Blood sample volumes in child health research: review of safe limits

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Objective To determine paediatric blood sample volume limits that are consistent with physiological "minimal risk."
Methods A literature review was performed to search for evidence concerning the adverse effects of blood sampling in children and for guidelines on sampling volume in paediatric research. The search included Medline, EMBASE, other web-based and non-web-based sources and the bibliographies of the sources identified. Experts were also consulted.
Findings Five studies and nine guidelines were identified. Existing guidelines specify paediatric blood sample volume limits ranging from 1% to 5% of total blood volume (TBV) over 24 hours and up to 10% of TBV over 8 weeks. The evidence available is limited and includes findings from non-randomized studies showing a minimal risk with one-off sampling of up to 5% of TBV.
Conclusion The evidence available is consistent with the conclusion that all identified guidelines are within the limits of "minimal risk." However, more and better evidence is required to draw firmer conclusions. Researchers and institutional review boards need to take into account the total sampling volume needed for both clinical care and research rather than for each alone. The child's general state of health should be considered and extra caution should be observed particularly with children whose illness can deplete blood volume or haemoglobin or hinder their replenishment. Local policies must also address the appropriateness and local acceptability of collection procedures and of the blood volumes drawn.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Safeguarding the interests of research participants is an ethical imperative that is conveyed in all accepted research guidelines and standards, and most prominently in the Declaration of Helsinki.[1] Because children are vulnerable, we have a special obligation to ensure their safety when they become research subjects. Blood sampling in children who participate in medical research is an issue of concern to parents, researchers and research ethics committees alike.

The Gambia Government–Medical Research Council Joint Ethics Committee, a long-established entity[2] of which the author is a member, frequently discusses blood sample volumes when considering research projects for approval. The committee decided to reassess its policy on safe limits for paediatric blood samples and asked the author to review the subject to assist its deliberations.

The concept of "minimal risk" is useful for the protection of children who take part in clinical research and was the guiding principle for the review. A full discussion of minimal risk, which figures prominently in research regulation in the United States of America,[3] is beyond the scope of this paper, but it is defined, in essence, as a low risk outweighed or balanced by potential benefits to the individual, society or both. Regulation in the United States, as elsewhere, recognizes that in certain situations consideration should be given to research that carries a greater than minimal risk to the participant, but stronger justification would be required in terms of the resulting benefit and far more stringent case-by-case assessment by the responsible ethics committee or institutional review board.

The objective of this review is to determine paediatric blood sample volume limits that are consistent with physiological "minimal risk." The review does not address other considerations that might influence local policy in this area, such as volume acceptability (to parents and society, for instance) or the most appropriate means of collecting blood samples.

Methods

Data for this review were identified by searching Medline, EMBASE, the Cochrane Library,[4] Clinical Evidence,[5] BloodMed,[6] the web sites of the American Academy of Paediatrics[7] and the Royal College of Paediatrics and Child Health,[8] Google,[9] paediatric texts (Nelson,[10] Rudolph[11]) and the reference lists of relevant articles for all the literature published up to September 2009 on safe blood draw volume limits in persons less than 18 years of age (the United Nations definition of a child). The Medline search was undertaken in two parts: (i) To identify the literature on the adverse effects of blood sampling, the following search strategy and terms were used: (blood specimen collection) AND (infant OR child, preschool OR child OR adolescent OR paediatrics) AND (anaemia OR adverse effect); (ii) to identify the literature on recommendations for blood sampling in clinical research, the following search strategy and terms were used: (blood specimen collection) AND (infant OR child, preschool OR child OR adolescent OR paediatrics) AND (guidelines OR practice guidelines). A similar strategy was followed for the EMBASE search using equivalent EMTREE terms. No language restrictions were placed on the Medline and EMBASE searches. The titles and abstracts of the references returned by these searches were screened and the full manuscripts of all references relevant to the review question were obtained.

The review was originally undertaken in October 2006 and updated in August and September 2009. In addition, on 17 October 2006 a draft of the review report was sent to 32 health professionals with relevant expertise, both within and

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Table 1. **References identified in literature review of blood volume sample safety limits in paediatric clinical research**

Source	Total	Relevant references	
		No.	Citation
Medline search[a]	179	3	Madsen et al. 2000[12] Testa et al. 2006[13] Broder-Fingert et al. 2009[14]
Medline search[b]	58	2	Cole et al. 2006[15] Broder-Fingert et al. 2009[14]
EMBASE search[a]	325	1	Hack et al. 2008[16]
EMBASE search[b]	62	0	–
Other[c]	NA	13	US Department of Health and Human Services[17] Pearson et al. 2003[18] Gibson et al. 2004[19] Cable et al. 2002[20] Schwartz et al. 2000[21] USC-LA Children's Hospital[22] Wayne State University[23] Partners Human Research Committee[24] University of California Davis[25] Duke University[26] KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya[d] Gambia Government–MRC Joint Ethics Committee[27] Kauffman 2000[28]

MRC, Medical Research Council; NA, not available.

