JFP Journal Club

SCREENING FOR CERVICAL CANCER

TITLE: Naked-eye inspection of the cervix after acetic acid application may improve the predictive value of negative cytologic screening
AUTHORS: Frisch LE, Milner FH, Ferris DG
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Background. A variety of adjunctive tests have been proposed to improve the performance of the Papanicolaou (Pap) smear as a screening test for cervical cancer. One such test is naked-eye inspection of the cervix (NIC), in which the clinician applies acetic acid to the cervix and looks for areas of acetowhite outside of the squamocolumnar junction. The test is similar to cervicography, but has the advantages of being less expensive, and results are available immediately to guide management.

Clinical question. Does naked-eye inspection of the cervix following acetic acid wash have a role in screening for cervical cancer?

Population studied. The authors studied 95 students over the age of 18 who presented to a student health center for either routine cervical screening or follow-up of a recent atypical test. The population had a very high rate of cervical abnormality (42%) and was largely nulliparous (96%). While typical of the population seen at a student health center, it is not necessarily typical of the population seen by most family physicians.

Study design and validity. All patients underwent cervical cytologic testing, NIC, and cervicography (similar to NIC, except that the cervix is photographed and the image examined by a cytopathologist). All patients with abnormal cytology, abnormal cervicography, or gross lesions consistent with human papillomavirus (HPV) also underwent colposcopy with biopsy. Patients with either entirely normal screening findings or with only an abnormal NIC did not undergo colposcopic biopsy to establish a definitive diagnosis.

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Outcomes measured. Screening yield (percentage of patients with any squamous lesion, including HPV), positive predictive value (the percentage of those with a positive test who actually have disease), and negative predictive value (the percentage of those with a negative test who do not have disease). Positive and negative predictive values are appropriate and useful outcomes for clinicians because they predict disease status based on the results of a test. Sensitivity and specificity, while often used, are less helpful since they predict test outcome based on knowledge of whether the patient has disease. We typically do not know whether the patient has disease at this stage: that is why we order the test in the first place!

Results. Abnormalities were found by NIC in 71 patients (75%), cervical cytology in 15, and cervicography in 28. Of the 71 with abnormal NIC, 23 had no other abnormalities and did not have colposcopic biopsy. Of the total of 52 with either abnormal cervical cytology, abnormal cervicography, or a gross HPV lesion, 40 had abnormal colposcopic biopsy. Of these, 36 had low-grade squamous intraepithelial lesions (SIL) or HPV, 3 had high-grade SIL, and 1 had invasive cervical cancer. Interestingly, 3 of the 4 patients with negative NIC who had colposcopic biopsy had abnormal findings.

The addition of NIC increased the screening yield from 14 abnormal biopsy results to 40, including an increase from 1 to 3 in the number of high-grade lesions detected. Adding NIC to cervical cytologic screening increases the negative predictive value from 67% to 91%, but decreases the positive predictive value from 82% to 57%.

Recommendations for clinical practice. As noted by the authors, the chief limitation of this study design is the lack of the use of colposcopy in all patients with negative NIC. That 3 of 4 patients with negative NIC had either SIL or HPV is of concern; this rate of abnormal findings is similar to that in patients with positive NIC. It would be helpful to perform colposcopic biopsies in patients with negative NIC, but the authors note that such biopsy on patients with normal screening tests is ethically questionable. They address the issue by calculating "worst case" scenarios which show that the negative predictive value is still increased by the addition of NIC.

Applying this methodology to a population with a lower prevalence of disease would increase the negative predictive value (which is good), but would lower the positive predictive value significantly. For example, in a more typ-

ical primary care population with an incidence of abnormal biopsy findings of 20%, only 30% of patients with an abnormal NIC result would have an abnormal colposcopic biopsy. As a result, many patients would unnecessarily undergo the expense and worry of invasive testing. As the authors state, this study is not able to address the issue of high-grade lesions and invasive disease in a statistically meaningful way.

