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Expired Air Carbon Monoxide Testing Is Effective for Preoperative Screening of Cigarette Use in Orthopaedic Patients: A Prospective Pilot Study of 70 Veterans

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ABSTRACT

Introduction: Screening for cigarette use is standard in the orthopedic pre-operative clinic, however traditional biochemical testing methods, including serum and urine cotinine assays, do not differentiate active smoking from nicotine replacement therapy (NRT). In this prospective pilot study, we hypothesize that exhaled carbon monoxide (eCO) testing will be non-inferior to the gold standard serum cotinine (SC) test in screening for pre-operative cigarette use, will differentiate active smoking from NRT, and will allow for substantial cost savings in a clinic setting. **Methods:** Adult orthopaedic veterans indicated for elective surgery at our institution were offered inclusion. Self-reported smoking status (SRS), eCO and SC levels were obtained preoperatively. An eCO level of >6 parts per million and a SC level >3 ng/ml were considered positive for recent cigarette use. Agreement between SRS, eCO levels and SC levels, and eCO level test-retest reliability were evaluated. **Results:** Of the 55 patients enrolled into the study, 4 were self-reported Current Smokers and 51 were self-reported Ex-Smokers or Non-Smokers. Combining SRS with eCO levels as a screening tool for recent cigarette use yielded a sensitivity of 100%, a specificity of 98%, a positive predictive value of 95% and a negative predictive value of 100%. eCO testing differentiated NRT from cigarette use in all non-smoking patients. Test-retest reliability for eCO levels showed perfect agreement for 16 patients that had two or more eCO levels pre-operatively. **Conclusion:** Exhaled CO testing is as effective as SC testing but can differentiate active smoking from NRT, while maintaining a high level of accuracy and reliability when combined with SRS as a screening tool.

Keywords: Orthopaedic surgery, smoking, surgical outcomes, nicotine replacement

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Introduction

Cigarette use is associated with worse outcomes in orthopaedic patients and is disproportionately higher among veterans, who have lower quit rates and higher discordance between self-reported quitters and biochemical tests.[1-5] Smokers undergoing elective procedures are at increased risk of wound complications, surgical site infection, pneumonia, and 1-year mortality. [6-7] However, about 1 in 5 self-reported "quitters" test positive for nicotine use, [8] highlighting a sub-population at risk for misclassification of smoking status.

Smoking status is typically obtained through self-reported smoking questionnaires or medical interviews in clinic. Because smoking may be underreported, especially in quitters, smoking cessation is often verified with biologic tests prior to elective orthopedic surgery, [6, 8-10] such as serum or urine cotinine assays which test for nicotine byproducts, or exhaled carbon monoxide (eCO) testing. Cotinine assays cannot distinguish between nicotine replacement therapy (NRT) and active smoking, and assay results typically take several days to become available.

Although seldom reported in the orthopaedic literature, it is well-established that an eCO level greater than 6ppm is a valid clinical marker for the detection of recent smoking in a variety of patient populations. [10-12] Compared to serum cotinine (SC) analysis, eCO testing offers immediate results, can differentiate between cigarette use and NRT, and is cost-effective. However, the utility of eCO testing in the orthopaedic population as a screening tool remains unknown. Our aim was to evaluate the effectiveness and cost savings of a point-of-care eCO breath test to verify smoking status and differentiate active smoking from NRT, as compared to the gold standard serum cotinine (SC) test. We hypothesize that eCO will be non-inferior to SC testing for screening of cigarette use, allow for differentiating from NRT, and provide significant cost-savings in the pre-operative clinic setting.

Patients and Methods

This was an IRB approved prospective, non-randomized cohort study that implemented the use of eCO testing as a point-of-care screening tool for pre-operative smoking status in orthopaedic patients. From August 2019 to March 2020, 71 patients who were indicated and consented for surgery in the orthopaedic clinic at the Portland VA Medical Center were offered inclusion in this study. Subjects were excluded if they were unable to provide informed consent, were treated non-operatively, were pregnant, or were prisoners. Eighty-nine eligible patients were not approached due to time constraints as the study was being initiated.