[a] For adverse effects of blood sampling in children.

[b] For guidelines and policies for blood sampling in paediatric research.

[c] Cochrane Library; Clinical Evidence; American Academy of Paediatrics; Royal College of Paediatrics and Child Health; Google; BloodMed; paediatrics textbooks (Nelson, Rudolph); review of bibliographies; expert consultation.

[d] Provided by the KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, October 2006 with an updated version provided to the author in August 2009.

outside the Medical Research Council's Gambian unit. Feedback was received from 14 of them and the report was revised accordingly.

Ethics approval: approval to undertake and publish this review was granted by the Gambia Government–Medical Research Council Joint Ethics Committee (L2009.E10).

Results

The references identified through the literature search are shown in Table 1. No review of the evidence surrounding the question of safe blood sampling volume limits was identified in Medline, the Cochrane Library or any other source. Several relevant sources addressing the underlying physiology and pathology of the effects of blood sampling were identified, together with several guidelines that are summarized in Table 2. The data collected are presented in sections on basic physiology and pathology, the empirical evidence available and existing guidelines. Key recommendations are provided in Box 1.

Basic physiology and pathology

Total blood volume

A person's total blood volume (TBV) is related to body weight. The TBV of a child is around 75–80 ml/kg and is higher in the neonatal period (from 85 ml/kg it rises to a peak of 105 ml/kg by the end of the first month and then drops progressively over ensuing months).[18] Thus, the TBV of a 3.5-kg 2-week-old will be about 350 ml while that of a 10-kg 15-month-old will be about 800 ml.

Impact of blood sampling on the circulation

A large acute loss of blood volume may compromise the circulation, though the blood volumes required for this to occur are generally much higher than those taken in child health research. According to the British Committee for Standards in Haematology Transfusion Task Force Guidelines for Transfusion,[19] in children having blood collected for possible future autologous transfusion it is safe to draw up to 12% of TBV (around 10 ml/kg) at each donation, provided the child is in a stable condition and has a normal blood haemoglobin (Hb) level.

Replenishing lost red cells and Hb

Red cells are usually replenished fairly rapidly, since the marrow can acutely double or triple its usual red cell replacement rate of 1% per day if necessary.[30,31] In patients with iron deficiency anaemia, blood Hb rises by up to 0.2–0.3 g/dl per day in adults on iron supplements[31,32] and possibly higher in children who have received iron supplements for a few days.[21] In a study of girls with central precocious puberty, Hb levels had recovered after 3 months of iron supplementation following a maximum draw of 12% of TBV, though how quickly recovery was achieved within those 3 months is not known.[14] Slower red cell replenishment is seen in patients with aplastic anaemia, renal failure and a variety of chronic conditions in which erythropoiesis is inhibited.[33]

Empirical evidence

Impact of blood sampling on Hb in children

Two studies that attempted to measure the impact of blood sampling for research in children were identified. The first was a retrospective review of 11 children (aged 1–19 years) undergoing chemotherapy.[15] In a single chemotherapy cycle (out of a total of six cycles given to each patient), between 1% and 15% of TBV was drawn for research purposes over a 3-day period, in addition to the blood samples needed for clinical care. The differences between pre-treatment Hb level and the lowest Hb level after treatment during "research" and "non-research" cycles were compared. The data were inconclusive. Overall Hb levels dropped by an additional 1.5 g/dl on average when research samples were taken, but unexpectedly no relationship was found between the change in Hb in an individual patient and the volume of blood drawn (as a percentage of TBV). The data showed that among children who lost around 5% or less of TBV over 3 days no meaningful change in Hb occurred (an average 0.1 g/dl increase, $n = 9$ children), while among those who lost well over 5% of TBV there was an appreciable drop in Hb (a drop of 2.75 g/dl on average, $n = 2$ children). These data need

Table 2. **Policies and recommendations on safe blood sample volume limits for paediatric clinical research as identified through a review of the literature**

