CLINICAL MANAGEMENT extra

Influence of Smoking on Wound Healing in Patients Undergoing Nail Matrix Phenolization: A Prospective Randomized Clinical Study

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This continuing education activity will expire for physicians on May 31, 2015.

PURPOSE:

To enhance the learner's competence with knowledge of the effect of smoking on wound healing in patients undergoing nail matrix phenolization.

TARGET AUDIENCE:

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:

After participating in this educational activity, the participant should be better able to:

1. Summarize factors that affect wound cicatrization and pathophysiologic mechanisms of impaired healing from smoking as found in prior studies from review of the literature.

2. Analyze components and findings of this research study on how healing from phenol ablation is influenced by smoking.

ABSTRACT

OBJECTIVE: Healing time can be delayed by extrinsic factors such as smoking. No controlled study has analyzed the influence of smoking on wound healing in patients undergoing nail matrix phenolization. The main objective of this work was to analyze wound healing burns after segmental phenolization in smoker versus nonsmoker patients; the secondary aim was to examine the influence of curettage in both groups.

DESIGN: In a prospective clinical study, 90 podiatric patients (53 smokers and 37 nonsmokers) with onychocryptosis were randomized to 1 of 2 treatment arms: phenolization with curettage and phenolization alone. The primary outcome was to analyze the healing time (in days) after the segmental phenolization in both groups. Healing was monitored for spontaneous wound closure by clinical assessments and by digital photographs.

MAIN RESULTS: The healing time in the curettage group was (8.80 ± 1.51 days in smokers vs 6.72 ± 1.26 days in nonsmokers; $P < .0001$) and (13.24 ± 1.8 days in the smoker group vs 10.67 ± 1.78 days in the nonsmoker group; $P < .0001$) in the phenolization alone group. Significant differences were found in respect to time to healing among smokers in both groups (13.24 ± 1.8 days in the phenolization group vs 8.80 ± 1.51 days in the curettage group; $P < .0001$). Similarly, significant differences were found with respect to time to healing among nonsmokers in both groups (10.46 ± 2.04 days in the phenolization group vs 6.71 ± 1.11 days in the curettage group; $P = .0001$).

CONCLUSION: Burn wounds of smokers take longer to heal than those of nonsmokers. Curettage of the cauterized tissue reduces healing time and should be systematically considered.

KEYWORDS: smoking, wound healing, phenol burn, nail matrix, ingrown toenails, curettage

ADV SKIN WOUND CARE 2014;27:229–36

INTRODUCTION

Healing time can be lengthened by factors that are intrinsic, for example, diabetes or the nature of the initial injury such as burn depth, and extrinsic, such as infection or smoking. The negative effects of tobacco smoking on acute wound healing have long been analyzed. Cigarette smoke contains more than 250 toxins, all of which are known to impair wound healing, through multiple mechanisms. The literature shows that smoking decreases tissue oxygenation and aerobe metabolism temporarily. The inflammatory healing response is attenuated by a reduced inflammatory cell chemotactic responsiveness, migratory function, and oxidative bactericidal mechanisms.[1] The relationship of smoking and delayed postoperative wound healing has been established in numerous prospective and retrospective cohort studies, and the current meta-analysis shows that postoperative healing complications occur significantly more often in smokers compared with nonsmokers.[2] Following surgery, patients who smoke usually present delayed wound healing and increased frequency of associated complications, such as skin and flap necrosis, infection, and dehiscence.[3–6] Similarly, literature meta-analyses report that an abstinence from smoking of at least 3 to 4 weeks reduces wound healing complications.[7,8]

Phenol has been used clinically for many years, primarily to create controlled chemical burns of the skin or skin appendages. Two examples are chemical facial peels and nail matrix cauterization (chemical matrixectomy). Phenol is a weak acid that causes denaturation and precipitation of the skin's proteins but without full-thickness dermal loss. Prolonged skin contact with phenol can, however, cause deep burns with enhanced inflammatory response and drainage and can elicit denaturation and gangrene followed by necrosis.[9]