Self-reported smoking status (SRS) was obtained pre-operatively to categorize patients as Non-Smokers, Ex-Smokers, or Current Smokers (Figure 1). Within 4-weeks prior to the planned surgery, SC blood assays and eCO levels were obtained in the orthopedic clinic. eCO levels were obtained utilizing the Smokerlyzer® Micro EC50 pre-operatively in the orthopedic clinic as well as in the pre-operative area on the day of surgery to evaluate for test-retest reliability. The surgeon was blinded to the day of surgery results.

Smoking prevalence in the military veteran population is reported as 27-28%.[13] Based on this prevalence, and assuming a power of 0.8 and an alpha of 0.5, we performed a simulation for a desirable Cohen's kappa coefficient between 0.6 and 0.7 to 0.99, with a predicted sample size (n) between 77 and 247 patients, respectively. However, due to the Covid-19 pandemic, the study was stopped prematurely in early March of 2020 due to concern for risk of exposure and patient harm, which limited recruitment.

Participants with an eCO level of greater than 6 parts per million were considered positive on the eCO test, and participants with a SC level greater than 3 ng/ml were considered positive for recent nicotine use based on cut-off values recommended by the Society for Research on Nicotine and Tobacco Treatment Research Network[14]. Agreement between SRS, eCO and SC levels, and eCO level test-retest reliability,

were evaluated. A cost comparison between SC and eCO testing was also conducted to determine the potential cost savings for a sample population.

Statistical Analysis

Participants were grouped into two groups based on their SRS. Those smoking on a daily or weekly basis were labeled 'Current Smokers'; those who did not smoke, had quit smoking, or smoked on a monthly or yearly basis were labeled 'Not Current Smokers'. Comparison of eCO testing to SRS, SC testing to SRS, and exhaled smoking testing to SC testing were evaluated using a two-by-two contingency table to calculate sensitivity, specificity, positive and negative predictive value, assuming an estimated prevalence of 24%.

Ethics, Funding, and Potential Conflicts of Interest

Approval was obtained for this study through the Portland Veterans Health Affairs Institutional Review Board. Funding was received from the Department of Orthopedics and Rehabilitation at Oregon Health & Science University for the purchase of two Smokerlyzer® Micro EC50's and associated equipment [15]. The authors report no conflicts of interest.

Table 1. Patient reported cigarette smoking history. Data are presented as n (%).

	Non-Smokers	Ex-Smokers	Current Smokers (daily or weekly)
	14 (25)	37 (67)	4 (7)
Report quitting <1 year ago	-	9 (24.4)	-
Report quitting 2-5 years	-	2 (5.4)	-
Report quitting >5 years	-	26 (70.2)	-
Smokes 1 to 4 cigarettes per day	-	-	1 (25.0)
Smokes less than 10 cigarettes per day	-	-	2 (50.0)
Smokes between ½ to 1 pack per day	-	-	1 (25.0)
Smokes greater than 1 pack per day	-	-	-

Table 2. Patient reported nicotine use and other smoked products. Data are presented as n (%).

	Non-Smokers	Ex-Smokers	Current Smokers (daily or weekly)
	14 (25)	37 (67)	4 (7)
Does not use other forms of nicotine	11(78.6)	33 (89.2)	2 (50.0)
Uses Cigars	-	1 (2.7)	-
Uses chewing tobacco	3 (21.4)	1 (2.7)	-
Uses NRT (gum/patches/e-cigarettes)	-	2 (5.4)	2 (50.0)
Does not smoke non-cigarette products	11 (78.6)	27 (73.0)	3 (60.0)
Smokes Marijuana	3 (21.4)	8 (21.6)	1 (20.0)
Smokes Cigars	-	1 (2.7)	-
Smokes E-cigarettes	-	1 (2.7)	-

Table 3. Screening results for 55 pre-operative patients

Serum Cotinine	Non-Smokers	Ex-Smokers	Current Smokers (daily or weekly)
CO ≥6ppm (positive)			
Not detected	0	1*	0
>3ng/mL (positive)	0	0	3
CO <6ppm (negative)			
Not detected	13	32	0
>3ng/mL (positive)	1	4	1
Total	14	37	4

