Nicotinamide for Keratinocyte Carcinoma Chemoprevention: A Nationwide Survey of Mohs Surgeons

We read with interest the article by Desai and colleagues[1] which reports results of a survey of members of the American College of Mohs Surgeons regarding nicotinamide and its prescribing practices. Of the 160 respondents, 20 percent had recommended nicotinamide to more than 100 patients in the past year, 70.0% considered nicotinamide for patients who develop at least 2 keratinocyte cancers (KCs) over 2 years and 44.4% frequently or always recommend nicotinamide to organ transplant recipients for squamous cell carcinoma (SCC) prevention. Nicotinamide is not formally recommended for chemoprevention of skin cancer. We are concerned that this use of nicotinamide may be ill advised because of potential systemic adverse effects, potential increased risk of aggressive KCs, and nicotinamide's modest efficacy in the prevention of KC.

Desai and colleagues mention previously reported associations of nicotinamide supplementation with increased all-cause mortality in cardiovascular patients as well as with increased insulin resistance, both relevant to the older population at a particular risk for KC. There has also been concern raised regarding an increased risk of infections associated with the use of nicotinamide.[2]

The efficacy of nicotinamide in KC prevention has been modest (23%).[3] In a randomized trial, overall rates of KC were indeed reduced with nicotinamide, but the proportions of aggressive basal cell carcinoma (BCC) and aggressive SCC were higher in the nicotinamide group, although numbers were small and hence of uncertain import. Notably, nicotinamide appeared more effective at preventing superficial BCC than nodular BCC.[4] These results suggest that nicotinamide may potentially play a role in promoting more aggressive forms of KC, and further research is warranted to elucidate this relationship.

Instead of nicotinamide, more effective forms of chemoprevention are needed. For example, 5-flurouracil cream has been associated with a 75% reduction (95% CI, 35%–91%) of SCC risk at 1 year in a randomized trial, although this effect was not sustained beyond 1 year, and no effect was observed for BCC.[5]

We thank the authors for their report of these practices among some Mohs surgeons and hope that these results direct future research into the long-term safety of nicotinamide as well as other potential KC chemoprevention strategies.

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Mohs Surgical Site Infection Rates and Pathogens for the Mask-Covered Face During the COVID-19 Pandemic Versus the Pre-COVID Era

During the COVID-19 pandemic, face masks have become a vital tool in limiting the transmission of the virus. Mask use is currently recommended by the Centers for Disease Control and Prevention, World Health Organization, and many local public health authorities. Although beneficial, face masks are associated with facial skin adverse reactions, including worsening of pre-existing dermatoses, pruritus, and abrasions.[1,2] Patients use masks made from a variety of materials, all of which cover the lower and mid face. The significance of this alteration in the epithelial environment regarding the surgical site infection (SSI) is not known.

The primary objective of this study was to identify shifts in SSI rates and causative microorganisms after Mohs micrographic surgery (MMS) on mask-covered areas during the COVID pandemic compared with the pre-COVID era.

Methods

Design, Setting, and Participants

Patient data were collected by the retrospective chart review of all MMS cases performed by a single Mohs college fellowship–trained dermatologic surgeon at an academic medical center outpatient clinic. Data were obtained retrospectively, in an identical manner, from two 7-month time periods, with August 6, 2019, to March 21, 2020, representing the prefacial mask "control" period and May 6, 2020, to December 21, 2020, representing the COVID pandemic with universal facial mask wearing. May 6, 2020, was selected as the start date of the facial mask period because the academic hospital system and all affiliates instituted a universal mask requirement for all healthcare workers, patients, and visitors at that time.

Surgical site infection was defined as a diagnosis of wound infection by the surgeon in addition to the isolation of pathogenic organisms from the bacterial culture of the operative wound within the first 30 days after surgery. Facial masked sites were defined as the nose, nasolabial fold, cutaneous or mucosal lip, and chin. Cheek locations were not included because of variability in lateral facial coverage between different types of masks (Figure 1). The exclusion criteria for SSIs included cultures from wounds not related to MMS, repeat cultures on the same patient within the study period, repeat cultures from infections initially occurring before the study period, and cultures which grew normal skin flora.