Institution/Body	Maximum volume allowed for a single draw		Maximum cumulative draw volume allowed
	% of TBV	ml/kg	
Toronto Hospital for Sick Children Research Ethics Board[29]	5	*3.75–4.0*[a]	5% of TBV within 3 months
USC/LA Children's Hospital[22]	*2.5–2.7 (within 24 hour)*[a]	2	4 ml/kg within 30 days
Wayne State University[23]	1	0.8	10% of TBV or 8 ml/kg within 8 weeks
Partners Human Research Committee[24]	*3.6–3.9*[a]	< 3	< 3 ml/kg within 8 weeks
University of California Davis[25]	*2.5* *Note: Minimum blood Hb required at time of blood draw, 7 g/dl (9–10 g/dl if cardiorespiratory compromise present)*	*2*[a]	5% of TBV within 30 days
Duke University[26]	For expedited IRB approval		3 ml/kg or 50 ml total (whichever is less) over 8 weeks
	2.5[a] (for review by convened IRB; *note: special precautions and justification required for more than this limit*)	2, up to 200 ml total	7 ml/kg over 8 weeks (up to 5 draws of 7 ml/kg per year)
KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya[b]	*1.9–2.3*[a] (2005 guideline for *total* volume drawn)	1.7–2.4	Not stated
	1.3[a] (2008 guideline for volume drawn for *research* purposes in addition to volume needed for routine care)	1	5 ml/kg within 8 weeks
US Dept of Health and Human Services, Office for Human Research Protections[17]	*3.8*[a]	3, up to 50 ml total	3 ml/kg, up to 50 ml total within 8 weeks
Kauffman 2000[28]	3.0	*2.4*[a]	Not stated
Gambia Government–MRC Joint Ethics Committee[27]	*Range: 2.4 (e.g.1-kg infant) to 0.3 (e.g. 20-kg 4-year-old or 30-kg 9-year-old)*[a]	2, up to max 5 ml (age 0–4 yr); 10 ml (age 5–9 yr); 15 ml (age 10–14 yr); 30 ml (age ≥ 15 yr)	Within 3 months same as for one draw, "usually"

Hb, haemoglobin; IRB, institutional review board; ml/kg, millilitres per kilogram of body weight; MRC, Medical Research Council; TBV, total blood volume.

[a] Calculated on the basis of a TBV of 75–80 ml/kg (in neonates, 100 ml/kg). Non-italicised content is quoted directly from the sources.

[b] Provided by the KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, in October 2006 with an updated version provided to the author in August 2009. These are local practice guidelines reflecting the latest recommendations of this institution.

to be interpreted cautiously as the numbers were small and the study was open to confounders, such as differences in blood transfusion practice among physicians.

The second study prospectively followed 34 girls aged 1.6 to 9.2 years who underwent repeated blood sampling as part of an intervention study for central precocious puberty in the United States.[14] Participants had 6–10 ml/kg of blood (7.5–12.5% of TBV) drawn over a 24-hour period every 3 to 6 months for up to 3 years. After each blood draw patients were given an equivalent volume of normal saline intravenously plus 1–6 mg/kg daily of elemental iron for 6 weeks. At first sampling, the average acute drop in blood Hb was 1.2 g/dl, and the maximum drop was 2.3 g/dl. Subsequent pre-sampling Hb levels, measured every 3 months, averaged 12.5 g/dl and did not differ significantly from baseline levels. In the author's view, the need for volume replacement and iron therapy along with the appreciable drop in Hb the participants experienced, albeit temporarily, places this volume of sampling in a category of greater than minimal risk. Nevertheless, the study provides direct evidence that supports the British Committee for Standards in Haematology Transfusion Task Force Guidelines for Transfusion policy in terms of the amount of blood that can be safely collected for autologous blood transfusion (10 ml/kg, or around 12.5% of TBV) and that is useful for ethics committees or institutional review boards attempting to quantify the risks and benefits associated with sampling in the "greater than minimal risk" category.

Neonates are one group in which the impact of blood sampling on Hb levels is particularly concerning. Three studies in neonates that were indirectly relevant to the question posed in the review were identified. The first was a study from a developed country in which 99 very premature neonates (gestational age 24–32 weeks) had an average of 13.6 ml/kg of blood (equivalent to around 13% of TBV) drawn for testing during the first month after birth, and 19% of the 99 neonates received at least one blood transfusion.[12] This study did not quantify the impact of blood sampling on Hb levels and did not attempt to separate the impact of blood loss through sampling from the effect of neonatal illness, but the findings do suggest that this level of sampling was often associated with the need for transfusion, which takes it out of the minimal risk category. This conclusion is consistent with the findings of a similar

study of 253 premature infants (gestational age 25–32 weeks) that showed a strong correlation between blood sample volume and the need for transfusion.[16] A median of 18 ml/kg (18% of TBV) of blood was taken and 53% of the infants required transfusion during their neonatal intensive care admission (median admission duration: 12 days; range: 0–135 days). A third study followed 50 very-low-birth-weight infants whose Hb was measured on admission and on day 8, along with the volume of blood taken for sampling.[13] The average blood volume collected was 4.5% of TBV and the average drop in Hb was 3.4 g/dl (from a mean of 19.8 g/dl to 16.4 g/dl). A proportion of this drop would be expected to result from the physiological fall in Hb that is expected in the neonatal period, but the contribution of this was not assessed. However, multiple regression analysis (which included severity of illness and blood volume in the regression model, but not birth weight or gestational age) indicated that illness severity had a greater impact on the drop in Hb than blood sampling losses. The fact that blood sampling can exacerbate the effect of illness on Hb levels should be taken into account when determining appropriate blood sample volumes in sick children.