**One Ex-Smoker reported smoking marijuana heavily on a daily basis*

Table 4. Serum cotinine test compared to self-reported smoking status

	Current Smokers	Not Current Smokers		
Cotinine positive	4	4	8	PPV 82%
Cotinine negative	0	47	47	NPV 100%
	4	51	55	
	Sensitivity 100%	Specificity 92%		

Table 5. Exhaled CO test compared to self-reported smoking status

	Current Smokers	Not Current Smokers		
CO test positive	3	1*	4	PPV 93%
CO test negative	1	50	51	NPV 91%
	4	51	55	
	Sensitivity 75%	Specificity 98%		

**One Ex-Smoker reported smoking marijuana heavily on a daily basis*

Table 6. Exhaled CO test compared to serum cotinine

	Cotinine positive	Cotinine negative		
CO test positive	3	1*	4	PPV 75%
CO test negative	5	46	51	NPV 90%
	8	47	55	
	Sensitivity 37.50%	Specificity 98%		

**One Ex-Smoker reported smoking marijuana heavily on a daily basis*

Table 7. Exhaled CO test + Self-reported smoking status

	Current Smokers	Not Current Smokers		
Either test (+)	4	1*	5	PPV 95%
Both tests (-)	0	50	50	NPV 100%
	4	51	55	
	Sensitivity 100%	Specificity 98%		

**One Ex-Smoker reported smoking marijuana heavily on a daily basis*

Figure 1. Smoking questionnaire

Question	Response
1. Have you smoked cigarettes in the past 3 months?	Yes/No
a) How frequently do you smoke?	○ Daily ○ Weekly ○ Monthly ○ Yearly
b) When was your last cigarette?	○ Today ○ Past 1-2 days ○ Past week ○ Past month
c) How many cigarettes do you smoke per day?	○ 1 to 4 ○ Less than 10 ○ ½ to 1 pack ○ >1 pack
d) How many years have your smoked daily?	○ <1 year ○ 2-5 years ○ 5-10 years ○ >10 years
2. How long ago did you quit smoking	○ I've never smoked ○ <1 year ○ 2-5 years ○ >5 years
3. Do you live or work in an environment where you are exposed to smoke?	Yes/No
4. Do you use other forms of nicotine?	○ NRT (gum/patches) ○ Cigars ○ Chewing tobacco ○ None
5. Do you smoke other products that are not cigarettes?	○ Marijuana ○ Cigars ○ E-cigarettes ○ None
6. Have you ever been diagnosed with a lung or breathing disease?	○ COPD ○ Asthma ○ OSA ○ Other/None

Results

Patient Demographics

Of 71 patients approached for the study, one patient declined participation. and complete data was available for 55 patients (Figure 2). Of these, there were 51 men and 4 women with an average age of 70 ± 9 years (range 41 to 87 years). Total joint arthroplasty was indicated for 50 patients, hardware removal for 3 patients, clavicle open reduction internal fixation for 1 patient, and exchange nailing for a tibial non-union for 1 patient. All data was collected pre-operatively and no follow up data was collected for this study.

Patient Smoking Habits and Nicotine Use

Of 55 participants with complete data, 14 (25%) reported that they had never smoked cigarettes, 37 (67%) reported they had quit smoking, and 4 (7%) reported smoking on a daily or weekly basis (Table 1). Of those who claimed to have quit smoking, 26 (70%) reported quitting greater than 5 years ago, 2 (5%) reported quitting between 2 and 5 years ago, and 9 (24%) reported quitting less than 1 year ago. Of the 4 who smoked on a daily or weekly basis, 2 reported smoking less than 10 cigarettes per day, 1 reported smoking 1 to 4 cigarettes per day, and 1 reported smoking between a half and a full pack of cigarettes per day.