Statistical Analysis

The study protocol was exempted by the Washington University Institutional Review Board. Differences between the two cohorts were compared using the chi-square and *t*-test. $p < .05$ was considered significant. Statistical analysis was performed using SPSS v26 (IBM, Armonk, NY).

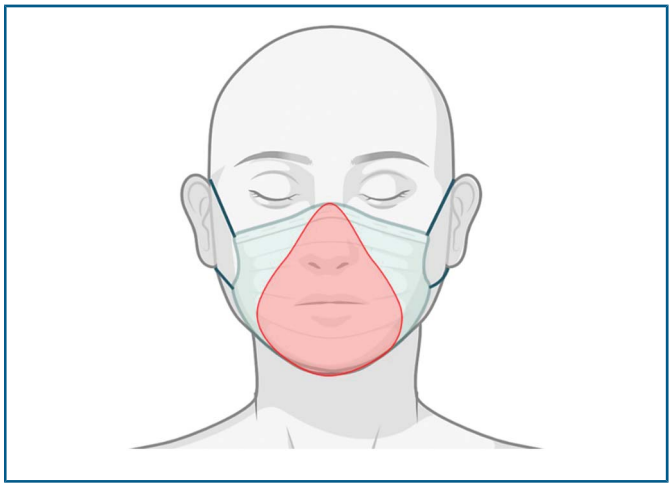

Figure 1. Facial locations included under the mask location definition highlighted in red. Cheek locations were not included because of variability in lateral facial coverage between the different types of masks. Created with BioRender.com.

Results

Eight hundred nineteen MMS cases were performed on 754 patients. Three hundred four cases were performed pre-COVID and 515 during COVID. Sixty-nine cases (22.7%) were performed on mask-covered facial locations pre-COVID with 100 such cases (19.4%) performed during COVID. For mask-covered sites, there were no significant differences in baseline demographics, skin cancer type, or surgical repair technique pre-COVID versus COVID ($p < .05$ for all) (Table 1).

Sixteen SSIs occurred, with 7 (2.3%) and 9 (1.7%) occurring during the premask and mask periods, respectively. For mask-covered locations, infection occurred in 0/69 cases pre-COVID (0%) versus 4/100 cases during COVID (4%) ($p = .09$) (Table 1). Mask location SSIs composed 44.4% of total infections during COVID. All mask location SSIs during the mask period were caused by gram-negative organisms, with *Pseudomonas aeruginosa* ($n = 2$) and *Enterobacter* ($n = 2$) species isolated. Three of 7 SSIs (42.9%) in the pre-COVID period were caused by gram-negative bacteria versus 7 of 9 SSIs (77.8%) during COVID ($p = .15$) (Table 1). Antibiotic prophylaxis management did not change during the 2 periods.

Seven infections occurred in nonmask locations pre-COVID (100%) and 5 occurred in nonmask locations during COVID (55.5%) (Table 1). Causative organisms for nonmask location infections pre-COVID included methicillin-sensitive *Staphylococcus aureus* ($n = 2$), mixed aerobic and anaerobic bacteria ($n = 2$), *P. aeruginosa* ($n = 2$), *Bacteroides fragilis* ($n = 1$), *Enterobacter cloacae* ($n = 1$), and *Escherichia coli* ($n = 1$). Causative organisms for nonmask location infections during COVID included methicillin-sensitive *S. aureus* ($n = 2$), *E. coli* ($n = 1$), *P. aeruginosa* ($n = 1$), *Klebsiella oxytoca* ($n = 1$), and *Proteus mirabilis* ($n = 1$).

