JUST A SPOONFUL OF SUGAR . . .

TITLE: The analgesic effect of sucrose in full term infants: a randomised controlled trial
AUTHORS: Haouari N, Wood C, Griffiths G, Levene M
JOURNAL: *BMJ*
DATE: June 10, 1995; Volume 310:1498–500

Clinical question. **Does a sucrose solution provide effective analgesia for a neonate undergoing a painful procedure?**

Background. Neonates typically undergo one or more painful procedures while in the hospital, including heel sticks, circumcision, intramuscular injections, and venous blood draws. Using a safe, easily administered analgesic would reduce the emotional and physical trauma experienced by the infant, and may also be of emotional benefit to parents and health care providers observing or administering these procedures. Intraoral sucrose has been shown in animal studies and one previous human study to reduce pain, an effect reversed by naltrexone hydrochloride and therefore probably mediated by endogenous opiates.

Population studied. The population consisted of 60 healthy, full-term infants undergoing routine heel prick within the first 6 days of life. Infants with 1-minute Apgar scores of less than 7 or who had received naloxone hydrochloride were excluded. No mention is made of how many infants were born during the 6-month study period, so it is unclear whether other factors, such as availability of staff or day of birth, affected the selection of participants. Lack of this information has been called a "denominator problem," and is a limitation of the current study. For example, knowing that the investigators had studied 60 out of 70 infants rather than 60 out of 500 would be more convincing when deciding if these results apply to all neonates.

Submitted July 24, 1995.

Dr Ebell is from the Department of Family Medicine, Wayne State University, Detroit, Michigan. Correspondence should be directed to Mark H. Ebell, MD, Department of Family Medicine, 505 S Woodward, Royal Oak, MI 48067.

Dr Newton is from the Department of Family Medicine, University of North Carolina, Chapel Hill. Correspondence should be directed to Warren Newton, MD, Aycock Family Medicine Bldg, Manning Dr, Chapel Hill, NC 27599–7595.

 ISSN 0094-3509

Study design and validity. The design was that of a randomized, double-blinded, placebo-controlled clinical trial. After obtaining informed consent from the parents, infants scheduled for heel stick were randomized to receive either sterile water or 12.5%, 25%, or 50% sucrose solution. The person administering the heel stick and making the measurements was blinded to the type of solution being delivered. The sampling procedure and the subsequent 3-minute period were audiotaped and reviewed later in a blinded fashion to measure the duration of crying.

Outcomes measured. The primary outcome measure was the duration of crying by the infant during the 3 minutes following the heel stick. Secondary outcome measures included duration of the first cry, facial expression compared with a list of four standardized expressions, change in heart rate, and change in percent oxygen saturation.

Results. For the primary outcome measure, the median crying time in the first 3 minutes among neonates receiving 50% sucrose solution was 45 seconds, compared with 135 seconds for those receiving sterile water (Mann-Whitney U test, $P=.02$). The trend was also significant, with increasing concentrations of sucrose solutions associated with a shorter duration of crying. The median duration of the first cry was also shorter for the 50% sucrose group than for the control group (20 seconds vs 95 seconds, $P=.004$). There was some evidence of less increase in heart rate among infants receiving the sucrose solutions, but no difference in oxygen saturation or facial expression. Interestingly, 7 of 15 of the infants receiving 50% sucrose cried for less than 30 seconds, compared with only 1 in 15 of the controls.

Recommendations for clinical practice. **Placing 2 mL of a 50% sucrose solution on the tongue of an infant 2 minutes before a heel stick made a clinically significant difference in the amount of crying. It seems safe to assume that both the amount of pain experienced by the infant and the emotional distress endured by their caretakers were also reduced. The reduction in discomfort, as indicated by less than one half the duration of crying, seems clinically significant. While additional well-designed trials are needed to assess the impact of the sucrose solution on the discomfort experienced during other painful procedures (an area for research by family physicians, perhaps?), family**

physicians should encourage the use of this technique in their institutions and among their patients.

