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Effect of Microdoses of Incisional Antibiotics on the Rate of Surgical Site Infections in Skin Cancer Surgery
A Randomized Clinical Trial

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IMPORTANCE Surgical site infections (SSIs) represent a costly and preventable complication of cutaneous surgery. However, there is a paucity of randomized clinical trials investigating antibiotic prophylaxis for reducing SSIs in skin cancer surgery, and evidence-based guidelines are lacking. Incisional antibiotics have been shown to reduce the rate of SSIs before Mohs micrographic surgery, but this represents a small subset of skin cancer surgery.

OBJECTIVE To determine whether microdosed incisional antibiotics reduce the rate of SSIs before skin cancer surgery.

DESIGN, SETTING, AND PARTICIPANTS In this double-blind, controlled, parallel-design randomized clinical trial, adult patients presenting to a high-volume skin cancer treatment center in Auckland, New Zealand, for any form of skin cancer surgery over 6 months from February to July 2019 were included. Patient presentations were randomized to one of 3 treatment arms. Data were analyzed from October 2021 to February 2022.

INTERVENTIONS Patients received an incision site injection of buffered local anesthetic alone (control), buffered local anesthetic with microdosed flucloxacillin (500 µg/mL), or buffered local anesthetic with microdosed clindamycin (500 µg/mL).

MAIN OUTCOMES AND MEASURES The primary end point was the rate of postoperative SSI (calculated as number of lesions with SSI per total number of lesions in the group), defined as a standardized postoperative wound infection score of 5 or more.

RESULTS A total of 681 patients (721 total presentations; 1133 total lesions) returned for postoperative assessments and were analyzed. Of these, 413 (60.6%) were male, and the mean (SD) age was 70.4 (14.8) years. Based on treatment received, the proportion of lesions exhibiting a postoperative wound infection score of 5 or greater was 5.7% (22 of 388) in the control arm, 5.3% (17 of 323) in the flucloxacillin arm, and 2.1% (9 of 422) in the clindamycin arm ($P = .01$ for clindamycin vs control). Findings were similar after adjusting for baseline differences among arms. Compared with lesions in the control arm (31 of 388 [8.0%]), significantly fewer lesions in the clindamycin arm (9 of 422 [2.1%]; $P < .001$) and flucloxacillin (13 of 323 [4.0%]; $P = .03$) arms required postoperative systemic antibiotics.

CONCLUSIONS AND RELEVANCE This study evaluated the use of incisional antibiotics for SSI prophylaxis in general skin cancer surgery and compared the efficacy of flucloxacillin vs clindamycin relative to control in cutaneous surgery. The significant reduction in SSI with locally applied microdosed incisional clindamycin provides robust evidence to inform treatment guidelines in this area, which are currently lacking.

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Visual Abstract

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Skin cancer represents the most common cancer worldwide,[1] and surgical excision is the most common treatment approach.[2] However, surgical site infections (SSIs) can complicate cutaneous surgery procedures.[3] Infections are painful, delay recovery, increase resource requirements (eg, follow-up visits and secondary interventions, including systemic antibiotics, wound debridement, topical wound care, and secondary wound closure), and are associated with a worse cosmetic outcome.[4] It has been estimated that up to 60% of SSIs could be prevented with evidence-based measures.[5]

High-quality evidence supports the use of prophylactic antibiotics in other surgical domains, including colorectal and orthopedic surgery.[6-8] Conversely, literature regarding prophylactic systemic antibiotics in other clean soft tissue surgery (eg, breast, thyroid, hernia) is controversial and less conclusive or unsupported.[9-11] However, there is a lack of randomized clinical trial evidence to determine the role of antibiotic prophylaxis for reducing SSIs in skin cancer surgery. All 3 existing consensus statements—from the World Health Organization,[12] the US Centers for Disease Control and Prevention,[13] and the joint American College of Surgeons and Surgical Infection Society[14]—lack guidelines for SSI prevention specific to cutaneous surgery.