Currently, chemical matrixectomy is one of the most common surgical procedures used to correct onychocryptosis or ingrown toenails. The advantages of phenol ablation include lower recurrence rates, performable in the presence of sepsis, less postoperative pain because of its aesthetic properties, and superior cosmetic results. The procedure has a number of disadvantages, however, resulting from the chemical cauterization of the tissue. These include delayed healing, prolonged serous drainage due to the acute reaction to the chemical agent, and increased risk of infection.[10] Indeed, some cases of full-thickness burns to the great toe following phenol ablation for an ingrown toenail resulting in amputation have been reported in the literature.[11]

Numerous modifications of the required concentrations and application times of phenol have been proposed to reduce the drawbacks of the technique. Some studies have described the advantages of using concentrations that are just sufficient to ensure the effectiveness of the technique, while minimizing its drawbacks,[12–15] and others have proposed curettage of the cauterized tissue following segmental phenolization to accelerate cicatrization.[16]

Only a few reports were found in the literature that address the impact of tobacco smoking on cutaneous procedures using chemical agents or laser treatments, and some of them find no differences in smokers versus nonsmokers.[17,18] To date, the authors have not found any controlled study analyzing the influence of smoking on cicatrization in patients undergoing nail matrix segmental phenolization. Therefore, the objective of this study was to conduct a prospective randomized clinical investigation to examine how tobacco smoking influences cicatrization following segmental phenolization. By reading this article, clinicians will better understand the effects of smoking on wound healing, specifically in burns after segmental phenolization.

METHODS

A prospective clinical study was conducted to analyze wound healing time after segmental phenolization in smoker versus nonsmoker patients. From October 2009 to January 2012, all the patients admitted with ingrown toenails in the Área Clnica de Podologa of the University of Seville and in the San Lazaro Hospital (Seville, Spain) were included as candidates for a randomized, double-blind, parallel-control-group clinical trial. A selection was made of those who presented ingrown toenails that had previously received conservative treatment (removal of the ingrown nail spicule and local antiseptic treatment) without definitive results.

The study was conducted according to the guidelines of the Declaration of Helsinki[19] and the European Guidelines for Good Clinical Practice on Ethical Conduct in Research Involving Humans[20] and was approved by the Ethics and Experiment Committee of the University of Seville (CEE 875/US). Informed consent was obtained from all the patients, including consent for publication of photographs.

Randomization was administered by an independent party, which assigned consecutive numbers to the patients' histories selected at random. This ensured that no member of the team was aware of the following allocation. Patients were randomly assigned between the 2 trial treatments as follows: even clinical history number = the patient's nail fold or folds underwent segmental phenolization; odd clinical history number = the patient's nail fold or folds underwent segmental phenolization plus curettage of the matrix and nail bed.

The criteria for inclusion in the study were as follows: Stage I, II, or III ingrown toenail, according to the classification proposed by Kline.[21] The exclusion criteria were as follows: patients exposed to secondhand smoke (someone in their home smokes), infected ingrown toenail with partial onycholysis of 1 or both nail borders, clotting problems, wound cicatrization disorders, uncontrolled diabetes (hemoglobin A1c [HbA1c] >7.5%), underlying bone pathology, allergy to local anesthetics, and treatment with steroids or immunosuppressants. Age was not a basis for exclusion.

The primary outcome parameter was the wound healing time after segmental phenolization, distinguishing between smoker and nonsmoker patients. The secondary outcome parameter was the influence of curettage of the cauterized tissue on healing time in both the aforementioned groups.

The surgical procedure consisted of partial ablation from segmental phenolization of the affected nail folds as follows. A digital block of the hallux was performed using 2% mepivacaine (Scandinibsa; Inibsa SA, Barcelona, Spain). After surgical lavage of the operative field, a digital tourniquet was applied for local hemostasis. Using a Freer elevator, the affected nail plate was conveniently separated from the nail bed and eponychium. Partial ablation of the nail plate was performed using a nail splitter and a hemostat. After removal of the portion of the nail, a cotton ball soaked in 100% phenol was applied with a swab for 1 minute to the matrix and the nail bed. The zone was then irrigated with 76% ethanol for 1 minute and then with physiological saline solution. In the experimental group, a Martini bone curette was used to carefully remove all cauterized tissue that had a whitish appearance. This procedure was performed on both nail folds of the hallux when the treatment was bilateral (80 cases) or on one when it was unilateral (13 cases). All the patients received oral antibiotic prophylaxis 60 minutes before the procedure in a single dose of cephalexin 2 g, or 500 mg levofloxacin if the patient was allergic to penicillin. All surgical wounds were dressed with a thin layer of sulfadiazine silver cream and covered with a sterile and nonadherent polypropylene dressing. Three gauzes were placed around the hallux and covered with a sterile compressive bandage.

