a critical congenital heart disease (CCHD) who otherwise might not have been recognized during the early neonatal period, preventing potentially disastrous clinical consequences [4]. The definition of critical CCHD is not consistent in the literature. Many definitions include the need for surgery or catheter-based intervention during the first year of life or as leading to mortality to define CCHD [2]. Others use the first month of life [4]. In 2018, the Cochrane collaborative study published a systematic review, which identified 21 studies including a total of 457,202 participants [4]. The meta-analysis conducted on these studies revealed that of 10,000 apparently healthy late pre-term or full-term newborn infants, approximately six would have CCHD, five would be detected by the screening, and one case would be missed by the screening.

Screening by pulse oximetry appeared to falsely identify 14 infants of the 10,000 as having suspected CCHD that was disproved by echocardiography. The specificity of the screening is 99.9% with a sensitivity of 76.3%; in view of these numbers, the authors of the Cochrane review concluded that routine screening for CCHD in asymptomatic newborn infants should be implemented prior to discharge from the well-baby nursery. Consequently, screening has become mandatory in many developed countries, starting in the United States [5]. It is currently not mandatory in Israel, while only past April a recommendation for it was formally passed by the Israeli Neonatology Association.

PATIENTS AND METHODS

We described the current status of pulse oximetry CCHD screening in Israel, with a special emphasis on the experience of the Shaare Zedek Medical Center in this field, and in an attempt to identify and correct the main barriers to screening.

ESTABLISHING A CONSENSUS AND SEARCHING FOR FUNDING (2013-2020)

In 2013, the Israeli Neonatology and Pediatric Cardiology associations formed a special committee composed of two neonatologists and two pediatric cardiologists. The committee was instructed to analyze the literature available at that time and to develop recommendations and guidelines to be voted on by both associations and then implemented nationwide. The committee was sufficiently convinced by the available evidence and wrote a final report recommending routine, mandatory pulse oximetry screening in all apparently healthy newborn infants in Israel prior to their discharge from the hospital. The guidelines were
formally presented by the chairman of the Israeli Neonatology Association to the Israeli Pediatric Council, the entity constituting the official advisor to the Israeli health ministry in matters of pediatric health. The guidelines were accompanied by a formal request that the screening program be adequately funded by additional personnel dedicated to the performance of the screening. The health ministry was not convinced that this screening would be cost effective in view of the fact that in Israel there is wide coverage for malformations screening by ultrasonography during pregnancy. However, it was known that specific large groups in Israel (ultra-religious Jews and Muslims in particular) often refuse to undergo such screening as they are strictly opposed to aborting even severely malformed fetuses. The health ministry initiated a research project that aimed to identify the added value (if any) of routine, universal pulse oximetry screening in populations already performing routine fetal ultrasonographic screening for structural fetal anomalies.

At the time this article was written, we were not aware that this research project had been completed or even performed and obviously not published. A verbal communication obtained on 20 January 2020 from the former director of the maternal and infant department at the health ministry revealed that for many technical issues in recording malformations and in particular, cardiac malformations, it had not been possible to retrospectively answer the question, but it was likely that indeed very few additional infants with normal fetal screening would have been detected by pulse oximetry as having CCHD. Nevertheless, no funds were allocated by the health ministry to support the costs of pulse oximetry screening. Moreover, the guidelines written by the special committee were never voted on, never published, and do not appear in the official website of the Israeli Neonatology Association or that of the Pediatric Cardiology Association.

**INDIVIDUAL INITIATIVES (2013–2020)**

Starting in 2013, several departments of neonatology in Israel decided to independently implement routine pulse oximetry screening for all apparently well newborn infants prior to discharge. Since these initiatives were voluntary, not funded, and of local impact, they did not follow any standardized protocol (e.g., post-ductal versus pre- and post-ductal, age at screening). Nevertheless, an en-quiry polling the directors of the 25 major birthing sites in Israel conducted by one author (ABN) in December 2019 revealed that 11 centers had independently implemented routine screening, 3 were developing protocols and were about to implement them, and 11 had no immediate plans to implement universal screening. Mean reported age at screening was 42 hours. Of 14 centers performing or intending to perform screening 4 chose measuring post-ductal SaO, only and 10 chose pre- and post-ductal measurements. Of these 14 centers only 1 indicated that screen was performed at 24 hours or less, and the others on the second day of life.