Systemic antibiotic prophylaxis is not usually recommended before clean cutaneous surgery.[15] Furthermore, systemic antibiotic utilization without clear indication constitutes poor antibiotic stewardship and contributes to antimicrobial resistance.[16] Localized delivery of microdosed incisional antibiotics represents an alternative to systemic antibiotics and has been shown to significantly reduce the rate of SSIs in patients undergoing Mohs micrographic surgery.[17,18] Mohs surgery reflects a relatively small proportion of skin cancer management and is characterized by unique procedural features that limit extension to general skin surgery, including longer duration of open wounds subject to multiple rounds of incisional injections prior to definitive closure and disproportionate application on the head and neck. While original and well conducted, these studies are also 2 decades old without published replication and did not include direct comparison between antibiotic drug classes. By far the most common form of skin cancer management worldwide is surgical excision with immediate closure. To our knowledge, there are no generally applicable or contemporary randomized clinical trials reporting evidence for prophylactic antibiotics (either systemic or incisional) for significantly reducing SSIs in general skin cancer surgery.

Localized administration of microdosed antibiotics within local anesthetic has a number of advantages. These include immediate and targeted delivery to the operative site, no additional punctures or injection volume requirements, guaranteed compliance with therapy, substantial reduction in systemic antibiotic selection pressure (particularly within gut flora), minimized risk of drug interactions, low cost, and a feasible and scalable applicability to high-volume skin cancer treatment centers.[19]

The aim of the current Prophylactic Incisional Antibiotics in Skin Cancer Surgery (PICASSo) trial was to evaluate the safety and efficacy of a single preoperative microdose of locally infiltrated flucloxacillin or clindamycin for reducing SSIs in cutaneous surgery for skin cancer. We hypothesized that a significant reduction in SSI could be demonstrated with a single microdose of locally applied antibiotic relative to controls without adverse effects.

Key Points

Question What effect does incision-site injection of microdosed antibiotics have on the rate of surgical site infection (SSI) before skin cancer surgery?

Findings In this randomized clinical trial, among 681 patients undergoing skin cancer surgery, intra-incisional microdosed clindamycin delivered along with local anesthetic significantly reduced the rate of SSI (defined as a postoperative wound infection score of 5 or more at any postoperative visit) compared with control (local anesthetic alone). In contrast, intra-incisional microdosed flucloxacillin had no significant effect on the SSI rate.

Meaning These data provide robust evidence to inform guidelines regarding SSI prophylaxis before skin cancer surgery, which are currently lacking.

Methods

Trial Design

This prospective, double-blind, parallel-design randomized clinical trial was conducted at one of the highest-volume skin cancer treatment centers in New Zealand (Middlemore Hospital, Auckland, New Zealand) over a 6-month period (February to July 2019). The study protocol was approved by the New Zealand Central Health and Disability Ethics Committee[15]; the study protocol can be found in Supplement 1, and the statistical analysis plan can be found in Supplement 2. Written informed consent was obtained preoperatively in parallel with routine surgical consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Participants

All adult patients presenting for skin cancer surgery under local anesthetic were eligible. Exclusion criteria were allergies to both penicillin and clindamycin, preoperative systemic intake of any antibiotic within 7 days before surgery, or inability to return for face-to-face postoperative wound assessment. Patients could be enrolled and randomized more than once if they underwent additional procedures within the study period, assuming all eligibility criteria remained met. Race and ethnicity were recorded according to patient self-identification, with options defined by the investigator as follows: Asian; European; Māori; Middle Eastern, Latin American, or African; and Pasifika.

Study Treatments

Patient presentations were randomized to receive incision site injection of buffered local anesthetic alone (control group;

Table 1. Postoperative Wound Infection (POWI) Scale[a]

Score	Condition
0	Normal healing
1	Normal healing but with 1 of the following signs of infection: erythema, edema, or increased pain
2	Normal healing but with 2 of the following signs of infection: erythema, edema, or increased pain
3	Normal healing but with 3 of the following signs of infection: erythema, edema, and increased pain
4	Hemoserous discharge combined with 2 of the following: erythema, edema, or increased pain
5	Pus combined with 1 of the following: erythema, edema, or increased pain; or hemoserous discharge combined with all of erythema, edema, and increased pain
6	Pus combined with 2 of the following: erythema, edema, or increased pain
7	Pus combined with all of erythema, discharge, and increased pain

[a] The POWI scale as defined by Heuther et al.[15]

lidocaine, 1%, plus adrenaline 1:100 000 standard solution [AstraZeneca] buffered 1:10 with sodium bicarbonate, 8.4% [Hospira]), buffered local anesthetic with microdosed flucloxacillin (500 µg/mL; Pfizer), or buffered local anesthetic with microdosed clindamycin (500 µg/mL; Pfizer). Antibiotic concentrations were extrapolated from existing data on peak serum levels with standard systemic dosing and designed to ensure minimum inhibitory concentrations for common skin flora.[20,21] Randomizations were made (1:1:1) using a custom database running a blinded schedule that managed randomization with random block sizes. Patients randomized to the flucloxacillin arm who had a penicillin allergy were automatically reallocated to the clindamycin arm (also blinded, assuming no clindamycin allergy), and patients randomized to clindamycin who had a clindamycin allergy were automatically reallocated to the control arm.

