Effectiveness of preoperative screening for sickle cell disease in a population with a newborn screening program: a cohort study

Efficacité du dépistage préopératoire de l'anémie falciforme dans une population à l'aide d'un programme de dépistage néonatal: une étude de cohorte

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Abstract

Purpose Published clinical practice guidelines recommend that all patients from ethnic groups with a high prevalence of sickle cell disease (SCD) undergo preoperative screening for this hemoglobinopathy. Newborn Screening Ontario initiated a universal sickle hemoglobinopathy screening program in 2006 as part of its regional newborn screening program. The primary objective of this study was to determine the effectiveness of selective preoperative screening for SCD based on at-risk

ethnicity in Ontario, a region that has a universal newborn sickle hemoglobinopathy screening program.

Methods The hematology laboratory database at our hospital was searched to identify all children who underwent preoperative sickle cell screening in the 42-month period starting in November 2006 (when the newborn sickle hemoglobinopathy screening program was introduced) and ending in April 2010. Medical records of all children testing positive on hemoglobin analysis were reviewed to determine perioperative outcomes.

Results Our search strategy identified 710 children who were born after the introduction of newborn screening and who underwent preoperative screening. Thirty-five of these children had abnormal sickle solubility tests – one (0.14%) was a new diagnosis (not identified by newborn screening), one had been diagnosed previously, and 33 (4.65%) were identified as having sickle cell trait. Sixty children had more than one preoperative screening test performed (range, 2–4). Six of the 35 children with abnormal sickle solubility results underwent repeated testing.

Conclusions Preoperative screening based on at-risk ethnicity alone is an ineffective method of identifying additional children with SCD in Ontario, a population with universal newborn sickle hemoglobinopathy screening. In an effort to avoid unnecessary repeat testing, we propose an algorithm to help physicians decide whether to initiate preoperative sickle cell screening for children.

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Résumé

Objectif Les directives de pratique clinique publiées recommandent que tous les patients provenant de groupes ethniques présentant une forte prévalence d'anémie falciforme subissent un dépistage préopératoire de cette

hémoglobinopathie. Le programme de Dépistage des nouveau-nés de l'Ontario a lancé un programme universel de dépistage de l'hémoglobinopathie falciforme en 2006 dans le cadre de son programme régional de dépistage néonatal. L'objectif primaire de cette étude était de déterminer l'efficacité du dépistage préopératoire sélectif de l'anémie falciforme fondé sur les groupes ethniques à risque en Ontario, une région qui dispose d'un programme universel de dépistage de l'hémoglobinopathie falciforme.

Méthode Nous avons procédé à une recherche dans la base de données du laboratoire d'hématologie de notre hôpital afin d'identifier tous les enfants ayant été soumis à un dépistage préopératoire de l'anémie falciforme au cours de la période de 42 mois allant de novembre 2006 (lorsque le programme de dépistage néonatal de l'hémoglobinopathie falciforme a été introduit) à avril 2010. Les dossiers médicaux de tous les enfants dont les tests étaient positifs lors de l'analyse de l'hémoglobine ont été passés en revue afin d'évaluer les devenir périopératoires.

Résultats Notre stratégie de recherche a permis d'identifier 710 enfants nés après l'introduction du dépistage néonatal et ayant été soumis au dépistage préopératoire. Les tests de solubilité falciforme de trente-cinq de ces enfants étaient anormaux – un cas (0,14 %) constituait un nouveau diagnostic (non identifié par le dépistage néonatal), un autre avait été diagnostiqué par le passé, et 33 (4,65 %) ont été identifiés comme possédant un trait falciforme. Soixante enfants ont subi plus d'un test de dépistage préopératoire (intervalle, 2-4). Six des 35 enfants présentant une solubilité falciforme anormale ont subi des tests à répétition.

Conclusion Le dépistage préopératoire fondé sur les groupes ethniques à risque seul est une méthode inefficace pour identifier les autres enfants atteints d'anémie falciforme en Ontario, une population qui bénéficie d'un dépistage néonatal universel de l'hémoglobinopathie falciforme. Dans le cadre d'efforts pour éviter les tests à répétition inutiles, nous proposons un algorithme afin d'aider les médecins à décider s'il faut initier un dépistage préopératoire de l'anémie falciforme chez les enfants.