Eleven (78.6%) of the 14 Non-Smokers did not use other forms of nicotine, and 3 (21.4%) used chew tobacco (Table 2). Thirty-three (89.2%) Ex-Smokers did not use other forms of nicotine, 1 chewed tobacco, 1 smoked cigars on a yearly basis, 1 reported NRT use, and 1 reported daily e-cigarette use. Of the 4 Current Smokers, 2 reported no other nicotine use, while the remaining 2 reported NRT use and were actively working towards smoking cessation. Self-reported marijuana use was present in 3 (21.4%) Non-Smokers and 8 (21.6%) Ex-Smokers. No Current Smokers reported marijuana use.

Not Current Smokers and Current Smokers

Serum cotinine and eCO values were collected for Non-Smokers, Ex-Smokers, and Current Smokers (Table 3). To further analyze groups based on smoking behavior, Non-Smokers and Ex-Smokers were grouped together as Not Current Smokers (those with no recent report of smoking) in comparison to the 'Current Smokers' (those who self-reported recent smoking on a daily or weekly basis).

Serum Cotinine Test

Eight patients tested positive for SC (range of 15.9 to 367.9 ng/ml); 4 were Current Smokers (triangles, Figure 3) and 4 were Not Current Smokers (circles, Figure 3). Three of 4 Current Smokers also had a positive eCO test. The only Current Smoker with a negative eCO test reported NRT use and was attempting smoking cessation. Four Not Current Smokers who tested positive for SC had a self-reported use of other nicotine products (Figure 3). Of 51 Not Current Smokers, 47 had a negative SC. Four of 4 Current Smokers had a positive SC test, with a sensitivity of 100% and specificity of 92% (Table 4).

eCO Test

Four patients had a positive eCO test (Table 5). Three were Current Smokers who reported smoking on a daily or weekly basis (range 14 to 21ppm). The only Not Current Smoker with a positive eCO test (8ppm) reported smoking marijuana on a daily basis and had a negative SC test. Fifty of 51 Not Current Smokers had a negative eCO test and 3 of the 4 Current Smokers had a positive eCO test, with a sensitivity of 75% and a specificity of 98% (Table 4). No Non-Smokers with a self-reported history of lung disease had a positive eCO test (Figure 3).

Comparing eCO to SC Tests

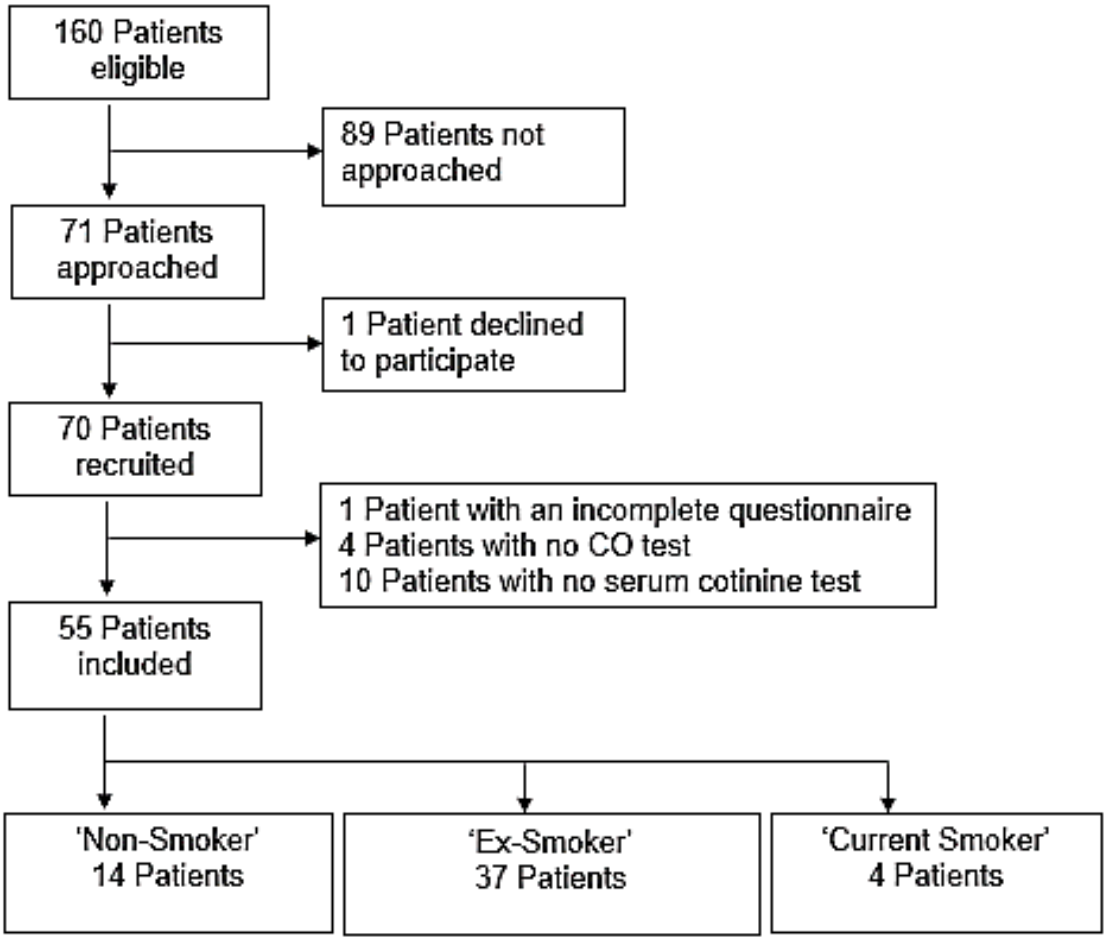
Three of 8 patients who tested positive for SC also tested positive for eCO, and 1 of the 47 who tested negative for SC tested positive for eCO, resulting in a sensitivity of 37.5% and specificity of 98% (Table 6).