Lesions were treated using a blinded prefilled infiltration syringe corresponding to allocation that had been prepared by a trial pharmacist in 10-mL aliquots. To promote blinding integrity, syringes were labeled in a random order within each batch. Syringes were stored at 4 °C, protected from light, and replaced with a fresh batch every 48 hours. Patients and all members of operative and follow-up teams were blinded to allocation until study conclusion. If more than 1 site was treated, the original allocation arm was maintained for that patient presentation. Participants enrolled more than once were independently randomized at each presentation. Any deviations to treatment received compared with protocol were recorded.

Procedures and Assessments

Surgical excision, wound closure/reconstruction, and postoperative management were performed according to standard of care. Patients were monitored for adverse reactions perioperatively and questioned about sensitivity reactions at each follow-up visit. Safety was monitored by an independent data monitoring committee throughout the trial.

All assessments were performed by clinical staff masked to allocation. All participants were invited for standardized postoperative assessment by a consistent trial nursing team between 7 and 21 days postoperatively. Additional assessments were performed opportunistically during any further encounters (for example, in case of wound healing concerns) as required. Each assessment included a patient questionnaire eliciting any adverse effects experienced, adverse events, and/or antibiotics prescribed for any reason (eMethods in Supplement 3). A standardized wound assessment was also performed for each operative site using a previously validated postoperative wound infection (POWI) scoring system (**Table 1**).[18] When more than 1 postoperative assessment was made, the highest POWI score recorded for each lesion was used for analysis. For wounds closed directly, length of closure was recorded.

Patient-specific factors were recorded for each participant, including medical immunosuppression, diabetes, history of prior SSI, and smoking status. In any case of overt infection, culture swabs were obtained for microbiological analysis to guide tailored antibiotic treatment.

Outcomes

The primary end point was the rate of SSI (defined as POWI score of 5 or more at any postoperative assessment), calculated as the number of lesions with SSI per total number of lesions in the group. Secondary end points included safety and patient, lesion, and infection factors associated with SSI.

Sample Size

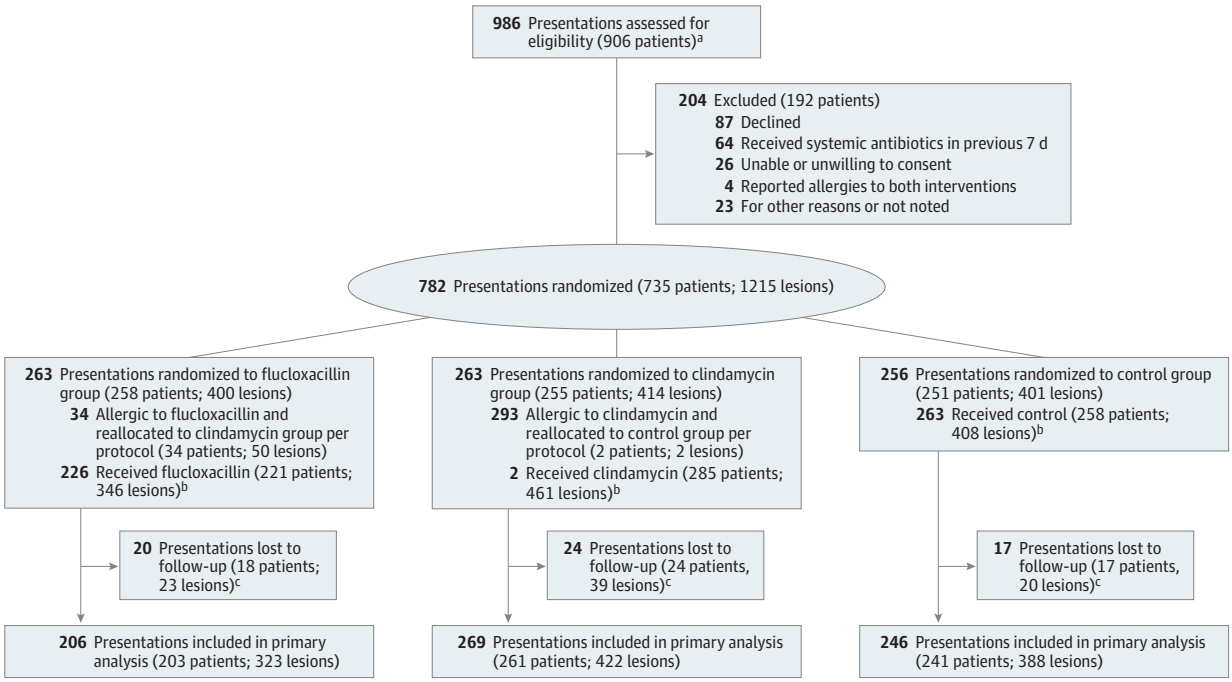
A prerecruitment power analysis calculation was performed based on a retrospective analysis of skin cancer operations undertaken at the same unit over a 6-month period between February and July 2015. In total, 2088 lesions were excised from 938 patients in 1053 procedures; rates of documented and possible SSI were 3.3% and 11.3%, respectively. These rates were averaged to estimate the expected SSI rate (7%); the anticipated SSI rate in the treatment group was estimated to be 2%. To achieve 80% power with a 5% level of significance (to which a false discovery rate correction was applied to allow comparison between each active treatment and control), it was calculated that 987 lesions would need to be recruited.