Existing guidelines

Indirect guidance from transfusion guidelines

The British Committee for Standards in Haematology endorses the following formula for calculating the volume of packed red cells that should be given to a patient for a top-up transfusion:[19]

Volume to transfuse = (desired Hb – actual Hb) × weight × 3

where Hb is measured in g/dl and weight in kg. So for example, to raise the Hb from 6.5 g/dl to 7.5 g/dl in an anaemic 10-kg 18-month-old one would need to give 30 ml (3 ml/kg, or 4% of TBV) of packed red cells. Packed red cells have a Hb level around twice as high as a normal child's blood (haematocrit 50–80% versus around 33–40%)[20] so, conversely, the taking of 30 ml as a sample from a normal child would be presumed to drop the Hb by half as much as the giving of 30 ml of packed red cells would raise it (and the drop may be less than half as much if the child were anaemic given that the absolute loss of Hb would be less). Therefore a sample of 3 ml/kg (4% of TBV) taken on one occasion in the same 10-kg 18-month-old with a Hb of 7.5 g/dl would be expected to reduce the Hb to no less than 7.0 g/dl. This loss would normally be replenished within days.

Box 1. **Key recommendations regarding blood sampling in children involved in clinical research**

- Existing guidelines for blood sample volume limits (ranging from 1–5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks) are consistent with the limited evidence available on "minimal risk" to children.
- Lower limits for sick children are advisable, and a maximum of 3 ml/kg post-neonatally within 24 hours (3.8% of total blood volume), in line with United States policy, seems to be a reasonable guideline, although each study must be judged on its own merits and greater caution may be needed in children with illnesses that impair the replenishment of blood volume or haemoglobin.
- The blood volumes needed for clinical care and research should be carefully assessed and a clear justification should be provided to institutional review boards and ethics committees, which they can then assess and monitor.
- Effective coordination of clinical and research activities is needed to minimize the burden to the child.
- Collection procedures should minimize discomfort for the child as much as practically possible.
- Blood collection volumes and procedures should be acceptable to the community in which the research is conducted.
- More research on the impact of blood sampling is needed to better assess appropriate blood volume limits in particular patient groups.

Existing policies on blood draw volumes in paediatric research

Nine policies or guidelines directly relevant to this report were identified and their contents are summarized in Table 2, along with the Gambian Government–Medical Research Council Joint Ethics Committee policy.[17,22–29] Overall the policies and guidelines identified specify blood volume limits between 1% and 5% of TBV on a single draw (or over 24 hours) and of up to 10% of TBV over 8 weeks.

Discussion

This review has shown that while several guidelines are available for reference, there is a limited amount of direct evidence on which to base them. It is apparent that safety guidelines should be based on the size of the child instead of on his or her age. Beyond this, the evidence concerning the impact of blood sampling on a child's Hb or general well-being comes from specific contexts from which general guidelines should be cautiously drawn. Nevertheless, on the whole the available data are consistent with the conclusion that all guidelines for blood draw volumes identified in this review are within the limits of "minimal risk" to study participants. Notably, no reports of adverse events associated with the use of any of these guidelines were identified in the course of this review, although no data are available to indicate how well such guidelines are being followed. In any case, better evidence, based on larger numbers of study subjects, a wider range of study contexts and more robust study designs (randomized trials ideally), is clearly needed before firmer conclusions can be reached. Good studies conducted in important participant groups from which no data are currently available, such as children in resource-poor countries, would be particularly useful.

While the literature search for this review was comprehensive, some relevant data may not have been identified, particularly in the grey literature. Such a limitation is potentially more important in an area such as this, which has a very small body of evidence.

Ethics committees and institutional review boards should consider several factors when deciding how to apply general volume guidelines for blood sampling. A lower blood volume limit for sick children, i.e. children with either acute or chronic disease, is advisable, and a maximum of 3 ml/kg within 24 hours (3.8% of TBV) post-neonatally is in line with United States policy applying to instances where expedited institutional review board chair's approval for a research project could be given.[17] However, a more cautious approach will be needed in the presence of particular illnesses, such as those associated with a low blood Hb level or blood volume depletion. Renal failure, bone marrow dysfunction, a variety of chronic illnesses and certain treatments

can inhibit erythropoiesis and shorten red cell survival, thereby reducing the body's ability to replenish the blood taken through sampling. Chemotherapy is an example of such a treatment, which makes the data supplied by Cole and colleagues particularly relevant.[15] Illnesses associated with depletion of blood volume and Hb, especially when this is rapid (such as severe malaria or disseminated intravascular coagulation from severe sepsis), also call for greater caution. Baseline anaemia itself requires caution, particularly if the Hb is very low or is associated with haemodynamic compromise. In settings where environmental factors such as endemic malaria or widespread iron deficiency tend to lower average Hb levels and may slow the recovery of Hb levels after sampling, these factors should also be taken into account.

The limits discussed here are total blood sample volumes that include what is required for both clinical care and for research purposes exclusively. It is very important that an ethics committee or institutional review board have a full picture of the sampling demands that will be placed on a child in a particular study, including those for routine clinical care, to best determine what limits should be placed on volumes.