Combined eCO Test and SRS

We combined SRS with eCO testing as a screening test and assumed that if either test

was positive then the result was positive and that a negative result required both tests be negative. Four of 4 Current Smokers tested positive and only 1 of 50 Not Current Smokers tested positive, resulting in a sensitivity of 100%, a specificity of 98%, a positive predictive value of 95% and a negative predictive value of 100% (Table 7). Test-retest reliability of the eCO test showed perfect agreement for the 16 patients that had both pre-operative and day of surgery eCO levels available.

Figure 2. Patient inclusion flowchart.



Cost Comparison of eCO and SC Testing

The cost of eCO and SC tests were also compared (Figure 4). Each SC lab test has a fixed price of $28.00 at our institution. The Smokerlyzer® Micro EC50 initially costs $1,190.00 for the hand-held device, and yearly maintenance costs about $100. To perform individual eCO tests requires a disposable straw, which costs 15 cents per unit. When estimating a theoretical test size of 500 patients, the break-even point for cost occurs after the 42nd test, and the estimated cost savings of using the Smokerlyzer® Micro EC50 after 500 tests is approximately $12,390.00.

Discussion

Compared to serum cotinine testing, eCO testing combined with patient reported smoking status was non-inferior in detecting pre-operative cigarette use. eCO testing allowed for differentiation between active smokers and those on nicotine replacement therapy compared to serum cotinine testing. Additionally, eCO testing proved to be significantly more affordable and offered immediate results as compared to serum cotinine testing.

Figure 3. Expired CO level compared to serum cotinine levels in patients who tested positive for serum cotinine.