Perioperative morbidity and mortality for children with sickle cell disease (SCD) is greater than that for non-SCD children.¹ Published clinical practice guidelines recommend that all patients from ethnic groups with a high prevalence of SCD undergo preoperative screening for this hemoglobinopathy.^{2,3} Nevertheless, selective preoperative screening of patients of at-risk ethnicities does not meet several criteria for an effective screening strategy,⁴ and selecting at-risk children is a subjective process that may miss positive cases.⁵ Additionally, with the introduction of universal (as opposed to selective) newborn sickle

hemoglobinopathy screening in some regions, children considered at risk for SCD may be screened preoperatively even though they have already undergone newborn screening. Duplicate screening is seldom cost-effective; it may not benefit the child, and unnecessary venepuncture is to be avoided in children.

The merits of newborn screening for SCD and other hemoglobinopathies are well established, and universal newborn sickle hemoglobinopathy screening has become an accepted standard of care in much of North America and Western Europe.^{6,7} The prevalence of SCD in non-urban areas of Canada is low, but increases in immigration and population migration have led to changes in population ethnicity and an increase in the incidence of affected newborns. In the province of Ontario, Newborn Screening Ontario (Dépistage des Nouveau-nés de l'Ontario) (NSO) (www.newbornscreening.on.ca) initiated a sickle hemoglobinopathy screening program in November 2006 as part of its provincial newborn screening program for the province of Ontario. The NSO laboratory at the Children's Hospital of Eastern Ontario, Ottawa, screens more than 140,000 children annually for congenital diseases, and sickle hemoglobinopathies account for approximately 10% of positive screens. Prior to the widespread introduction of newborn sickle hemoglobinopathy screening, children with SCD were typically identified by clinical diagnosis no later than three years of age, and the majority of children (up to 96%) were identified by the age of ten.⁸ However, in childhood, the highest mortality from SCD occurs in the first five years of life, and the greatest period of risk is in the second six months of life.⁹ The aim of newborn screening for SCD is to identify affected children early in order to implement medical care, including education and counselling, penicillin prophylaxis, and prompt treatment of febrile episodes to decrease sickle-related morbidity and mortality.

Although the sickle screening program at NSO started six years ago, few anesthesiologists and perioperative care providers in Ontario are aware of its existence, and it remains largely unrecognized and unused by anesthesiologists in Ontario. The primary objective of the present study was to determine the effectiveness of selective preoperative screening for SCD based on at-risk ethnicity in Ontario, a region that has a universal newborn sickle hemoglobinopathy screening program. A secondary objective of this report is to increase awareness among perioperative care providers that NSO screens newborns for sickle hemoglobinopathies and these results are available to care providers in Ontario.

Methods

With approval from the Research Ethics Board of The Hospital for Sick Children, Toronto, the hematology

Table Selected perioperative data for children identified with SCD by selective preoperative screening

Family history	Newborn screening	Sickle genotype	Type of surgery	Preoperative Hb conc. (g·dL ⁻¹)	Pre-op / Intra-op RCC transfusion	Hb (%)	Adverse outcomes
1 Sick cell trait	No	SS	Ventricular septal defect	11.0	No/Yes	HbS = 52 HbA2 = 3 HbF = 45	None
2 None	Yes	SS	Laparoscopic splenectomy	9.3	Yes/No	HbS = 24 HbA = 69 HbA2 = 3 HbF = 4	None

SCD = sickle cell disease; SS = homozygous hemoglobin S; RCC = red cell concentrate; Hb = hemoglobin; HbS = sickle hemoglobin; HbA = hemoglobin A; HbA2 = hemoglobin A2; HbF = fetal hemoglobin

laboratory database at our hospital was searched to identify children who underwent preoperative screening for SCD in the 42-month period starting in November 2006 (when the newborn sickle hemoglobinopathy screening program was introduced in Ontario) and ending in April 2010. A convenience sample of all children who received a preoperative screen for SCD in the 42-month period was studied.

At our hospital, children older than six months are screened initially using a sickle solubility test. Abnormal samples undergo high performance liquid chromatography (HPLC) for confirmatory testing. Infants younger than six months are screened using HPLC only because fetal hemoglobin interferes with solubility testing. During the study period, clinical practice guidelines at our hospital recommended preoperative screening for all at-risk children; however, the decision to perform SCD screening was at the discretion of the anesthesiologist or referring physician, except for those children undergoing cardiopulmonary bypass who all underwent preoperative screening for SCD. Prior to this study, the healthcare team at our hospital did not routinely contact NSO to determine the sickle status of the child before surgery. Accordingly, the sickle status of the child would not have been known before surgery on the basis of the newborn screen.

The medical records of all children who tested positive for SCD on preoperative screening were reviewed. Data collection was performed in June 2010, and the data collected for each patient included demographics, documented family history, sickle genotype, preoperative hemoglobin concentration, surgical procedure, and perioperative outcomes. Data were recorded in Microsoft Office Excel 2010. Descriptive statistics were determined as appropriate.