To put these limits in perspective, most paediatric research that calls for blood sampling would not require blood volumes anywhere near the higher limits seen in the guidelines reviewed. Nonetheless, it is important to decide where to set the limits for minimal risk. Ethics committees and institutional review boards may consider approving studies involving larger volumes of blood than those associated with minimal risk, but only after fully weighing the risks and benefits and the well-being of the child participant. Pharmacokinetic research is an area with comparatively large sampling requirements and a dearth of paediatric data, partly because of the large sampling requirements. As the regulatory environment pushes sampling requirements further, sound paediatric data may become even scarcer, placing an onus on institutional review boards and regulators to walk a fine line between over-caution and under-caution.[34,35]

One issue not addressed in this review but that should be addressed in local policies is the means by which blood is obtained, for instance, the acceptable number of needle pricks. Policy applied in this area may, in many studies, have a greater impact on a child's overall well-being than the question of blood volume, to the point of restricting the blood volume obtainable to far less than is allowed by physically safe limits. Blood drawing by experienced phlebotomy staff and the use of local anaesthetic creams can make the experience less traumatic for the child. It is very important that the blood required for clinical care and for research be collected at the same time whenever possible to minimize discomfort for the child, and this requires effective coordination. In some settings communication between health-care and research staff may not be good and research samples may be taken without regard for the sample volumes already obtained for clinical care. It is up to researchers to show ethics committees and institutional review boards that systems are in place to ensure that the procedures followed and the combined blood volumes obtained are within the limits established by agreed guidelines. Having been satisfied on this point at the approval stage, ethics committees and institutional review boards can assess compliance by requiring that blood sampling be included in monitoring and progress reports on the study.

Most policies identified by this review set blood drawing limits well below the boundaries of what is likely to represent "minimal risk," and relaxing those limits might enhance the potential benefits of research for children overall. However, while good health policy takes account of physiology, it must also take account of acceptability within the population it serves. Data regarding the limits of physical safety can make an important contribution to locally-formulated policy but are not sufficient in isolation to determine that policy. The outcome of the policy reappraisal that prompted this review is an example of this. After the review, the Gambian ethics committee felt reassured that its policy on blood drawing was well within physically safe limits, based on the available evidence, but did not change its guideline except to allow requests for greater volumes to be judged on a case-by-case basis. A conservative guideline was deemed appropriate in a setting where much of the population does not consider blood a "renewable resource."[27] Responsible bodies should determine how to apply the available safety information in their local context in a manner that both protects the immediate well-being of children who participate in clinical research and also promotes the future well-being of all children. ■

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ملخص

أحجام عينات الدم المطلوبة في البحوث الصحية لطب الأطفال: مراجعة لحدود الأمان

الغرض تحديد حدود حجم عينة الدم المطلوبة لطب الأطفال بحيث تتماشى فسيولوجياً مع "أدنى حدود الخطر" المحتمل حدوثه للطفل.

الطريقة أجريت مراجعة للنشريات بحثاً عن البيّنات المتعلقة بالتأثيرات الضائرة لأخذ عينات الدم من الأطفال وعن الدلائل الإرشادية لحجم العينة المطلوبة في بحوث طب الأطفال. وتضمن البحث خط استرجاع النشريات الطبية Medline، وقاعدة المعلومات EMBASE، والمصادر الأخرى على الإنترنت وغير الإنترنت، وقد جرى تحديد ببلوغرافيا هذه المصادر، كما أجريت استشارات للخبراء.

النتائج حُـددَت خمس دراسات وتسعة دلائل إرشادية. وذكرت الدلائل الإرشادية المَوجودة حدود حجم عينة الدم للأطفال في ما يتراوح بين 1% إلى 5% من إجمالي حجم الدم خلال 24 ساعة، وحتى 10% من إجمالي حجم الدم خلال 8 أسابيع. والبينات المتاحة كانت محدودة واشتملت على نتائج دراسات غير مُعَشَّاة أظهرت أن أدنى حد للخطر هو أخذ عينة تصل إلى 5% من إجمالي حجم الدم.

الاستنتاج تتماشى البيّنات المتاحة مع استنتاج أن جميع الدلائل الإرشادية التي تم التعرف عليها تقع ضمن نطاق "أدنى حدود الخطر". إلا أن هناك حاجة لبيّنات أكثر وأفضل للحصول على استنتاج أكثر صلابة. ويبغي أن يأخذ الباحثون ولجان المراجعة المؤسسية في اعتبارهم حجم العينة الكلي اللازمة لكل من الرعاية الإكلينيكية والبحوث أكثر من أخذ اعتبار كل منهما على حدة. ويجب مراعاة الحالة الصحية العامة للطفل مع إيلاء المزيد من الحرص لاسيما للأطفال المصابين بعلل تؤدي إلى نقص حجم الدم أو الهيموغلوبين، أو المصابين بالنزف أو ما يحد من القدرة على إحلال الدم. ويجب أن تولي السياسات المحلية الاهتمام بالملائمة والقبول المحلي لإجراءات جمع الدم والكمية المسحوبة منه.