**RESULTS**

**THE SHAARE ZEDEK EXPERIENCE**

**SCREENING GUIDELINES AND ALTITUDE DILEMMA**

The Shaare Zedek neonatologists have been particularly interested in the screening program because of a specific technical issue: altitude. In 2013, we published a study comparing SaO2 of 80 healthy term newborn infants born at the Tel Aviv Medical Center (approximately sea level) to that of 199 healthy, term newborn infants born at the Shaare Zedek Medical Center (Jerusalem, approximately 780 meters altitude) [3]. As hypothesized, both pre- and post-ductal mean SaO2 levels were lower by 0.4% on average in Jerusalem [6], which we attributed to the differences in altitude. Such a difference may appear to be minimal and clinically insignificant. The formal cut-off value of < 95% was chosen by the American Academy of Pediatrics (AAP) to fit the needs of infants born at or close to sea level [7,8]. However, it was calculated that using this cut off in Jerusalem would increase significantly the rate of false positive screens and multiply the number of echocardiograms by a factor of 3.5. Indeed, Gua et al. [9] showed the effect of even moderate altitude on the SaO2 distribution. Consequently, they revised their cut off to < 93% for mild altitudes (500–1500m).

**PROTOCOL IMPLEMENTATION**

During a pilot period of our pulse oximetry screening program, and in order to not saturate our Pediatric Cardiology Department with too many echocardiography requests because of false positive results, we decided to consider only SaO2 ≤ 94% as positive results, since pulse oximeters available on the market do not use decimals, and round the number to the closest value of 95% or 94%.

In June 2018 an internal policy was developed at Shaare Zedek to measure post-ductal SaO2 (right leg) in all newborn infants on day 2 of life. The policy was initially implemented in one of the four nurseries of Shaare Zedek (Bait VeGan campus) and then generalized to all four nurseries, in addition to the Bikur Holim campus, between August 2018 and September 2019. This program remains unfunded. Measurements were performed by a nurse on shift after appropriate training of all the nurses on staff. In January 2020 we conducted a quality control review of the year 2019 to determine the level of adherence to the policy and its results.

In the summer of 2019, we found that one infant born at Shaare Zedek and considered to have passed the screen with a SaO2 of 94% suffered a severe decapsulation 36 hours after discharge and was later diagnosed with severe coarctation of the aorta. This infant had no murmur at birth, and was reported to have normal femoral pulses prior to discharge. In view of this sole event, the protocol was modified in August 2019 to define, as suggested by AAP, the threshold for normal screen a post-ductal value of ≥ 95%, regardless of the altitude in Jerusalem.
Figure 1 shows the introduction of each nursery over time, with the percentage of infants who underwent screening. The figure shows that it took nearly 1.5 years for all nurseries to reach a screening rate close to 100%. However, in each individual nursery the figure shows that within 2 months the compliance rate approached 100%.

In 2019 we presented the data obtained only on well, term or near-term infants (born at > 36 weeks gestation) admitted to the well newborn nurseries and extracted from their electronic records (the screening SaO\textsuperscript{2} measurement and the age at which it is obtained are prospectively recorded). Of the 20,385 babies eligible, screening was performed on 19,763 (96.9%) and either forgotten or performed but not recorded in 622 (3.1%). An examination of the most recent data since the change in protocol (1 September–31 December 2019) showed that 71 infants (1%) missed the screen for the following reasons: 27 because of early discharge and belief by the nurses and physicians that early discharge prevents from performing the screen (similar to metabolic screen), 1 because of parental refusal, 11 because non-respect of the doctor's written order to perform the SaO\textsuperscript{2} screen, and 32 real misses that were not noticed by either a physician or nurse who discharged the infant (0.6%).

The results for the 19,763 who underwent screening in 2019 are as follows: 48 (24/10,000) infants were identified by the screening (a much higher number than the 14/10,000 predicted by the Cochrane meta-analysis). Of these, only one was confirmed to be true positive by echocardiography. This child had hypoplastic heart syndrome and was completely asymptomatic, had no murmur, had palpable femoral pulses, had no obvious clinical cyanosis, and had a screening SaO\textsuperscript{2} of 90%. Incidentally, another infant was also missed by the screen, and 3 days after discharge, was admitted to a different hospital and diagnosed with hypoplastic left heart syndrome. This child's screening SaO\textsuperscript{2} was 97% at 36 hours of life. We speculate that the higher number of infants who were noted by the screening in our institution may indeed have been due to the altitude differences in SaO\textsuperscript{2} between Jerusalem and coastal regions [6].

