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Perioperative Use of Angiotensin Inhibitors and Their Complications in Mohs Surgery: A Retrospective Cohort Study

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INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are among the most commonly prescribed antihypertensives worldwide.[1] While these agents are effective in managing hypertension, recent studies suggest that modulation of the renin-angiotensin-aldosterone system (RAAS) may influence cutaneous wound healing, angiogenesis, and fibrosis.[1-3] Nearly half of adults have a diagnosis of hypertension, and approximately 35% of all prescriptions written for antihypertensive medications in the United States are for ACEi.[5] With the prevalence of hypertension as a worldwide medical comorbidity and the rising incidence of cutaneous neoplasms in an aging population, understanding the perioperative effects of commonly used medications such as ACEis and ARBs, which inhibit the RAAS system, is increasingly important. This study aims to evaluate the association between ACEi/ARB use and perioperative complications in patients undergoing Mohs micrographic surgery (MMS).

MATERIALS AND METHODS

A global retrospective cohort study was conducted utilizing TriNetX, a database containing records from over 120 million patients across 80 health care organizations worldwide. Adults (≥18 years) who underwent MMS were identified using ICD-10 codes and stratified by the presence of an active prescription for an ACEi or ARB at the time of surgery. Propensity score matching (PSM) was performed to control for potential confounders, including age, sex, comorbidities (eg, diabetes, CKD, cardiovascular disease), and concurrent medication use. Analysis of risk and overall survival (OS) between cohorts was undertaken, examining the likelihood of developing intraoperative or postprocedural complications within 30 days after MMS. A 5-year OS analysis was conducted using the Kaplan-Meier method. Statistical significance was defined at two-tailed *P*-values <0.05.

RESULTS

After PSM, we identified 102,242 patients taking ACEis/ARBs and a matched cohort not on these medications at the time of MMS.

TABLE 1.

Perioperative Complications in Patients Taking ACE Inhibitors or ARBs at the Time of Mohs Compared to Matched Patients Not Taking These Medications

Category of Complication	Risk Ratio (RR)	RR 95% CI	Risk with ACEi/ARB	Risk without ACEi/ARB	Risk Difference (RD)	RD 95% CI	*P*-value
Cutaneous abscess, furuncle, carbuncle	1.63	(1.28,2.08)	0.17%	0.10%	0.07%	(0.03%,0.10%)	<0.0001
Follicular cysts	1.14	(1.01,1.29)	0.56%	0.49%	0.07%	(0.01%,0.13%)	0.0322
Scarring/fibrosis	1.22	(1.17,1.27)	4.44%	3.65%	0.79%	(0.62%,0.96%)	<0.0001
Localized edema	1.47	(1.32,1.64)	0.77%	0.52%	0.25%	(0.18%,0.32%)	<0.0001
Anesthesia of skin	1.22	(1.07,1.38)	0.52%	0.42%	0.09%	(0.03%,0.15%)	0.0021
Cellulitis, acute lymphangitis	1.51	(1.32,1.72)	0.53%	0.35%	0.18%	(0.12%,0.24%)	<0.0001
Hemorrhage	1.11	(1.05,1.18)	0.53%	0.35%	0.18%	(0.12%,0.24%)	<0.0001
Wound dehiscence	1.20	(1.01,1.43)	0.27%	0.22%	0.05%	(0.002%,0.09%)	0.0398
Intra/Postoperative complications	1.35	(1.15,1.60)	0.33%	0.24%	0.08%	(0.04%,0.13%)	0.0003

Risk ratios (RR), 95% confidence intervals (CI), absolute risk differences, and associated *P* values are shown for each complication category following propensity score matching. a bolded *P*-value indicates < 0.05, suggesting statistical significance.

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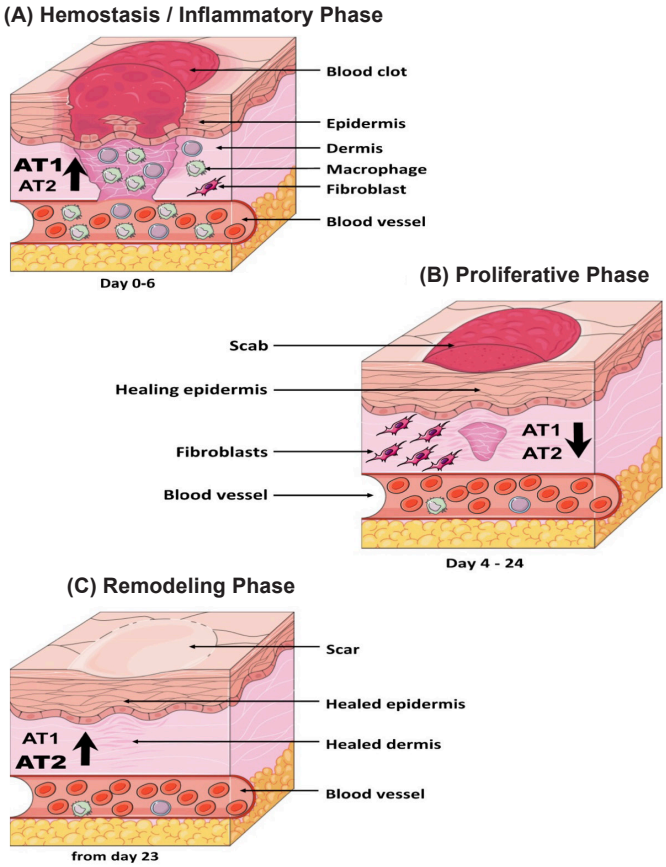
FIGURE 1. Angiotensin signaling supports key stages of cutaneous wound healing. Upregulation of AT1 and AT2 receptors after injury promotes keratinocyte migration, epidermal regeneration, and angiogenesis. During subsequent stages of wound healing and remodeling, reduced Angiotensin activity helps limit persistent inflammation and fibrosis while allowing growth-factor networks to predominate.