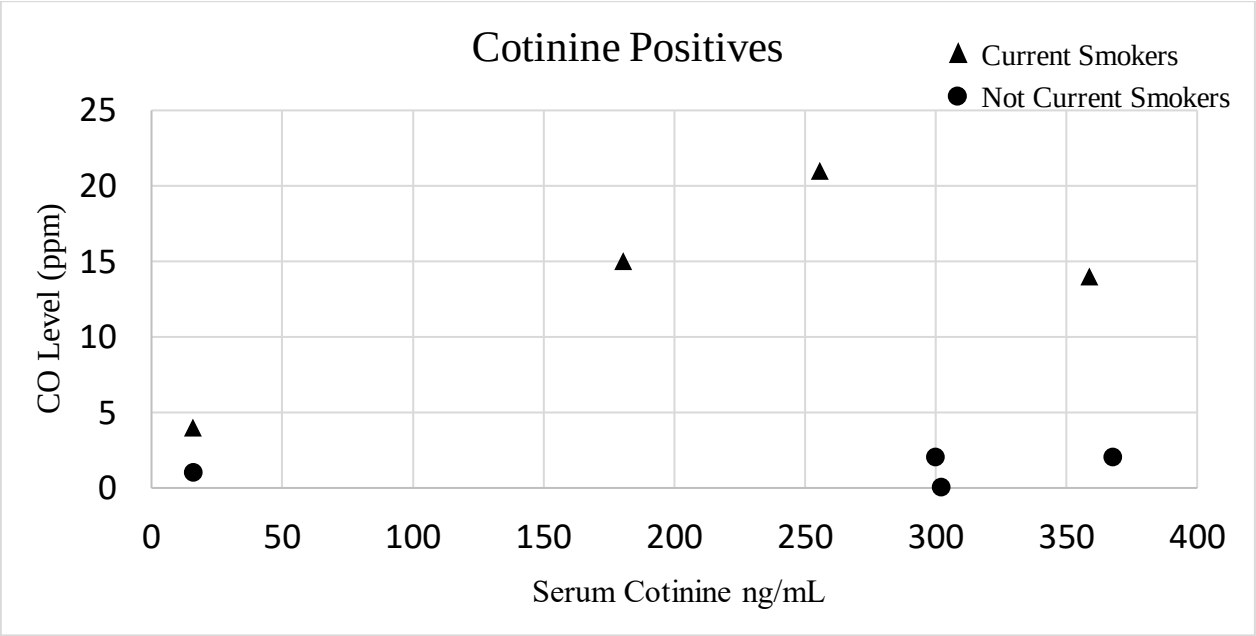
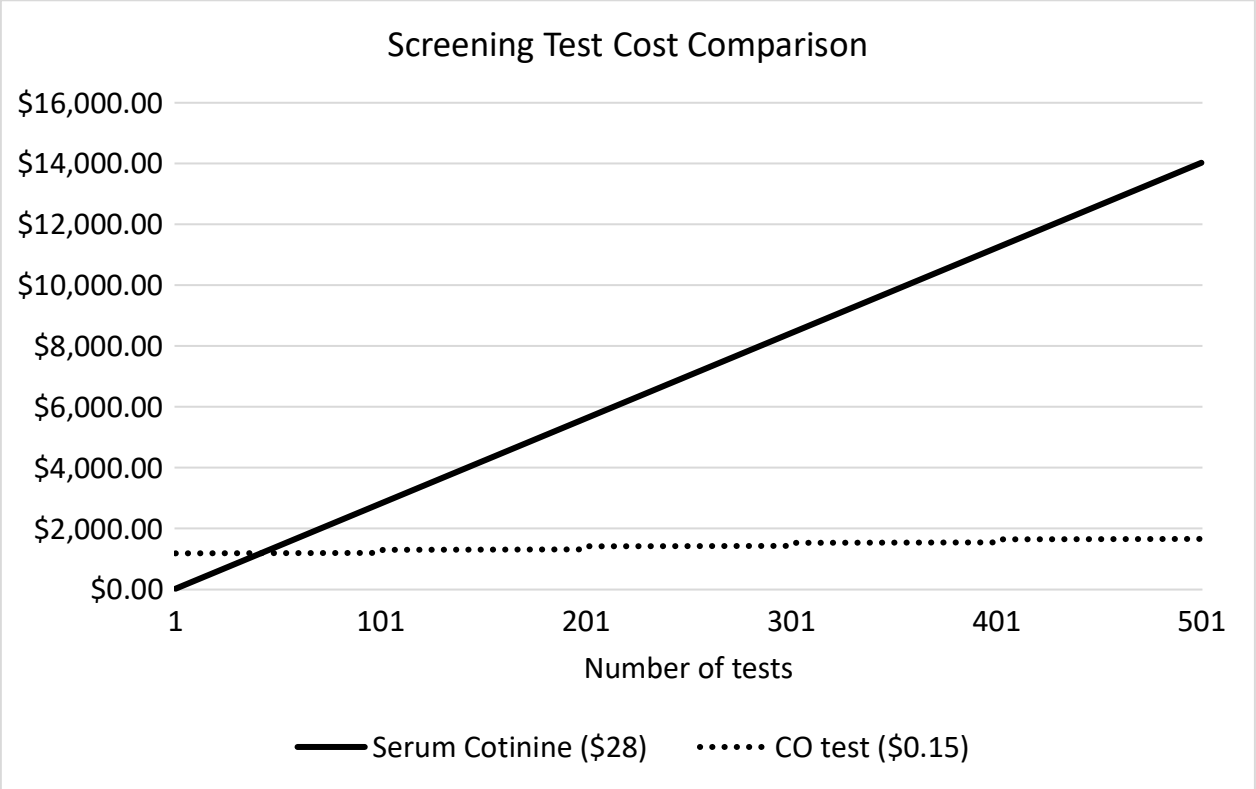