Israel has a very strong policy of routine prenatal ultrasonographic screening for congenital malformations. Nevertheless, as shown recently by Cloete et al. [10] even in countries with high antenatal detection rates, universal postnatal oximetry screening has the potential to improve early detection of CCHD.

DISCUSSION

Nearly 10 years have passed since physicians in the developed world concluded that cardiovascular catastrophes may be avoided in young neonates when CCHD is diagnosed at an early stage by a simple measurement of SaO\textsuperscript{2} by non-invasive pulse oximetry. While a large proportion of developed countries have adopted this screen as universal, less than half of Israeli birthing centers are performing it, and it is still not declared as mandatory by the health ministry. There is no specific funding allocated for the screening, which is performed on a voluntary basis by several, but not all birthing centers. We found that systematically implementing such a policy change does not occur in 1 day. It is possible, however, that much smaller birthing centers may be able to do so in a smoother fashion. In addition, similar quality assessment programs must be conducted.

Monthly audits should be performed. In fact, the 1% miss rate during the last 3 months of 2019 is a sharp improvement compared to the 3% miss rate of 2019 as a whole. By early 2020 there was full compliance in the screening performance in all the nurseries.

Educational interventions are also needed. They should consist of lectures to nurses, juniors, and senior physicians. A software adjustment is needed in the electronic medical record, which will give an automatic computerized alarm to the discharge nurse in case SaO\textsuperscript{2} has not been measured or has been measured but is abnormally low.

The Israeli Neonatology Association had revived the special committee that is in charge of updating it 2013 document to be submitted to the health ministry and a new protocol recommending universal screening had been written and accepted by vote. Funding issues have not been resolved, but we believe and are hopeful that the infants who can potentially be saved by universal SaO\textsuperscript{2} screening will tip the balance of risk-benefit considerations.
CONCLUSIONS

We recommend that quality control reviews be conducted soon after implementation of infant screening to promptly diagnose compliance failures and solve them rapidly.

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REFERENCES


Capsule

Multi-omics analyses reveal that HIV-1 alters CD4+ T cell immunometabolism to fuel virus replication

Individuals infected with human immunodeficiency virus type-1 (HIV-1) show metabolic alterations of CD4+ T cells through unclear mechanisms with undefined consequences. Gou et al. analyzed the transcriptome of CD4+ T cells from patients with HIV-1 and revealed that the elevated oxidative phosphorylation (OXPHOS) pathway is associated with poor outcomes. Inhibition of OXPHOS by the US Food and Drug Administration–approved drug metformin, which targets mitochondrial respiratory chain complex-I, suppresses HIV-1 replication in human CD4+ T cells and humanized mice. In patients, HIV-1 peak viremia positively correlates with the expression of NLRX1, a mitochondrial innate immune receptor. Quantitative proteomics and metabolic analyses reveal that NLRX1 enhances OXPHOS and glycolysis during HIV-1-infection of CD4+ T cells to promote viral replication. At the mechanistic level, HIV infection induces the association of NLRX1 with the mitochondrial protein FASTKD5 to promote expression of mitochondrial respiratory complex components. This study uncovers the OXPHOS pathway in CD4+ T cells as a target for HIV-1 therapy.

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Capsule

CAR-T cells collaborate to fight tumors

Chimeric antigen receptor (CAR)–T cells have achieved clinical success in treating B cell malignancies. Boulch and colleagues used intravital microscopy to visualize in situ interactions between tumors and anti-CD19 CD4+ or CD8+ CAR T cells and single-cell transcriptomics to examine subsequent changes to the tumor microenvironment in an immunocompetent mouse model of B cell lymphoma. Although CD4+ CAR-T cells were more effective at stimulating host immune responses-intrinsic interferon (IFN)-γ expression, host sensing of IFN-γ and interleukin-12 production were also required for CAR-T cell function, supporting the idea that crosstalk between CAR-T cells and the tumor microenvironment is necessary for optimal CAR-T cell efficacy against tumors.

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