Pharmacologic inhibition of RAAS signaling through ACEi or ARB may disrupt these regenerative pathways, resulting in delayed re-epithelialization, aberrant collagen deposition, impaired scar maturation, and increased risk of postoperative infection.

Nine types of perioperative complications were significantly more common in the ACEi/ARB cohort (Table 1). These included cutaneous abscesses (RR[95% CI] = 1.63[1.28–2.08]), follicular cysts (1.14 [1.01–1.28]), scarring and fibrosis (1.22 [1.17–1.27]), localized edema (1.47 [1.32–1.64]), persistent anesthesia of the skin (1.22 [1.07–1.38]), cellulitis and acute lymphangitis (1.51[1.32-1.72]), surgical hemorrhage (1.11[1.05-1.18]), wound dehiscence (1.20[1.01-1.43]), and other intra/postprocedural complications (1.35[1.15-1.60]).

DISCUSSION

These findings may be explained by the essential role of the RAAS system in normal wound healing. Angiotensin 1 (AT1) and angiotensin II (AT2) are dynamically expressed and upregulated in keratinocytes immediately after cutaneous injury.[1] Activation of these receptors promotes keratinocyte migration, epidermal regeneration, and angiogenesis.[2,3] Epidermal stem cells rely on AT1 and AT2 receptor signaling to maintain self-renewal and proliferative capacity during tissue repair.[3] ACE activity in wounded skin has also been linked to the initiation of epidermal regeneration.[1,2]

Inhibition of RAAS through ACEi or ARB can disrupt these processes, leading to delayed re-epithelialization, aberrant collagen deposition, and reduced tensile strength of healing skin.[3,6] Moreover, RAAS blockade may diminish the local inflammatory signals required for efficient bacterial clearance, potentially increasing susceptibility to postoperative infections such as cellulitis or abscess formation.[6] While ACEis have been explored for potential benefit in fibrotic skin conditions and keloid prevention, their systemic use in the perioperative period may adversely affect normal wound healing and increase surgical complication risk.[7] These stages of wound healing and their potential disruption under RASS inhibition are summarized in Figure 1. Collectively, these mechanisms may underlie the elevated rates of both surgical and infectious complications observed in patients taking an ACEi or ARB at the time of Mohs surgery.

Given the high prevalence of hypertension, frequent use of ACEis and ARBs, and the increasing incidence of cutaneous malignancies requiring Mohs surgery, dermatologic surgeons should be aware of the potential perioperative risks associated with these medications. An enhanced understanding of these processes and potential complications may promote closer monitoring and informed decision-making by dermatologic surgeons.

DISCLOSURES

Dr Tolkachjov is an investigator and speaker for CASTLE Biosciences, Kerecis, Boehringer Ingelheim, and Bioventus. No relevant COI. Other authors have no COI to disclose.

REFERENCES

1. Morihara K, Takai S, Takenaka H, et al. Cutaneous tissue angiotensin-converting enzyme may participate in pathologic scar formation in human skin. *J Am Acad Dermatol.* 2006;54(2):251-257. doi:10.1016/j.jaad.2005.09.027
2. Silva IMS, Assersen KB, Willadsen NN, et al. The role of the renin-angiotensin system in skin physiology and pathophysiology. *Exp Dermatol.* 2020;29(9):891-901. doi:10.1111/exd.14159
3. Liao X, Xiao J, Li SH, et al. Critical role of the endogenous renin-angiotensin system in maintaining self-renewal and regeneration potential of epidermal stem cells. *Biochim Biophys Acta Mol Basis Dis.* 2019;1865(10):2647-2656. doi:10.1016/j.bbadis.2019.07.006
4. Centers for Disease Control and Prevention. Hypertension cascade: hypertension prevalence, treatment and control estimates among US adults aged 18 years and older applying the criteria from the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2017–March 2020. Accessed May 3, 2024. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html
5. Seyhan M, Aki T, Karincaoglu Y, Ozcan H. Psychiatric morbidity in dermatology patients: Frequency and results of consultations. *Indian J Dermatol.* 2006;51(1):18–22.
6. Stuermer EK, et al. Side effects of frequently used antihypertensive drugs on wound healing in vitro. *Skin Pharmacol Physiol.* 2019;32(3):162–172.
7. Iannello S, Milazzo P, Bordonaro F, Belfiore F. Low-dose enalapril in the treatment of surgical cutaneous hypertrophic scar and keloid--two case reports and literature review. *MedGenMed.* 2006;8(4):60.

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