Figure 4. Cost comparison of using serum cotinine or expired carbon monoxide tests as a screening test.



Tobacco use is significantly greater among the veteran population for nearly all forms of tobacco including e-cigarettes, cigars, and chew tobacco; yet, discrepancy between self-reported smoking and results from biochemical testing is significantly higher than in the general population, presenting a unique challenge and opportunity for health care providers[8]. Our study showed that combining eCO testing with SRS as a screening tool resulted in a high level

of accuracy in determining recent cigarette use, in comparison to SRS or SC testing alone. To our knowledge, this is the first study comparing eCO testing to SC for pre-operative evaluation of cigarette use prior to elective orthopedic surgery.

eCO and SC are two very different biochemical tests for recent smoking detection, and as found in this study, have different limitations. Cotinine is a metabolite of nicotine and, with an average half-life of 16 hours, can be measured in the saliva, urine, and blood two to three days after the use of nicotine products such as cigarettes, e-cigarettes, or smokeless tobacco. Serum levels of cotinine for daily smokers typically average from 100 to 250 ng/mL, while levels in those exposed to secondhand smoke are usually <3 ng/mL. [14] While SC testing has the benefit of detecting recent cigarette use for up to several days, it can be falsely elevated in those using NRT, e-cigarettes, or other tobacco products during smoking cessation, as evidenced by four Not Current Smokers in our cohort.

Conversely, carbon monoxide is produced as a byproduct of combustion from burning organic matter, such as tobacco or marijuana. Carbon monoxide can be measured in exhaled breath (eCO) in parts per million based on the conversion of CO to carbon dioxide (CO_2) over a catalytically active electrode, with a level of >6ppm being strongly associated with recent smoking. [16] As CO has a half-life of 4.5 hours in the blood, eCO levels can vary depending upon pulmonary ventilation, daily consumption of cigarettes or marijuana, and duration of smoking, and are typically limited in their detection within 24 hours after smoking. [12, 16-18] Because of this, detection of occasional or less frequent smoking is limited. In our cohort, one patient who had reported quitting cigarettes 2-5 years ago but also reported smoking marijuana daily had a positive CO test of 8ppm and an undetectable SC, underscoring the potential for false positive results. CO is also produced endogenously during oxidative stress and inflammation, thus the presence of respiratory diseases, such as COPD or asthma, can elevate eCO levels and confound testing results. [12] However, in our cohort no patients with co-morbid lung disease had an eCO test >6ppm.

Using biochemical testing to verify pre-operative SRS is commonly practiced in orthopedics and may be required for reimbursement. A level 1 diagnostic study of 136 pre-operative orthopedic patients showed that patients with a history of smoking were at elevated risk for underreporting, continued smoking, and, in patients who smoked preoperatively, were at high risk for continuing their habit. [19] This underscores the importance of biochemical testing; however, laboratory results are often not available during the clinic visit. In our lab, the SC nicotine results are available within 4 to 7 days. If labs are drawn on the same day as their clinic appointment, there will not be a result, which can lead to additional clinic visits to discuss results and provide care.