The results of this study are thought-provoking and should stimulate further research. In particular, the discussion should shift from sensitivity and specificity to the more useful test characteristics of positive and negative predictive values. Because of the limitations noted above, these results do not justify a change in the current practice of family physicians regarding screening for cervical cancer.

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LOW MOLECULAR WEIGHT HEPARINS FOR DVT

TITLE: Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis
AUTHORS: Leizorovicz A, Simonneau G, Decousus H, Boissel JP
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Background. Low molecular weight (LMW) heparins are a group of drugs derived from unfractionated heparin that have been shown to be effective in the prophylaxis of surgical patients for deep venous thrombosis (DVT). They have several advantages over unfractionated heparin, including greater bioavailability and uniformity of effect, subcutaneous administration once or twice daily that enables outpatient therapy, and no need for monitoring of activated partital thromboplastin time (APTT). Widely used in Europe, especially for DVT prophylaxis, the only available LMW heparin in the United States is enoxaprin (Lovenox, Rhône-Poulenc Rorer, Collegeville, Pa). Although a number of studies have compared the efficacy and safety of LMW heparins with unfractionated heparin in the treatment of DVT, many have been too small to show an advantage of one drug over another. A meta-analysis that combines data from many studies in a statistically valid way would be useful in demonstrating therapeutic advantages.

Clinical question. Are LMW heparins safe and effective in the treatment of deep venous thrombosis?

Population studied. Not given. The authors combined data from 16 randomized clinical trials that compared a LMW heparin with unfractionated heparin in the treatment of DVT.

Study design and validity. A meta-analysis is an appropriate approach to this clinical question, given the number of small studies with inadequate power to detect a clinically significant difference. In a meta-analysis, it is important that authors perform a thorough search of the literature which identifies all relevant studies, that they have explicit inclusion and exclusion criteria, that they identify clinically important outcomes, and that they use a statistically valid method to combine data from different studies (simple pooling is not acceptable). In this meta-analysis, all of the criteria are met. In addition to a MEDLINE search, the authors also contacted the manufacturers of LMW heparins to identify additional studies. Data were extracted from relevant papers by each of the authors, and a conference was held to resolve any differences among authors. The authors also analyzed subgroups of studies, comparing subcutaneous injection vs intravenous infusion of both drugs, as well as the effect of blood monitoring for patients receiving LMW heparin.

Outcomes measured. Recurrent thromboembolic events during the study period, in-hospital major hemorrhage, extension of thrombus, and total mortality.

Results. LMW heparin demonstrated a statistically significant advantage in terms of thrombus extension (odds ratio 0.51, 95% confidence interval 0.32 to 0.83) and a nonsignificant trend toward an advantage over unfractionated heparin for the remaining three outcomes (overall mortality, recurrent thromboembolic events, and major bleeding). Analysis of subgroups did not reveal a significant difference in outcomes for the route of administration of either drug or for the dosage adjustment in the LMW heparin group.

Recommendations for clinical practice. The results of this study suggest that LMW heparins are equivalent, and possibly superior to, unfractionated heparin in the treatment of DVT. Two major limitations should be noted. In many studies, patients were followed only during hospitalization, which is inadequate since many recurrences and deaths occur in the months following hospital discharge. Also, most of the studies took place in Europe, and utilized LMW heparins different from the single such

agent available in the United States. Like many meta-analyses, this study should guide future research; this would include a domestic, multicenter trial involving at least 2000 patients. Although it may be expensive, a treatment for DVT that reduces the complication rate while allowing many patients to be treated as outpatients offers potentially immense benefits. For now, LMW heparin should be considered for patients requiring DVT prophylaxis (ie, before long journeys and perioperatively) and for treatment of DVT in patients refusing hospitalization. However, widespread adoption of LMW heparin for the treatment of DVT should be preceded by a large, domestic randomized clinical trial.

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