Results

Our search strategy identified 710 children who were born after the introduction of newborn sickle hemoglobinopathy screening in Ontario and who underwent preoperative screening for SCD. Thirty-five (4.93%) of these children had a positive sickle solubility test and underwent HPLC

for confirmatory testing. Thirty-three of the 35 children (4.65% of the total number) were identified as having sickle cell trait, and two (0.28%) were identified as having SCD (SS disease).

One (0.14%) of the two children diagnosed with SCD by preoperative screening was a new diagnosis previously not identified by newborn screening. This child had been transferred to our hospital on day one of life for emergency management of complex congenital heart disease (double outlet right ventricle, atrial septal defect, and ventricular septal defect) before newborn screening could be done at the referring centre. Preoperative screening for SCD was performed prior to repair of the cardiac anomaly. Subsequently, this case prompted the introduction of a policy mandating that all newborns transferred to our hospital at birth must undergo the newborn screen upon admission to hospital. Of note, there was a significant family history of sickle cell trait.

The second child had a documented history of severe SS disease (splenic sequestration, vaso-occlusive crises, and cerebral infarcts) diagnosed after a positive newborn screen and presented for laparoscopic splenectomy. The reason for the repeat screen is unclear. Relevant medical histories and selected clinical data from the perioperative period for both children with SCD are summarized in the [Table](#). The intraoperative course was uneventful for both children and neither developed sickle-related complications.

Sixty children had more than one preoperative screening test performed (range 2–4). Six of the thirty-five children with abnormal screening results underwent repeated preoperative sickle solubility testing.

Discussion

Preoperative screening of 710 children born after the introduction of universal newborn screening for SCD in Ontario identified one child (0.14%) with previously undiagnosed SS disease and 33 children (4.65%) with sickle cell trait. These findings suggest that selective preoperative screening of children based on at-risk ethnicity is

an ineffective method of identifying children with SCD in a population that has a newborn sickle hemoglobinopathy screening program.¹⁰ The previously undiagnosed case of SCD in this cohort prompted the introduction of a policy mandating that all newborns transferred to our hospital at birth must undergo the newborn screen upon admission to hospital, regardless of any history of newborn screening at the transferring hospital. The aim of this policy is to ensure that all newborns transferred to our hospital for emergency care undergo the newborn screen. In the case of Ontario, NSO has also initiated a surveillance system for children who have not received the newborn screen using the BORN (Better Outcomes Registry and Network) Ontario registry (www.bornontario.ca). Children who have a birth recorded in Ontario but who have not received a newborn screen are identified, and the birthing hospital is contacted by NSO to ensure that a screen is offered to the child's parents.

Current clinical practice guidelines recommend preoperative screening as a method to decrease perioperative morbidity and mortality in at-risk ethnicities.² Ethnicities deemed to be at risk include African, Greek, Southern Italian (including Sicilian), Turk, Arab, and Indian.² Prior to the introduction of newborn screening in Ontario, selective preoperative screening identified fewer than two new cases of SCD per 1,000 at-risk children (0.16%) at our institution, and screening did not alter the perioperative course of any child not previously diagnosed with SCD.¹⁰ Following the introduction of newborn screening, the benefit of a continued policy of selective preoperative screening of all children of at-risk ethnicities has diminished.

Selective preoperative laboratory screening in this cohort also identified 33 children with the sickle cell trait. The clinical significance of this is questionable given that sickle cell trait has no effect on perioperative outcomes in most clinical settings,^{11,12} perhaps with the exclusion of surgical techniques, such as deliberate hypothermia, cardiopulmonary bypass, and cell salvage. In Ontario, NSO reports the carrier state only if the child's parent, guardian, or healthcare provider requests the result of the newborn screen.

Although the cost of a universal newborn screening program is significant, the cost of newborn sickle cell screening occurs in the context of a preexisting system for collection and transportation of samples from birthing centres to the provincial screening laboratory. The individual cost of performing each preoperative screening test – including equipment, consumables, and time – is considerably greater when the screen is done in a hospital laboratory compared with a regional screening laboratory. The estimated cost to our hospital (for laboratory equipment, personnel, and consumables) to identify the single

new case of SCD in this cohort was approximately \$47,000. Using similar variables, the estimated cost per case of SCD identified by NSO is approximately \$8,000 based on a time and motion study completed in 2007 (unpublished data); however, these data may not be directly comparable without knowledge and consideration of other economic data, including financial and non-financial costs and benefits to the patient, the family, and the hospital.¹³ A detailed comparative economic analysis of preoperative vs newborn screening is a focus of a current investigation by our group.