Statistical Analysis

Outcomes analysis was performed on all patients who had at least 1 postoperative assessment in both the intention-to-treat (per protocol) population and on the basis of actual treatment received (as treated). Descriptive statistics (means with SD and ranges with ranges and IQRs) were used to describe continuous variables. Categorical measurements are reported as counts and frequencies of nonmissing observations and proportion in each valid category.

The multinomial counts for POWI as well as the binomial counts for SSI were analyzed with (multiple) logistic regression using the lme4 package,[22] with treatment as a fixed model term. Residual analysis was done using the DHARMAa package. A mixed-effects model with patient identifier as the random term was compared with the model without a random term. The models without random effects had lower Akaike information criterion values as well as nonsignificant model assumptions.[23] The random term was therefore dropped in the final analysis.[24] Pairwise comparisons were calculated after

Figure 1. CONSORT Diagram



[a] Some patients presented more than once over the study period and were therefore eligible for enrollment and randomization on more than 1 occasion. These patients could be randomized to different treatment arms at each presentation.

[b] A total of 11 lesions (11 of 1215 [0.9%]; 9 patients in 9 presentations) erroneously received a treatment that differed from the randomized allocation; of these, 7 (7 of 1133 lesions [0.6%]; 5 patients in 5 presentations) completed follow-up and were included in the as-treated analysis.

[c] Follow-up included patients who completed at least 1 postoperative assessment.

the model fit using the estimated parameters and covariance matrices assuming multivariate normal distributions. Statistical significance was defined as a *P* value less than .05, and all *P* values were 2-tailed. Statistical analyses were performed using R version 4.0.3 (The R Foundation).

Results

Study Population and Treatments

A total of 906 patients were screened over 986 presentations, and 735 patients (782 presentations; 1215 lesions) were randomized and completed treatment (**Figure 1**). Some patients presented more than once and were assessed for eligibility at each presentation, with 28 patients randomized to multiple treatment arms over the recruitment period (eFigure in Supplement 3). Most patients had more than 1 lesion excised per presentation (mean [SD] lesions, 1.6 [1.13]; maximum, 9 lesions).

A total of 681 patients (1133 lesions [93.3%] over 721 operative presentations) returned for at least 1 postoperative assessment and were included in outcome analyses. Of these, 413 (60.6%) were male, and the mean (SD) age was 70.4 (14.8) years. European individuals predominated overall (634 [93.1%]), followed by Pasifika individuals (15 [2.2%]), Māori individuals (14 [2.1%]), Asian individuals (12 [1.8%]), and Middle Eastern, Latin American, or African individuals (6 [0.9%]). Patient characteristics are detailed in **Table 2**. The proportion of lesions completing treatment but failing to return for postoperative assessment (ie, lost to follow-up) was 8.5% (39 of 461), 6.6% (23 of 346), and 4.9% (20 of 408) in the clindamycin, flucloxacillin, and control groups, respectively.