Discussion

Facial masks are a vital tool in limiting the transmission of severe acute respiratory syndrome coronavirus 2. Widespread, the regular use of face masks represents a significant behavioral change for most dermatologic surgery patients. At our institution, a mask requirement for health care workers and patients was issued on May 6, 2020, in addition to mandates issued by local public health authorities. After the universal mask mandate, we observed an increased rate of SSIs at mask-covered areas of the face compared with a similar time period before widespread facial mask usage. Interestingly, a higher proportion (77.8% vs 42.9%) of gram-negative bacterial infections was identified during the COVID period, and either *P. aeruginosa* or *Enterobacter* species were isolated in all mask location cases.

Although relatively rare, SSIs are the most common complication after MMS, with previously reported infection rates ranging from 0.4% to 2.5%.[3,4] Known potential risk factors for post-MMS infections include wedge excisions of the lip, flaps performed on the nose, as well as skin grafting and pre-existing patient comorbidities.[5] However, in this study, repair types were similar for surgical defects within

TABLE 1. Demographic, Procedure, and Surgical Site Infection Data

	All Cases			Mask Location Cases		
	Pre-COVID (n = 304)	COVID (n = 515)	p*	Pre-COVID (n = 69)	COVID (n = 100)	p*
Age (median)	67	70	.15	63	66	.09
Gender			.02			NS
Male	167 (55%)	325 (64%)		28 (41%)	49 (49%)	
Female	137 (45%)	187 (36%)		41 (59%)	51 (51%)	
Cancer type			NS			NS
BCC	178 (59%)	295 (57%)		58 (84%)	77 (77%)	
SCC/SCC in situ	124 (40%)	213 (42%)		11 (16%)	23 (23%)	
Others	2 (1%)	6 (1%)		0 (0%)	0 (0%)	
Location			NS			
Mask location	69 (23%)	100 (19%)		—	—	
Nonmask location	235 (77%)	415 (81%)		—	—	
Mask location			NS			NS
Nose	57 (19%)	79 (15%)		57 (83%)	79 (79%)	
Nasolabial fold	2 (1%)	3 (1%)		2 (3%)	3 (3%)	
Lip	7 (2%)	14 (3%)		7 (10%)	14 (14%)	
Chin	3 (1%)	4 (1%)		3 (4%)	4 (4%)	
Repair type			NS			NS
Second intention	20 (7%)	12 (2%)		4 (6%)	1 (1%)	
Linear closure	218 (72%)	395 (77%)		34 (49%)	51 (51%)	
Flap or graft	66 (22%)	108 (21%)		31 (45%)	48 (48%)	
Surgical site infections†	7 (2%)	9 (2%)	NS	0 (0%)	4 (4%)	.09
Gram-negative infection	3/7 (43%)	7/9 (78%)	NS	0 (0%)	4/4 (100%)	.09
Others	4/7 (57%)	2/9 (22%)		0 (0%)	0 (0%)	

*p-values reported as nonsignificant (NS) if $p > .15$. Values reported for $p \leq .15$.
†Bacterial culture data reported as a proportion of cases with surgical site infection.

masked sites during both the premask and mask periods. In addition, there were no identified comorbidities among the patients who developed masked site SSIs. Antibiotic prophylaxis management did not change during the 2 periods.

Although the underlying mechanisms remain unclear, our findings suggest that the occlusive environment generated by mid and lower face masking may have potential implications, not only for the incidence of SSIs but also for the etiologic bacterial agents as well. The increased propensity toward gram-negative infections, whether related to resident oral flora, mask-mediated abrasions, or simply frequently used but infrequently laundered facial masks, may require alternative considerations in postoperative antimicrobial management. As facial masks will likely remain necessary for the foreseeable future, larger studies are needed to further elucidate the potential role of facial masking on SSIs.