摘要

儿童健康研究中的血液样本量：安全限度综述

目的 确定符合生理“最小风险”的儿科血液样本量极限。

方法 本文进行了文献综述，旨在搜集关于儿童中血液采样不良反应的证据和儿科研究中关于采样量的指导方针。搜集对象包括联机医学文献分析和检索系统、荷兰医学文摘数据库、其他基于网络的和不基于网络的数据来源和所确定来源的参考文献。同时，也向专家咨询意见。

结果 共确定了五项研究和九项指导方针。现行指导方针详细说明如超过24小时儿科血液样本限量为血液总量的1%到5%，如超过8周为血液总量的10%。可用证据有限，包括显示高达5%血液总量的一次性采样的最小风险的非随机化研究结果。

结论 所掌握的证据与结论相吻合，即所有验证的指导方针均在“最小风险”范围之内。然而，仍需更多更好的证据来下肯定性结论。研究人员和机构审查委员会需要考虑用于临床护理和研究的总采样量，而不是单一采样量。还应考虑儿童总的健康状况，对于患有能耗尽血容量或血红蛋白或阻碍其补充的疾病的儿童，应特别注意观察。地方政策也需解决采样程序和采集血量的适当性和地方可接受性问题。

Résumé

Les volumes des échantillons sanguins dans la recherche en matière de santé infantile: examen des limites de sécurité

Objectif Déterminer les limites du volume de l'échantillon sanguin pédiatrique qui soient pertinentes avec le «risque minimal» physiologique.

Méthodes Il a été procédé à un examen de la documentation afin de trouver d'une part, des éléments probants concernant les effets indésirables du prélèvement d'échantillons sanguins chez l'enfant et d'autre part, des directives relatives au volume de l'échantillonnage dans la recherche pédiatrique. Cette recherche englobait Medline, EMBASE, d'autres sources Internet et non-Internet et les bibliographies des sources identifiées. Des experts ont également été consultés.

Résultats Cinq études et neuf directives ont été identifiées. Les directives existantes spécifient que les limites du volume de l'échantillon sanguin pédiatrique varient de 1 à 5% du volume sanguin (VST) sur 24 heures et jusqu'à 10% du VST sur 8 semaines. Les preuves dont on dispose sont limitées et comprennent les constatations d'études non randomisées montrant un risque minimal avec un échantillon ponctuel allant jusqu'à 5% du VST.

Conclusion Les éléments de preuve dont nous disposons sont en cohérence avec la conclusion selon laquelle toutes les directives identifiées sont comprises dans les limites du «risque minimal». Toutefois, davantage de preuves plus solides sont nécessaires pour tirer des conclusions irréfutables. Les chercheurs et les comités institutionnels d'évaluation doivent prendre en compte le volume d'échantillon total nécessaire à la fois aux soins cliniques et à la recherche, plutôt que leurs besoins respectifs pris séparément. L'état de santé général de l'enfant doit être évalué et un surcroît de précautions doit être pris, notamment chez les enfants dont la pathologie est susceptible d'appauvrir le volume sanguin ou l'hémoglobine ou de freiner leur reconstitution. Les politiques locales doivent également traiter de l'adéquation et de l'acceptabilité locale des procédures de collecte et des volumes sanguins prélevés.

Резюме

Объемы проб крови при исследовании здоровья детей: обзор безопасных доз

Цель Определить предельно допустимые дозы забора крови в педиатрии, соответствующие «минимальному физиологическому риску».

Методы Был проведен обзор литературы с целью поиска данных, касающихся отрицательного воздействия взятия проб крови у детей, а также рекомендаций относительно объема проб в педиатрических исследованиях. Поиск охватывал Medline, EMBASE, другие источники в Интернете и не в Интернете, а также библиографии, приведенные в выявленных источниках. Проводилось также консультирование с экспертами.

Результаты Было выявлено пять исследований и девять рекомендаций. Существующие рекомендации определяют предельно допустимую дозу забора крови в педиатрии в пределах от 1–5% общего объема крови (ООК) в течение 24 часов до 10% ООК в течение восьми недель. Доступные данные ограничены и включают результаты нерандомизированных исследований, показывающих минимальный риск разового забора крови дозой до 5% ООК.

Вывод Доступный опыт согласуется с выводом о том, что все выявленные рекомендации соответствуют рамкам «минимального риска». Однако, чтобы сформулировать

более определенные выводы, необходимы больший объем и более высокое качество данных. Исследователи и институциональные наблюдательные советы должны учитывать дозу забора крови для клинических и научных целей в сумме, а не по отдельности. Необходимо принимать во внимание общее состояние здоровья ребенка и проявлять особую осторожность в случае заболеваний, которые могут истощать объем крови или гемоглобина либо тормозить его восполнение. Настоятельно необходимы также мероприятия на местах, регулирующие целесообразность и допустимость в местных условиях процедур забора крови и взятых доз.