The rate of self-reported allergy to flucloxacillin and clindamycin was 9.5% (65 of 681) and 0.6% (4 of 681), respectively. A total of 34 patients (50 lesions) and 2 patients (2 lesions) with conflicting allergies to flucloxacillin or clindamycin were blindly reallocated to clindamycin or control, respectively, per study protocol. Five patients (7 lesions [0.6%]) were administered nonintended treatment due to protocol errors (eTable 1 in Supplement 3).

Based on actual treatment received, 388 of 1133 lesions analyzed (34.2%) were in the control group, 323 (28.5%) were in the flucloxacillin group, and 422 (37.2%) were in the clindamycin group (**Table 3**). There were more ulcerated lesions in the control arm (86 [22.1%]) than the flucloxacillin and clindamycin arms (46 [14.2%] and 52 [12.3%], respectively). The most common surgery type was excision and direct closure (approximately 80% across all arms). The mean (SD) volume injected per length of direct closure was 1.5 (1.0) mL/cm. The most common location was the head and neck (approximately 55% across arms), followed by the trunk and extremities.

SSI

Based on actual treatment received, the proportion of lesions with a clinically significant SSI (POWI score of 5 or higher at

Table 2. Participant Characteristics

Characteristic	No. (%)			
	Overall (N = 681)	Control group (n = 241)	Flucloxacillin group (n = 203)	Clindamycin group (n = 261)
Sex				
Female	268 (39.4)	84 (22.7)	86 (51.5)	105 (40.2)
Male	413 (60.6)	157 (77.3)	117 (48.5)	156 (59.8)
Age, y				
Mean (SD)	70.4 (14.8)	71.9 (14.0)	70.7 (14.5)	69.3 (15.5)
Median (IQR)	73 (62-81)	74 (65-82)	73 (64-80)	71 (60-81)
Age group, y				
<40	24 (3.5)	7 (2.9)	5 (2.5)	12 (4.6)
40-49	42 (6.2)	10 (4.9)	13 (5)	20 (8.3)
50-59	70 (10.3)	20 (7.7)	20 (8.3)	31 (15.3)
60-69	147 (21.6)	54 (22.4)	42 (20.7)	56 (21.5)
70-79	207 (30.4)	81 (39.9)	68 (26.1)	65 (27)
≥80	190 (27.9)	69 (26.4)	55 (22.8)	76 (37.4)
Missing	1 (0.1)	0	0	1 (0.4)
Race and ethnicity[a]				
Asian	12 (1.8)	6 (2.5)	4 (1.5)	2 (1)
European	634 (93.1)	223 (109.9)	192 (79.7)	243 (93.1)
Māori	14 (2.1)	4 (1.5)	3 (1.5)	7 (2.9)
Middle Eastern, Latin American, or African	6 (0.9)	0	1 (0.4)	5 (2.5)
Pasifika	15 (2.2)	8 (3.9)	3 (1.2)	4 (1.5)
Current smoker				
Yes	48 (7.0)	13 (6.4)	16 (6.6)	20 (7.7)
No	633 (93.0)	228 (94.6)	187 (92.1)	241 (92.3)
Immunosuppressed	12 (1.8)	19 (9.4)	17 (7.1)	16 (6.1)
Diabetic	47 (6.9)	13 (6.4)	16 (6.6)	20 (7.7)
History of prior SSI				
Yes	37 (5.4)	16 (6.1)	9 (3.4)	17 (6.5)
No	643 (94.4)	225 (93.4)	194 (80.5)	243 (100.8)
Missing	1 (0.1)	0	0	1 (0.5)
Self-reported drug allergy				
Flucloxacillin	65 (9.5)	NA	NA	NA
Clindamycin	4 (0.6)	NA	NA	NA
Presentations per patient				
1	644 (94.6)	NA	NA	NA
2	35 (5.1)	NA	NA	NA
3	1 (0.1)	NA	NA	NA
4	1 (0.1)	NA	NA	NA
Lesions per patient				
1	424 (62.3)	NA	NA	NA
2	153 (22.5)	NA	NA	NA
3	54 (7.9)	NA	NA	NA
4	27 (4.0)	NA	NA	NA
5	15 (2.2)	NA	NA	NA
6	2 (0.3)	NA	NA	NA
7	3 (0.4)	NA	NA	NA
8	2 (0.3)	NA	NA	NA
9	1 (0.1)	NA	NA	NA

Abbreviations: NA, not applicable; SSI, surgical site infection.