Of additional interest is the cost-savings associated with use of a point-of-care devices such as the Smokerlyzer® Micro EC50. Although there is an initial cost to purchase a hand-held device, as well as maintenance, the cost per use is essentially the cost of the disposable straw, which was 15 cents in our study, as compared to the laboratory cost of $28 for a single serum cotinine test. We had a break-even point for cost after the 42nd test, and subsequently found a cost savings of approximately $12,390.00 after only 500 tests. G

Recent literature highlights the benefits of point-of-care biochemical testing for cigarette use. Salandy et al. evaluated the use of a point-of care urine cotinine test as compared to traditional SC testing and found similar effectiveness. [20] They found the urine dipstick test to be a quick, easy, accurate and cost-effective screening tool which was less expensive, non-inferior to SC testing, and provided results within minutes. They noted, however, that it was not possible to confirm whether patients with a positive assay were

under-reporting their smoking, as cotinine levels can be raised for other reasons. [20] We also found false positive results with nicotine testing when a patient was on NRT or using other nicotine products despite abstaining from cigarette use.

Matuszewski et al. reported that use of eCO monitors resulted in a willingness to quit smoking in 71% of orthopaedic trauma patients, and 40% requested enrollment in smoking cessation programs. [21] They attributed this impact to the effectiveness of the 'teachable moment' afforded by point-of-care testing, as well as immediate results with visual and auditory feedback which have been shown to produce a heightened response. Their study did not include a control group or evaluate the accuracy of eCO as a biochemical test.

Rothschild-Pearson et al. published an abstract describing the use of using an eCO test to evaluate smoking habits in pre-operative orthopedic patients. [22] They reported using a cutoff of 7pmm resulted in a sensitivity of 65.4% and a specificity of 96.1%, whilst a cutoff of 10 ppm gave a sensitivity of 57.6% and specificity of 99.2%.[22] Due to the specificity, speed, and cost-effectiveness, they recommended the routine use of the test to identify patients at risk from smoking-related complications in pre-assessment clinics. Although their study did not state the cost-savings compared to SC testing, our cost analysis showed a cost savings of $12,390.00 after a sample size of just 500 tests. Our study also reported similar results of the eCO test (a sensitivity of 75% and specificity of 98%) but superior results when SRS was used as a 'rule-in' test in combination with the eCO test (sensitivity of 100%, a specificity of 98%, a positive predictive value of 95% and a negative predictive value of 100%).

Limitations

Limitations of our study included lower than expected enrollment, lower than expected recruitment of daily or weekly smokers, discrepancies in test results related to patient use of other products such as marijuana, e-cigarettes, and smokeless tobacco, and lack of post-operative or long term follow up data. Although an apriori calculation was performed with an anticipated enrollment of nearly 250 patients, the recruitment was stopped early due to the Covid-19 pandemic which greatly limited our sample size for analysis. Additionally, because many patients are screened for smoking prior to referral for elective orthopedic surgery, our sample population had significantly fewer daily and weekly smokers than reported in the VA patient population, leaving only 4 current smokers for analysis. Additionally, our clinic did not uniformly recruit patients on a regular basis, leaving 89 eligible patients unapproached. Undoubtedly this affected the power of our study; however, our test results maintained high levels of sensitivity and specificity despite this.

The strengths of our study included the prospective nature, a published protocol prior to patient enrolment, [23] and inclusion of both eCO and SC testing to differentiate cigarette smoking from NRT or other forms of nicotine. The use of both biochemical tests was able to highlight the inherent limitations of both eCO and SC testing; notably the 4 Not Current Smoking patients who tested positive on SC but negative on eCO testing, and the 1 marijuana smoker who tested positive on eCO but negative on SC. Additionally, our study highlighted the complexity of some patients who are in the midst of smoking cessation and on NRT therapy, where dual testing may be needed to establish smoking status.

Conclusion

Our findings show that eCO testing differentiates self-reported Current Smokers from Not Current Smokers who use NRT or other nicotine products, while maintaining a high level of accuracy and reliability. The eCO test produces immediate results in clinic but has false positivity with marijuana smoking and may have limitations of detecting recent smoking beyond 24-48 hours. eCO combined with a smoking history can confidently be used as an initial pre-operative screening tool, with the added benefit

of immediate results and substantial cost-savings.

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