Mark H. Ebell, MD, MS
Wayne State University
Detroit, Michigan

LABORATORY DIAGNOSIS OF IRON DEFICIENCY ANEMIA

TITLE: Laboratory diagnosis of iron-deficiency anemia: an overview
AUTHORS: Guyatt GH, Oxman AD, Mahmoud A, et al.
JOURNAL: *Journal of General Internal Medicine*
DATE: March-April 1992; Volume 7:145–53.

Clinical question. **What is the most appropriate laboratory test for the evaluation of a patient with suspected iron deficiency anemia?**

Background. Iron deficiency is very common, but physicans' approaches to laboratory evaluation of this condition vary greatly. Physicians use many different strategies, including mean cell volume (MCV), transferrin saturation, serum ferritin, red cell volume distribution, red cell protoporphyrin, and red cell ferritin. The purpose of this overview was to compare these strategies and identify the most useful test for the evaluation of possible iron deficiency anemia.

Studies reviewed. The literature search was well described and thorough, employing a broad search for articles on MEDLINE between 1966 and 1990, including foreign language papers, and citations from those articles as well as reviews. A manual search of *Index Medicus* before 1966 would have been helpful, as would polling experts to see what is missing. Formal reviews such as this should also describe the authors' standards for including studies for review. Inclusion criteria for this article were: (1) age greater than 18 years old and hemoglobin below 13 for men and below 11 for women; (2) quantitation of at least one of the diagnostic methods; and (3) use of bone-marrow aspiration as a reference standard for comparison with the diagnostic test. These criteria are appropriate.

Study design and validity. Receiver-operator characteristic (ROC) curves, which plot the test's sensitivity against 1 minus its specificity, are the preferred method for comparing diagnostic tests. The area under an ROC curve (AUROCC) represents the probability, from 0 to 1, that a test will correctly identify the diseased person. A higher AUROCC, ie, close to 1.0, represents a better test, while an AUROCC of 0.5 describes a test that does not yield any useful information, ie, its ability to classify patients is no better than tossing a coin. In this overview article, the AUROCCs of different diagnostic tests were plotted and compared, and the pooled data were used to generate likelihood ratios for different test results. A likelihood ratio is the odds that a given level of a diagnostic test will be found in a patient with (as opposed to without) the disease in question.

A particular strength of this study was the authors' assiduity in evaluating study relevance and methodologic quality, ie, population, interventions, outcomes measurement. These were reviewed independently by two observers, and agreement was calculated by the weighted kappa statistic. Agreement for relevance was outstanding (κ=0.82), and for quality, very good. (0.40 to 0.63).

Outcomes measured. The authors used histologic examination of bone marrow as their principal outcome, which is a clinically appropriate standard. In some studies, bone marrow aspiration was not done on all subjects; these data were included if results on individual subjects could be obtained.

Results. The serum ferritin performed much better than any other diagnostic test or combination of tests for iron deficiency; however, serum ferritin performed differently in different populations: patients with "inflammatory disease," including infection, malignancy, connective tissue disease, and liver disease, and a group without inflammatory conditions. The cutpoint for iron deficiency, ie, the point at which the test defines iron deficiency, is higher in patients with "inflammatory" conditions, but the relationship is relatively predictable. For example, a serum ferritin of 30 would have a likelihood ratio of 2 in a mixed population and a ratio of 4 in patients with underlying inflammatory disease.

Clinical recommendations. **This overview provides strong evidence for using serum ferritin as an initial laboratory test for the evaluation of iron deficiency anemia. Ferritin retains its usefulness in patients with underlying inflammatory or liver disease, but the cutpoint should be altered. Assuming that a likelihood ratio of more than 4 indicates disease, while less than 0.25 rules out disease, the data in this article suggest that in patients with inflammatory disease, a ferritin test result of less than 30 indicates iron deficiency; greater than 130 rules out iron deficiency. For patients without inflammatory disease, a ferritin test result of less than 20 indicates iron deficiency; greater than 100 rules out this condition. Other testing, including bone marrow aspiration, should be consid-**