All the procedures were performed by the same clinician (J.A.-J.). Clinical efficacy and adverse effects were evaluated by a single observer (A.C.-F), who was blinded as to which procedure had been applied. Healing was monitored for spontaneous wound closure by clinical assessments and by digital photographs over 1 month. Patients were seen every 48 hours. From the fourth day onward, the treatment administered to both groups consisted of applying povidone-iodine antiseptic solution. Daily checks were made until the healing time criteria were completely satisfied. The clinical criteria of early healing time were considered to be absence of drainage (no exudate evident), granulation tissue covered by a scab (no evidence of hypergranulation tissue), and no signs of infection (ie, no pain or clinical evidence of discharge in association with redness extending proximally). The patient was then allowed to bathe. All criteria had to be met before the wound was considered cicatrized (ie, healed). Similar criteria have been used in other clinical trials for matrix phenolization wounds.[22,23]

The sample size required for the study was calculated using the computer program CTM-1.1 (Glaxo Wellcome SA, Madrid, Spain). The result of the computation was that, to detect a clinically relevant difference of 5 days in mean healing time between the experimental and control groups for a significance level of $\alpha = .05$ and an error $\beta = .15$, a minimum of 19 patients would be necessary in each group.

Statistical analyses were performed using SPSS 17.0 (SPSS Science, Chicago, Illinois). A first exploratory analysis was made of the data to detect outliers and to characterize differences between subgroups of individuals. The ^{2} test was applied for the variables ''sex'' and ''diabetes,'' and the Mann-Whitney U test for the variable ''age'' to check the homogeneity of the groups (''phenolization'' and ''curettage'') and subgroups (''smokers'' and ''nonsmokers''), so as to ensure that any differences in the

dependent variables were because of the independent variable and not the heterogeneity of the groups. For all 3 variables, the result was $P > .05$, so the groups could be considered homogeneous and therefore comparable for inferential analyses.

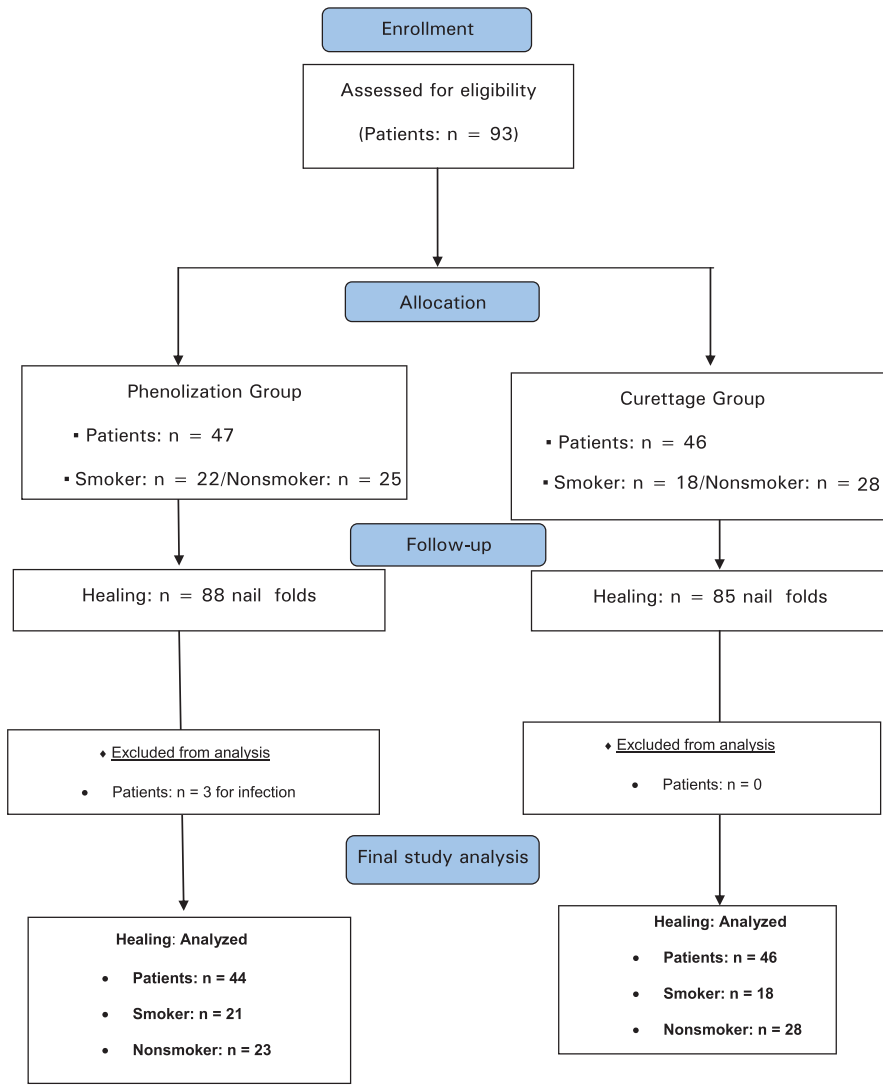
Quantitative variables were summarized in terms of their means and SDs; qualitative variables were expressed as percentages. The Mann-Whitney U test was applied for comparisons of the variable "healing time" (measured in days). Between-group differences were considered statistically significant when $P < .05$.