In this cohort, 60 children underwent preoperative screening on more than one occasion (range, 2–4). It is important to record information in a manner that ensures avoidance of unnecessary repeat testing. Innovation in information technology and improved infrastructure of e-health systems may improve delivery and monitoring of screening results. E-health systems provide the opportunity to facilitate communication between healthcare providers and, consequently, to improve effectiveness, efficiency, and cost-effectiveness of patient care.

The [Figure](#) outlines a suggested algorithm for SCD screening prior to elective surgery in Ontario, a region with a universal newborn sickle hemoglobinopathy screening program. For children born after the introduction of the newborn sickle screening program, the sickle status of the child can be determined from the family, relevant screening authority, primary care physician, or medical notes. The absence of a screening result does not necessarily indicate that newborn screening was not performed, and each hospital should be familiar with the practices of the regional authority responsible for screening. Currently, NSO reports only a positive newborn screen for SCD (not sickle cell trait or a negative screen) to parents and healthcare providers. In the context of universal newborn screening, it can be assumed that the child does not have SCD if the family was never contacted by the screening authority or healthcare provider. Where confirmation is required before surgery, NSO will release screening results to healthcare providers following a formal request containing at least three patient identifiers (e.g., patient name, date of birth, healthcare number, birth hospital, or mother's name). To facilitate clinical care, NSO provides a same-day response (during weekdays) to enquiries received by fax from healthcare providers. Nevertheless, we emphasize that such requests need to be provided in a timely manner to avoid unnecessary delay on the day of surgery.

Where indicated by family history and/or clinical findings, children who were born before the introduction of universal newborn screening for SCD may benefit from preoperative screening ([Figure](#)). At the time of writing, SCD children born in Ontario before the introduction of newborn screening are aged six years or older; thus,

Figure Suggested screening algorithm for sickle cell disease prior to elective surgery in children born in a region with a universal newborn sickle hemoglobinopathy screening program

approximately 70% have been identified on the basis of clinical presentation.¹⁴ Four years hence, when these children are aged ten years or older, over 90% will have been diagnosed.^{8,14} Accordingly, the prevalence of undiagnosed SCD in this population and thus the number of children needing preoperative screening is expected to decrease over time. Regardless of a child's ethnicity, we recommend that all children undergoing cardiopulmonary bypass and born before the introduction of newborn screening be tested for SCD, given the pathophysiological insult to red blood cells exposed to the bypass circuit. In addition, the algorithm is not intended for children undergoing urgent or emergency surgery where screening may unnecessarily delay surgery.

In populations with a newborn screening program, selective preoperative screening may still be indicated for at-risk children in certain scenarios, including parental refusal of the newborn screen or confirmatory testing after two months of age, extreme prematurity at the time of screening, or a negative result following a blood transfusion at birth.¹⁵ Many screening programs, including that in Ontario, include mechanisms to request repeat screens in premature babies and those who have previously received transfusions.

Although HPLC confirmation may not be available prior to scheduled surgery, a peripheral blood smear can be examined for the presence of sickle cells. At our institution,

sickle solubility testing is performed daily and peripheral blood smears can be performed on abnormal samples and reviewed by a hematologist prior to surgery. Definitive laboratory confirmation by HPLC is required for all abnormal solubility tests.

This study has several limitations. It is susceptible to ascertainment and clinical bias because of the retrospective nonrandomized design. Despite a lack of randomized controlled trials of newborn screening for SCD,¹⁶ there is clear benefit to newborn screening in certain populations.¹⁷⁻²⁰ Similarly, the feasibility of an adequately powered randomized trial for the purpose of evaluating preoperative screening is unlikely, and we may have to rely on large epidemiological studies. The external validity of our results may be limited, as the prevalence of SCD may vary amongst different populations, as may screening techniques, social attitudes towards screening, available resources, and surgical caseloads.

In summary, selective preoperative screening based on at-risk ethnicity alone is an ineffective method of identifying additional children with SCD in Ontario, a region with universal newborn sickle hemoglobinopathy screening. For children born in Ontario, information obtained from the parents, primary care physician, or newborn screening authority will obviate the need for additional screening in the preoperative period. It is hoped that these findings will increase awareness of NSO among

anesthesiologists and educate this population that sickle screening is a part of the newborn screen in Ontario and the results of this screen are accessible to healthcare workers upon request.

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Conflicts of interest None declared.

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