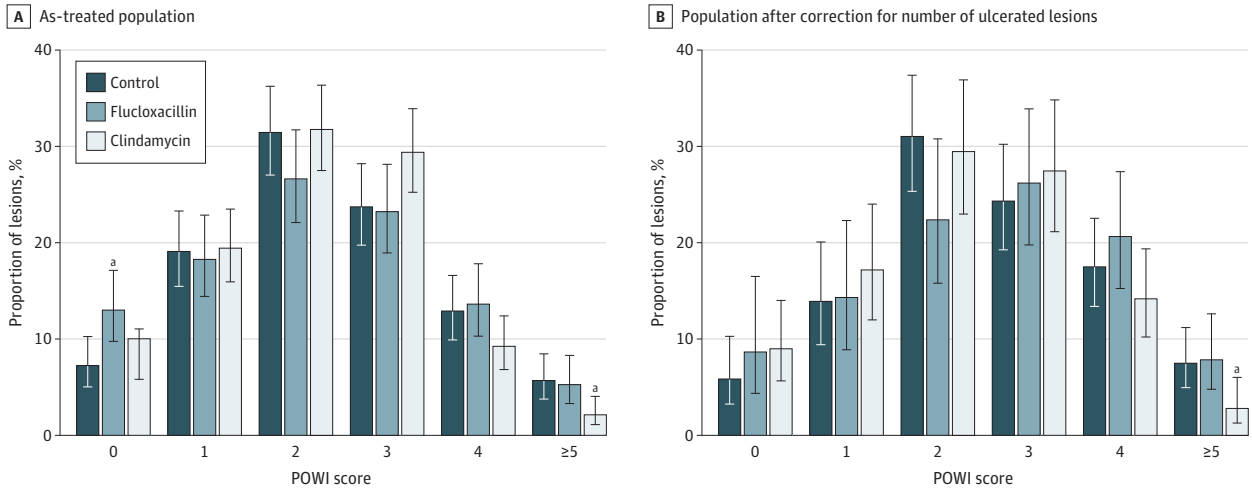
[a] Ethnicity was recorded according to patient self-identification, with options defined by the investigator as follows: Asian; European; Māori; Middle Eastern, Latin American, or African; and Pasifika.

any postoperative assessment) was 5.7% (22 of 388) in the control group, 5.3% (17 of 323) in the flucloxacillin group, and 2.1% (9 of 422) in the clindamycin group (**Figure 2**A). Results in the intention-to-treat population were almost identical (eTable 2 in Supplement 3). Statistically significant differences in SSI rate persisted after adjustment for baseline differences in lesion

Table 3. Lesion and Intervention Characteristics by Treatment Group

Characteristic	No. (%)				
	Control (n = 388 lesions)	Flucloxacillin (n = 323 lesions)	*P* value vs control	Clindamycin (n = 422 lesions)	*P* value vs control
Sex					
Female	141 (36.3)	130 (40.2)	.29	163 (38.6)	.50
Male	247 (63.7)	193 (59.8)		259 (61.4)	
Lesion ulceration					
Yes	86 (22.2)	46 (14.2)	.007	52 (12.3)	<.001
No	301 (77.6)	275 (85.1)	.01	368 (87.2)	<.001
Missing	1 (0.3)	2 (0.6)	.47	2 (0.5)	.62
Surgery type					
Excision and direct closure	319 (82.2)	255 (79.0)	.03	347 (82.2)	>.99
Length of closure, mean (SD), cm	3.5 (2.4)	3.4 (2.5)	.37	3.6 (2.4)	.27
Volume injected, mean (SD), mL	5.1 (4.6)	5.2 (4.8)	.37	5.6 (4.7)	.12
Excision and grafting	50 (12.9)	59 (18.3)	.048	63 (14.9)	.40
Excision and local tissue rearrangement	19 (4.9)	9 (2.8)	.16	12 (2.8)	.13
Surgery location					
Head	207 (53.3)	179 (55.4)	.54	229 (54.3)	.74
Neck	14 (3.6)	14 (4.3)	.62	17 (4.0)	.76
Trunk	67 (17.3)	49 (15.2)	.45	95 (22.5)	.06
Upper extremity	44 (11.3)	26 (8.0)	.14	31 (7.3)	.05
Lower extremity	55 (14.2)	55 (17.0)	.30	47 (11.1)	.19
Other	1 (0.3)	0	.97	3 (0.7)	.38
Postoperative antibiotics					
Yes	31 (8.0)	13 (4.0)	.03	9 (2.1)	<.001
No	355 (91.5)	310 (96.0)	.02	413 (97.9)	<.001
Missing	2 (0.5)	0	.98	0	.98