RESULTS

Three patients of the phenolization group were excluded from completion of the study because they presented a clinical pattern of postoperative infection. The final study sample included 90 patients, of whom 51 were nonsmokers and 39 smokers (participant flow and reasons for exclusion are shown in Figure 1). The phenolization group comprised 44 patients (88 nail folds); the curettage group comprised 46 patients (85 nail folds). The general features of patients regarding sex, treatment received,

Figure 1.

FLOW CHART OF THE PARTICIPANTS DETAILING THEIR FOLLOW-UP OR EXCLUSION THROUGH EACH PHASE OF THE STUDY



number of operated nail folds, and smoker or nonsmoker are given in Table 1.

The primary outcome parameter analyzed was the wound healing time after segmental phenolization in smoker and nonsmoker patients as described in Methods. The secondary outcome parameter analyzed was the influence of curettage of the cauterized tissue on healing time in the 2 groups of patients.

In both treatment groups, the healing time was significantly longer ($P < .0001$) in the smokers than in the nonsmokers. It was also significantly longer in patients who underwent phenolization alone than in those who also underwent curettage. This latter difference was also found to be statistically significant ($P < .0001$) when comparing only the smokers of the 2 treatment groups (phenolization vs curettage).

The healing times and their distribution in each group are listed in Tables 2 to 5.

DISCUSSION

Although numerous clinical and experimental studies have examined the effect of nicotine on wound healing and surgical procedures, there are few published reports in the dermatological surgery literature.[24] The evidence now shows that tobacco smoking is associated with a higher incidence of postoperative complications including wound dehiscence, flap or graft necrosis, prolonged healing time, and infections.[1–8]

With respect to the impact of smoking on cutaneous procedures using phenol, in 1983, Klein and Little[25] reported a case series of 3 chronic smokers who developed laryngeal edema manifesting as stridor, hoarseness, and shortness of breath as a complication after phenol peels. Besides this single case series, there are no other reported associations between smoking and chemical cutaneous cauterization with phenol in the literature.[25]

Several studies have examined mean healing time after segmental phenolization, but the results they report are disparate, and they use different criteria as to what is meant by a healed or cicatrized wound.[12–16] In the present study, conducted to evaluate the effects of smoking on wound healing after segmental phenolization, the authors applied early cicatrization criteria similar to those used in other clinical trials. The results show that

Table 1.
GENERAL FEATURES OF PATIENTS

	Phenolization Group	Curettage Group	Total Analyzed
Patients	44 (48.9%)	46 (51.1%)	90
Males	20	17	37 (41.1%)
Females	24	29	53 (58.9%)
Nail folds	88 (50.87%)	85 (49.13%)	173
Males	38	31	69 (39.9%)
Females	50	54	104 (60.1%)
Average age	35.31	32.10	33.68
SD	18.01	13.41	15.82
Diabetics	7	4	11
Smoker	21	18	39
Males	6	6	12
Females	15	12	27
Nonsmoker	23	28	51
Males	14	12	26
Females	9	16	15
Average healing time	11.72	7.47	9.55
SD	2.32	1.58	2.91