Resumen

Investigaciones sanitarias sobre el volumen de las muestras de sangre en niños: revisión de los límites de seguridad

Objetivo Determinar los límites del volumen de las muestras de sangre en pacientes pediátricos para alcanzar el «mínimo riesgo fisiológico».

Métodos Se realizó una revisión bibliográfica para buscar datos relacionados con los efectos adversos de la extracción de muestras de sangre en niños y para hallar unas directrices sobre el volumen de extracción en las investigaciones pediátricas. La búsqueda incluyó fuentes como Medline, EMBASE, otras fuentes, electrónicas o de otro tipo, y las bibliografías de las fuentes identificadas. También se consultó sobre este tema a los expertos.

Resultados Se identificaron cinco estudios y nueve directrices. Las directrices ya existentes especifican que los límites del volumen de sangre en las muestras pediátricas deben oscilar entre el 1% y el 5% del volumen total de sangre del paciente a lo largo de 24 horas y que pueden llegar hasta un máximo del 10% del volumen total de sangre del paciente a lo largo de 8 semanas. Los datos disponibles resultaron ser limitados e incluyeron hallazgos procedentes de estudios no aleatorizados que mostraban un riesgo mínimo con una sola muestra de hasta el 5% del volumen total de sangre.

Conclusión Los datos disponibles concuerdan con la conclusión de que todas las directrices identificadas se encuentran dentro de los límites de un «riesgo mínimo». No obstante, es necesario contar con más y mejores datos para extraer conclusiones más firmes. Los investigadores y los comités institucionales de evaluación deben tener en cuenta el volumen total de la muestra necesario, tanto en la asistencia clínica como en la investigación, y no de manera independiente. Deberá tenerse en cuenta el estado general de salud del niño y deberá prestarse una atención especial a los niños cuyas enfermedades puedan disminuir la volemia o la hemoglobina, o bien impedir la reposición sanguínea. Las directivas locales deberán considerar también la idoneidad y la aceptabilidad local de los métodos de extracción y de los volúmenes de sangre extraídos.

References

1. *Declaration of Helsinki: ethical principles for medical research involving human subjects* (2008 amendment). Ferney-Voltaire: World Medical Association; 1964 Available from: http://www.wma.net/en/30publications/10policies/b3/17c.pdf [accessed 22 September 2010].
2. *The ethics of research related to healthcare in developing countries.* London: Nuffield Council on Bioethics; 2002. Available from: http://www.nuffieldbioethics.org/go/ourwork/developingcountries/publication_309.html [accessed 22 September 2010].
3. Code of Federal Regulations. Title 45 "Public welfare", Part 46 "Protection of human subjects" (revised 23 June 2005). Washington: United States Department of Health and Human Services; 2005. Available from: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm [accessed 22 September 2010].
4. The Cochrane Library [Internet]. Oxford: UK Cochrane Centre. Available from: http://cochrane.co.uk/en/clib.html [accessed 22 September 2010].
5. Clinical evidence [Internet]. London: BMJ Group. Available from: http://clinicalevidence.bmj.com/ceweb/index.jsp [accessed 22 September 2010].
6. BloodMed.com. the global source for hematology education, practice and research [Internet]. Oxford: Blackwell Publishing Ltd. Available from: http://www.bloodmed.com [accessed 22 September 2010].
7. American Academy of Pediatrics Policy [Internet]. Elk Grove Village: American Academy of Pediatrics. Available from: http://aappolicy.aappublications.org [accessed 22 September 2010].
8. Royal College of Paediatrics and Child Health: leading the way in children's health [Internet]. London: Royal College of Paediatrics and Child Health. Available from: http://www.rcpch.ac.uk [accessed 22 September 2010].
9. Google search engine [Internet]. Mountain View: Google Inc. Available from: http://www.google.com [accessed 22 September 2010].
10. Behrman R, Kliegman R, Jenson H, editors. *Nelson textbook of pediatrics.* 17th ed. Philadelphia: WB Saunders; 2000.
11. Rudolph C, Rudolph A, editors. *Rudolph's pediatrics.* 21st ed. New York: McGraw-Hill; 2003.
12. Madsen LP, Rasmussen MK, Bjerregaard LL, Nøhr SB, Ebbesen F. Impact of blood sampling in very preterm infants. *Scand J Clin Lab Invest* 2000;60:125–32. doi:10.1080/00365510050184949 PMID:10817399
13. Testa M, Birocchi F, Carta P, Fanos V. Causes of anaemia in very low birth weight infants. Phlebotomy losses are not the first accused. *Minerva Pediatr* 2006;58:263–7. PMID:16832331
14. Broder-Fingert S, Crowley WF Jr, Boepple PA. Safety of frequent venous blood sampling in a pediatric research population. *J Pediatr* 2009;154:578–81. doi:10.1016/j.jpeds.2008.10.007 PMID:19026428
15. Cole M, Boddy AV, Kearns P, Teh KH, Price L, Parry A et al.; UKCCSG Pharmacology group. Potential clinical impact of taking multiple blood samples for research studies in paediatric oncology: how much do we really know? *Pediatr Blood Cancer* 2006;46:723–7. doi:10.1002/pbc.20463 PMID:16007598
16. Hack KE, Khodabux CM, von Lindern JS, Brouwers HA, Scherjon SA, van Rijn HJ et al. [Need for blood transfusion in premature infants in 2 Dutch perinatology centres particularly determined by blood sampling for diagnosis]. *Ned Tijdschr Geneeskd* 2008;152:1419–25. PMID:18624005
17. *Categories of research that may be reviewed by the institutional review board (IRB) through an expedited review procedure.* Rockville: US Department of Health and Human Services, Office for Human Research Protections. Available from: http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm [accessed 22 September 2010].
18. Pearson H. Blood and blood forming tissues. In: Rudolph C, Rudolph A, editors. *Rudolph's pediatrics.* 21st ed. New York: McGraw-Hill; 2003. p. 1521.
19. Gibson BE, Todd A, Roberts I, Pamphilon D, Rodeck C, Bolton-Maggs P et al.; British Committee for Standards in Haematology Transfusion Task Force: Writing group. Transfusion guidelines for neonates and older children. *Br J Haematol* 2004;124:433–53. doi:10.1111/j.1365-2141.2004.04815.x PMID:14984493
20. Cable R, Carlson B, Chambers L, Kolins J, Murphy S, Tilzer L, et al. *Practice guidelines for blood transfusion: a compilation of recent peer-reviewed literature - Second edition.* Washington: American National Red Cross; 2007. Available from: http://www.redcrossblood.org/sites/arc/files/pdf/practiceguidelinesforbloodtrans.pdf [accessed 22 September 2010].
21. Schwartz E. Iron deficiency anemia. In: *Nelson textbook of pediatrics.* 16th ed. Philadelphia: WB Saunders; 2000. p. 1471.