Figure 2. Maximal Postoperative Wound Infection (POWI) Scores As Treated and After Correction for Differences in Number of Ulcerated Lesions Among Study Groups



Error bars indicate 95% CIs.

[a] *P* < .05 vs control.

ulceration (Figure 2B). The proportion of lesions with a POWI score of 0 was highest in the flucloxacillin group, but this difference was no longer significant after adjustment for lesion ulceration (Figure 2). Significantly fewer lesions in both treatment arms were prescribed postoperative antibiotics during follow-up compared with controls (clindamycin, 2.1% [9 of

422]; flucloxacillin, 4.0% [13 of 323]; control, 8% [31 of 388]) (Table 3).

Adverse Events

No adverse events, including abnormal patient-reported pain, wound complications, or anaphylaxis, were observed.

Discussion

This double-blind, prospective randomized clinical trial showed that microdosed incisional antibiotic treatment with clindamycin significantly reduced the rate of SSI before skin cancer surgery. The use of postoperative systemic antibiotics significantly reduced with incisional antibiotics by one-half (flucloxacillin) or one-quarter (clindamycin) relative to the control group. Treatment with locally infiltrated microdosed incisional flucloxacillin and clindamycin was safe and well tolerated. Findings were consistent in the intention-to-treat and as-treated analyses. Based on these results, we recommend the routine adoption of incisional microdosed clindamycin for patients undergoing skin cancer surgery. This strategy appears suitable for widespread implementation because of the magnitude of the effect observed and the absence of adverse events.

Evidence-based antibiotic prophylaxis poses several benefits in skin cancer surgery. SSIs represent one of the most serious potentially avoidable complications affecting patient experience, cost, and surgical outcome in skin cancer surgery. Both melanoma and nonmelanoma skin cancers are frequently chronically ulcerated and colonized.[25,26] Operative sites are subject to altered perfusion with gravity dependency as well as tension and undermining that can impair immunity during wound healing.[27] Finally, tumor sites may experience fundamentally impaired local immunity, potentiating localized tumorigenesis and subsequent neoplasia.[28]

Despite this, to our knowledge, there have been no evidence-based recommendations on antibiotic prophylaxis in skin cancer surgery to date. Although guidelines can be extrapolated from other surgical settings,[9-14] they are not specific to skin cancer surgery. Preoperative infusion of systemic antibiotics is not necessarily warranted or practical in high-throughput, local anesthetic skin surgery. Oral clindamycin is an option for the ambulatory setting, although nonessential systemic antibiotic administration constitutes a recognized risk for antibiotic resistance,[16] which has been declared a global public health threat by the World Health Organization.[29,30] Nevertheless, evidence for alternative approaches to the prevention of SSIs in patients undergoing skin cancer surgery has been lacking. The Centers for Disease Control and Prevention guidelines currently state that nonparenteral antimicrobial prophylaxis of SSIs represents an unresolved issue.[13] Finally, to our knowledge, no guidelines advocate postoperative antibiotics for uncomplicated dermatologic surgery.[31]

This study confirms safety and efficacy reported in patients undergoing Mohs surgery[17,18] and substantially extends evidence supporting the use of incisional antibiotics to patients undergoing standard excisional skin cancer surgery. Mohs surgery reflects a specialized form of skin cancer excision using microscopic analysis of tissue margins in steps until no remaining cancer is seen.[32] However, standard surgical excision is more available, less costly, and represents the most common management approach for skin cancer worldwide.