Table 2.
DISTRIBUTION OF HEALING TIME IN SMOKERS VS NONSMOKERS DURING FOLLOW-UP OF PHENOLIZATION ALONE GROUP

	Smoker	Nonsmoker	*P* Between Groups
Healing			
Patients, n	21	23	Mann-Whitney *U* test
Nail folds, n	46	42	
Average healing time, mean (SD), d	13.11 (1.79)	10.46 (2.04)	$P = .0001$
Range of healing time, d	8–16	7–15	

Table 3.
DISTRIBUTION OF HEALING TIME IN SMOKERS VS NONSMOKERS DURING FOLLOW-UP OF CURETTAGE GROUP

	Smoker	Nonsmoker	*P* Between Groups
Healing			
Patients, n	18	28	
Nail folds, n	35	50	Mann-Whitney *U* test
Average healing time, mean (SD), d	8.64 (1.50)	6.71 (1.11)	$P = .0001$
Range of healing time, d	6–11	4–8	

Table 4.
DISTRIBUTION OF HEALING TIME DURING FOLLOW-UP OF SMOKERS IN BOTH GROUPS

	Phenolization Alone Group	Curettage Group	*P* Between Groups
Healing			
Patients, n	21	18	Mann-Whitney *U* test
Nail folds, n	46	35	
Average healing time, mean (SD), d	13.11 (1.79)	8.64 (1.50)	*P* = .0001
Range of healing time, d	8–16	6–11	

healing times are significantly longer in smokers than in nonsmokers, independently of whether the patient underwent phenolization alone or phenolization followed by curettage.

In a clinical trial, Sorensen et al[26] demonstrated that smoking has a transient effect on the tissue microenvironment but a prolonged effect on cellular inflammatory and reparative functions, leading to delayed healing and complications. Cessation of smoking restores the tissue microenvironment rapidly and the cellular inflammatory functions within 4 weeks, but the proliferative response remains impaired.[26] A similar study conducted by that same research group showed that wound contraction and collagen metabolism are disturbed by smoking because of a decrease in vitamin C and a change in inflammatory cell response.[27] This would explain why in the present study the wound healing process of the smoker group was observed to be slowed down, possibly due to a temporary stagnation of the acute inflammatory phase of healing.

Phenol's potential toxic effects and the intense inflammatory changes that it produces in the skin increase inflammation and delay wound healing.[11] The excessive inflammatory response caused in part by the toxic effect of phenol on the wound and in part by the altered inflammatory phase of healing originated by smoking would explain the longer healing times the authors observed in the group of smokers who underwent segmental phenolization alone. Furthermore, the authors believe that curettage of the tissue cauterized by phenol restores the tissue microenvironment and cellular inflammatory functions with the consequent immediate reactivation of the inflammatory phase and subsequent fibroplasia, thus speeding up the repair process. Indeed, the results showed that the wounds healed faster with curettage of the cauterized tissue in both the smoker and the nonsmoker groups. Based on these results, the authors propose that curettage should systematically be performed after segmental phenolization to reduce the healing time of smoker patients.

There have been few studies conducted to determine the optimal concentration of phenol to reduce the inflammatory response, drainage, and risk of infection. Boberg et al[12] established that the destructive effects of phenol depend in part on its concentration, but that there is no linear relationship between skin necrosis and phenol concentration. That study showed that the application of 89% phenol solution for 1 minute is the minimum time and concentration required for complete destruction of the germinal nail matrix. Similarly, Tatlican et al[15] compared different lengths of 89% phenol application to determine the efficacy and safety of the technique. The best results with regard to postoperative complications (pain, drainage, and tissue damage) and complete cure times were obtained in the group to which phenol was applied for 1 minute, with mean complete cure times similar to the healing times obtained in the authors' phenolization group of nonsmoker patients with pure phenol application.