22. USC-LA Childrens Hospital. New study application smart form guidance. Section 22d.2.Available from: https://istar-chla.usc.edu/istar/Rooms/DisplayPages/LayoutInitial?Container=com.webridge.entity.Entity[OID[B9C8FE3780E19D4F9DB0D872221A43C6] [accessed 22 September 2010].
23. *Research studies involving the collection of blood samples* (HIC research policy/procedure). Detroit: Wayne State University Human Investigation Committee; 2008. Available from: http://www.hic.wayne.edu/policies/12-3_research_studies_involving_the_collection_of_blood_samples.pdf [accessed 22 September 2010].
24. *Blood sampling guidelines*. Boston: Partners Human Research Committee. Available from: http://healthcare.partners.org/phsirb/bldsamp.htm [accessed 22 September 2010].
25. *CMRC IRB maximum allowable total blood draw volumes (clinical + research)*. Davis: University of California; 2006. Available from: http://www.ucdmc.ucdavis.edu/clinicaltrials/documents/Blood_Draws_Maximum_Allowable.doc [accessed 9 October 2009].
26. *Blood drawing for human subject research*. Durham: Duke University; 2008. Available from: http://irb.duhs.duke.edu/wysiwyg/downloads/Blood_Collect_Policy_Statement_Revised.pdf [accessed 22 September 2010].
27. *Guidelines for scientists*. Banjul: Gambia Government–Medical Research Council Joint Ethics Committee; 2000.
28. Kauffman RE. Clinical trials in children: problems and pitfalls. *Paediatr Drugs* 2000;2:411–8. doi:10.2165/00128072-200002060-00001 PMID:11127842
29. *Blood sampling guidelines*. Toronto: The Hospital for Sick Children (SickKids) Research Ethics Board; 2004. Available from: http://www.sickkids.ca/pdfs/Research/REB/12349-Bloodguidelines.pdf [accessed 22 September 2010].
30. Segel G. Hemolytic anemias. In: *Nelson textbook of pediatrics*. 16th ed. Philadelphia: WB Saunders; 2000. p. 1472.
31. Sánchez-Medal L, Pizzuto J, Rodríguez-Moyado H, Espósito L. Haemolysis and erythropoiesis. II. Reticulocytosis and rate of haemoglobin rise in haemolytic and deficiency anaemias. *Br J Haematol* 1969;17:343–50. PMID:5346407
32. Swan HT, Jowett GH. Treatment of iron deficiency with ferrous fumarate. Assessment by a statistically accurate method. *BMJ* 1959;2:782–7. doi:10.1136/bmj.2.5155.782 PMID:13836020
33. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest* 2004;113:1271–6. PMID:15124018
34. *Guideline on the investigation of bioequivalence* (Doc. ref. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). London: Committee for Medicinal Products for Human Use, European Medicines Agency; 2010.
35. Committee for Medicinal Products for Human Use (CHMP). *Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population* (Doc. ref. EMEA/CHMP/EWP/147013/2004 Corrigendum). London: European Medicines Agency; 2006.