Flucloxacillin and clindamycin were chosen for the intervention arms in this study because of their activity against common skin flora, generic availability, solubility, and amenability for codelivery with standard lidocaine-based local anesthesia using standard injection equipment, reported efficacy in Mohs SSI prophylaxis,[17,18] and clinically invisible/blindable incorporation into existing practice. Penicillin-class antibiotics are inexpensive and readily available with time-honored utility in skin infections, but their use is limited by a 10% to 20% rate of self-reported penicillin allergy[33,34] (9.5% in our study). Clindamycin provides an equivalently priced, well-tolerated alternate antibiotic for prophylactic use and is commonly recognized as a primary alternative with penicillin allergy.[35,36]

Clindamycin was significantly more effective at preventing SSI than flucloxacillin in our study. Possible reasons include slightly broader coverage of commonly cultured bacteria in skin and soft tissue infections, including community-associated methicillin-resistant *Staphylococcus aureus*,[35,36] efficacy against anaerobic bacteria that may be relevant to chronically ulcerated skin lesions, and lesser local tissue inflammation compared with flucloxacillin. Clindamycin's lower allergic contraindication (0.6% in our study) facilitates practical implementation as a first-line SSI prophylaxis agent in skin cancer surgery.

The technique of locally administered microdosed clindamycin with local anesthetic enables several benefits, including easy standardization and patient inclusion, perfect compliance, immediate targeted delivery to the operative site, low cost vs systemic antibiotic administration, economy of scale in high-volume treatment centers, limited drug-drug interactions, and decreased potentiation of antibiotic resistance. In terms of pharmacokinetics, local administration achieves predictable and immediate effective concentrations at the cutaneous operative site, including equal or better penetration into zones of impaired circulation relative to systemic delivery routes.[37] Additional factors relevant to implementation include cost of antibiotic (approximately ¢1.2 to ¢4.9 per 10-mL syringe of local anesthetic, based on average wholesale price),[21,36] and pharmacist time for preparation.

Limitations

This study has limitations. While the study provides high-quality evidence that responsibly improves clinically important outcomes for an extremely common indication where there was previously a lack of evidence, limitations include single-center recruitment and the inability to analyze wounds in patients who did not return for postoperative assessment. However, the lost to follow-up population was small (81 of 1214 randomized lesions [6.7%]) and least likely to include patients requiring management of postoperative complications, thus biasing toward overestimation of the true rate of SSI in our study. Notably, lost assessments were highest in the clindamycin group (39 of 461 lesions [8.5%]) vs the flucloxa-

cillin and control groups (23 of 346 lesions [6.6%] and 20 of 408 lesions [4.9%], respectively).

Another limitation was the presence of significantly fewer ulcerated lesions in the treatment groups relative to control, creating a potential source of bias toward a higher rate of SSI in the control group. However, the decrease in SSIs with incisional clindamycin vs control remained significant after adjusting for lesion ulceration.

Patients receiving systemic antibiotics for any indication within 7 days before surgery (eg, for coincidental urinary or upper respiratory tract infection) were excluded from eligibility. This was done to avoid any confounding influence on skin flora during the perioperative period that might have an impact on intervention effect, but this would not contraindicate incisional antibiotics in standard practice.

This was a single-center trial performed within a predominantly European study population, in a country bearing one of the highest incidences of skin cancer worldwide[1] and in a publicly funded health care system with universal access to skin cancer surgery, which may influence generalizability to other environments. While the significant decrease in postoperative antibiotic use after incisional antibiotics tracks with the primary outcome measure, its translational validity would benefit from further prospective study.

European individuals predominated the study population, mirroring the demographic characteristics of patients with skin cancer overall. However, it has been shown that racial and ethnic minority groups and socioeconomically deprived populations demonstrate higher rates of community-associated methicillin-resistant *S aureus* both regionally and internationally.[38-44] Therefore, there may be a role for further personalizing incisional antimicrobial choice for maximal clinical benefit based on race and ethnicity or even individual cutaneous microbiomes, and this represents an opportunity for further study.

Conclusions

To our knowledge, this is the first report on the safety and efficacy of incisional antibiotics for SSI prophylaxis in routine excisional skin cancer surgery. In a double-blinded, prospective randomized clinical trial, microdosed clindamycin delivered simultaneously with local anesthetic significantly reduced both the rate of SSI overall and the prescription of systemic antibiotics during postoperative follow-up. The intervention is safe, easily implemented in routine practice, and substantially reduces unintended antimicrobial selection outside the targeted operative field. These results establish evidence-based guidelines for antibiotic prophylaxis in one of the most common surgical interventions performed worldwide, where they have been previously absent.

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