Most recommendations for smokers who are to undergo surgery are based on evidence suggesting that smoking-related complications can be significantly reduced when the patient abstains for at least 3 to 4 weeks before surgery.[7,8] However, there have been no controlled studies examining the time for the reversal of nicotine-induced wound complications when exposure to nicotine ceases. The evidence suggests that perioperative smoking cessation intervention reduces surgical site infections, but not other healing complications.[2] The optimal duration of preoperative smoking cessation for reducing wound complications is unclear. Existing evidence suggests that the optimal duration of preoperative cessation is 4 to 8 weeks.[28–30] One recent article on chemical peels and laser resurfacing advocates stopping smoking from 1 month before to 6 months after the procedure, but without providing literature to support this suggestion.[31]

Furthermore, there have been studies showing that, despite warnings from physicians to cease smoking, a large proportion of patients will continue to smoke.[30,32] Given those results, some

Table 5.
DISTRIBUTION OF HEALING TIME DURING FOLLOW-UP OF NONSMOKERS IN BOTH GROUPS

	Phenolization-Alone Group	Curettage Group	*P* Between Groups
Healing			
Patients, n	23	28	Mann-Whitney *U* test
Nail folds, n	42	50	
Average healing time, mean (SD), d	10.46 (2.04)	6.71 (1.11)	*P* = .0001
Range of healing time, d	7–15	4–8	

authors recommend that, for heavy smokers who are unable to quit, it may be more practical to recommend that they cut down to less than 1 pack per day.[24] In the present study, there were more nonsmokers than smokers (51 vs 39), of whom more than 75% reported consuming more than 1 pack of cigarettes per day. The authors agree with most authors that, despite any recommendations that they might offer patients, a large proportion of them will continue to smoke. Although smoking is certainly not recommended in surgical patients, the authors consider that it may be more reasonable to ask patients to cut down rather than abstain completely. A limitation of this study is that, although it was recommended reducing consumption of cigarettes to smokers of more than 1 pack per day, no reliable test was made to verify if this occurred.

It is commonly accepted that good blood glucose control is required to facilitate the healing of diabetic foot wounds. Several studies have suggested that phenol matrixectomies may be safely performed on patients with diabetes who do not have severely compromised arterial outflow.[33,34] Their results indicated no significant difference in healing times or postoperative infection rates. Unfortunately, these retrospective studies evaluated only fasting blood level glucose, but it was not an exclusion criterion. In the present study, the presence of uncontrolled diabetes (HbA1c >7.5%) was a criterion for exclusion so the results are not comparable. Additional studies are necessary to correlate healing times in chemical matrixectomies to HbA1c values. Nevertheless, in the authors' study, the 2 treatment groups and the age, sex, and presence or absence of diabetes subgroups were homogeneous, so that it can be suspected that the presence of diabetes was neither a confounding factor nor a source of bias in the results.

In conclusion, the segmental phenolization burn wounds of smoker patients take longer to heal than those of nonsmokers. Curettage of the cauterized tissue after segmental phenolization shortens healing time in both smokers and nonsmokers. Therefore, curettage after phenolization should be systematically considered in patients who smoke to reduce the healing time following the procedure.

PRACTICE PEARLS

- Tobacco smoking is associated with a higher incidence of postoperative complications including wound dehiscence, flap or graft necrosis, prolonged healing time, and infections.
- Smokers may reduce smoking-related complications by abstaining from smoking 3 to 4 weeks before their surgery.
- Research has shown that wound contraction and collagen metabolism are disturbed by smoking because of a decrease in vitamin C and a change in inflammatory cell response.
- Burn wounds of smokers take longer to heal than those of nonsmokers. Curettage of the cauterized tissue reduces healing time and should be systematically considered.
- Study results demonstrate that results showed that the wounds from nail matrix phenolization healed faster with curettage of the cauterized tissue in both the smoker and the nonsmoker groups.

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- A passing score for this test is 13 correct answers.
- Nurses: Need CE STAT? Visit **http://www.nursingcenter.com** for immediate results, other CE activities, and your personalized CE planner tool. No Internet access? Call 1-800-787-8985 for other rush service options.
- Questions? Contact Lippincott Williams & Wilkins: 1-800-787-8985.

Registration Deadline: May 31, 2016 (nurses); May 31, 2015 (physicians).

PAYMENT AND DISCOUNTS

- The registration fee for this test is $24.95 for nurses; $22 for physicians.
- Nurses: If you take two or more tests in any nursing journal published by LWW and send in your CE enrollment forms together by mail, you may deduct $0.95 from the price of each test. We offer special discounts for as few as six tests and institutional bulk discounts for multiple tests. Call 1-800-787-8985 for more information.