Limitations

Limitations of this study include the small sample size and variability in the patient mask type and wearing habits. The potential for selection bias and increased vigilance in tracking SSIs on mask-covered sites during the COVID period must be considered; however, the retrospective nature of this study and lack of change in clinical practices pertaining to SSI diagnosis during the pre-COVID and COVID periods greatly mitigate this risk.

Conclusion

In this retrospective study of 819 MMS cases, there was an increase in the rate of SSI on the mask-covered face during the COVID-19 pandemic that approached statistical significance (0 vs 4%). All mask-covered face infections were caused by gram-negative bacteria. The mechanism underlying these findings, whether directly mask related or secondary to changes in patient behaviors, remains unclear. Larger studies are needed to further elucidate the potential role of facial masking on SSIs.

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Patient Discomfort During Mohs Surgery Compared with Other Common Medical Procedures

Nonmelanoma skin cancer (NMSC) in the most common type of cancer in the United States, far surpassing all other types of malignancies. With rising incidence of NMSC, there is an increase in Mohs micrographic surgery (MMS) as a modality to treat these cancers.[1] Although the Mohs Appropriate Use Criteria guide which tumors are appropriate, medical decision-making is more complex and takes into account patient preferences and tolerability of the treatment options.[2] The purpose of this study is to evaluate how patients' level of discomfort during MMS compares with other routine medical procedures.

This prospective, cross-sectional, study was approved by the University of Nebraska Medical Center Institutional Review Board. Patients were recruited at the time of their MMS at a university-based dermatology clinic with 2 dermatologic surgeons over a 7-month period. Two hundred seventy-three consecutive patients were approached for participation with 227 agreeing to participate on the day of surgery (participation rate of 83%). Participants were then contacted by telephone at 1 month postoperatively; if unable to reach after 2 attempts, an email was sent if available. Of this cohort, 160 were able to be reached by telephone at 1 month follow-up and included in this analysis (survey completion rate of 70%). Patients were asked about the level of discomfort they experienced during their MMS as well as with other routine medical procedures (Table 1). Patients rated discomfort on a 4-point Likert Scale from "very much" to "not at all." Statistical analyses were performed using chi-squared in SPSS to compare discomfort levels. Patients' willingness to undergo MMS in the future, if medically appropriate, was also assessed.

Most patients 141/160 (88%) indicated they experienced "none at all" or "a little bit" discomfort during MMS. Only 4% of patients undergoing MMS reported experiencing "very much" discomfort. There was no significant difference between those who experienced "quite a bit" or "very much" (19/160, 12%) discomfort with MMS compared with other common procedures, including teeth cleaning (12/150, 8%), prostate examination (7/72, 10%), or mammogram (12/63, 19%). Interestingly, a significantly larger proportion of patients experienced "very much" or "quite a bit" discomfort with liquid nitrogen therapy (25/97, 26%) compared with MMS ($p = .004$, Table 1). Fewer patients reported "quite a bit" or "very much" discomfort with colonoscopy than they did with MMS ($p = .004$). There was no significant difference in reported discomfort with MMS with respect to surgical and demographic factors such as final defect size, previous MMS, anticoagulation status, diabetes, quality of life index, smoker, age, and sex. When patients were asked if they would be willing to undergo Mohs in the future if recommended by their physician, 97% reported they would have no hesitations.

TABLE 1. Discomfort During Common Medical Procedures

	Medical Procedure					
	MMS	Liquid Nitrogen	Colonoscopy	Teeth Cleaning	Prostate Examination	Mammogram
Total responses, *n*	160	97	125	150	72	63
Discomfort level, *n* (%)						
Very much	7 (4)	5 (5)	4 (3)	3 (2)	4 (6)	1 (2)
Quite a bit	12 (8)	20 (21)	3 (2)	9 (6)	3 (4)	11 (18)
A little bit	77 (48)	48 (50)	33 (26)	78 (52)	33 (46)	37 (59)
Not at all	64 (40)	24 (25)	85 (68)	60 (40)	32 (44)	14 (22)