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ORIGINAL ARTICLE

Angiotensin II receptor blockers as a risk factor for skin ulcers

Bloqueadores de angiotensina II como factor de riesgo para úlceras cutáneas

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Abstract

Objective: *The aim of the study was to determine the risk factors associated with skin ulcers that were not of vascular, paraneoplastic, rheumatologic, or pressure origin.* **Methods:** *This was an observational, case- and control-designed, and retrospective trial. The group of cases was patients who presented skin ulcers that were not of vascular, paraneoplastic, or pressure origin. The control group was formed by ill subjects with no skin ulcers paired in age, sex, and chronic diseases. The cases were defined with the presence of an ulcer, at the 1st time consultation; treatment with medication, symptoms, progression time, and substance abuse were entered in a database. The statistical analysis of the results was performed using the EpiInfo software, version 7.2.2.6.* **Results:** *Between July 2005 and December 2020, 69 patients suffering from skin ulcers without apparent etiology were enrolled. Following the statistical analysis of all variables, a significant difference in favor of the cases with antihypertensive treatment with angiotensin II receptor blockers (ARBs) was obtained, with p ≤ 0.02 and odds ratio 2.24 with confidence interval 95 % (1.1–4.5).* **Conclusion:** *ARB medications are a risk factor for the presence of skin ulcers.*

Key words: *Skin ulcers. Angiotensin II receptor blockers. Nonvascular ulcers.*

Resumen

Objetivo: *Determinar los factores de riesgo que se asocian a úlceras cutáneas que no fueran de origen vascular, paraneoplásico, reumatológicas o por presión.* **Métodos:** *Estudio observacional con diseño de casos y controles, retrospectivo. El grupo de casos fueron pacientes que presentaban úlceras cutáneas que no fueran de origen vascular, paraneoplásico, reumatológicas o por presión. El grupo control se integró con enfermos sin úlceras cutáneas pareados por edad, sexo y enfermedades crónicas. Se definieron los casos con presencia de úlcera en la consulta de primera vez. Se capturó en una base de datos el tratamiento con medicamentos, los síntomas, el tiempo de evolución y las toxicomanías. El análisis estadístico de los resultados se realizó utilizando el programa de EpiInfo versión 7.2.2.6.* **Resultados:** *Entre julio del 2005 y diciembre del 2020 se registraron 69 pacientes con úlceras cutáneas sin etiología aparente. Después del análisis estadístico de todas las variables se obtuvo una diferencia significativa en favor de los casos con tratamiento antihipertensivos con antagonistas de los receptores de la angiotensina II (ARA II), con p < 0. 02 y razón de momios 2.24 (intervalo de confianza del 95%: 1.1-4.5).* **Conclusiones:** *Los medicamentos tipo ARA II son un factor de riesgo para la presencia de úlcera cutáneas.*

Palabras clave: *Úlceras cutáneas. ARA II. Úlceras no vasculares.*

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Introduction

The most common area of side effect manifestations provoked by medication is given in the most extensive organ we have in our body, which is the skin, in up to 30% of the total of these complications,[1,2] and range from rash, dermatitis, different types of purpura, angioedema, and blisters to necrosis, such as skin ulcers or more severe: epidermolysis.

According to the world data, the greatest number of skin drug-related side effects (SDRSE) is mainly due to antibiotics, followed by nonsteroidal anti-inflammatory drugs.

However, antihypertensive drugs are not complication-free. Institutions such as the Drug Adverse Reaction Committee of the National Healthcare Board of Denmark report that in the SDRSE in this case, antihypertensive drugs have a skin complication rate varying from 10% to 60%[3].

Among the most common SDRSE of such drugs, one may find angioedema, urticaria, pruritus, vasculitis, exanthematous pustulosis, bullous rash, erythroderma, photosensitivity, and eczema, and *inter alia*; being the angiotensin-converting enzyme inhibitors (ACEI) and antihypertensive drugs the ones that the most commonly provoke these issues.

More SDRSE publications have been submitted by angiotensin II receptor blockers (ARBs)[4] as well as reports of more severe skin complications, such as the exhibition of ulcers from the oral mucosa[5] or severe pustular vasculitis with the use of these medications, although they have been only single-case reports[6-9]. Nonetheless, there are no reports in the references mentioning that ARBs or ACEI are responsible repeatedly in a series of cases showing skin ulcers.

In this trial, the objective was to determine the risk factors for skin ulcers, being the results that caused this paper.

Materials and methods

A retrospective, observational, case-designed, and control-in-patient trial was performed from the San Luca Centro Vascular Medical Unit, located in Queretaro, Qro., Mexico, where such patients were assisted from July 14, 2005, to December 31, 2020. The inclusion criteria were the presence of cutaneous ulcers in any part of the skin, a detailed arterial and venous examination were performed on these subjects. Non-inclusion criteria were ulcers in a prone position; rheumatological disease, cancer, and a chronic venous disease are based on the CEAP classification[10] and patients with the absence or decrease of distal pulses, ankle/arm ratio < 1 or > 1.4,[11] and with abnormal foot and ankle blood Doppler waveform. Those patients who had an incomplete registration of the parameters aforementioned were withdrawn.

The control group was comprised patients with similar characteristics in age, sex, and pathological antecedents, but who did not have any ulcerous injuries of any kind on the skin.

Statistical analysis was performed by bivariate analysis with a Chi-squared test for the "p" value and the determination of odds ratio (OR) and confidence interval (CI 95%) using the EpiInfo software, version 7.2.2.6.

Results

The total universe as of December 31, 2020, in the vascular center was 6799 patients, out of which 69 (1.01%) were detected with skin ulcers from unknown etiology.

In the case group, 78% (n = 54) were women and 22% (n = 15) were men; the age range was 32–90 years, with a 70.3-year average, 88.4% (n = 61) patients were taking some medication previously and 11.6% (n = 8) were not. In their pathological antecedents, patients exhibited one or more of these diseases: high blood pressure 84.05% (n = 58); diabetes mellitus 44.92% (n = 31); heart failure 4.34% (n = 3); and various diseases 20.28% (n = 14).

Progression time of ulcers varied from 7 to 2160 days; the areas affected were the following: hands 1.4% (n = 1) and lower limb under the knee 98.6% (n = 68), with exhibition in neither thigh nor another part of the body; one-sided 73.9% (n = 51) and two-sided 26.1% (n = 18). Symptomatology in all skin ulcers in the lower limbs was always similar, being quite painful, and pain increased in *decubitus* or whilst lifting the limb, and involved only the skin and subcutaneous cellular tissue.

A significant difference was obtained in patients who exhibited skin ulcers and treatment with ARBs-type antihypertensive medication (losartan, telmisartan, irbesartan, valsartan, and candesartan were the drugs prescribed) versus the control group, with $p \leq 0.02$ and OR 2.24 with CI 95% (1.1–4.5) (Table 1).

Table 1. Medication as a risk factor for the formation of skin ulcers

Risk factor medications	Concerning group	Control group	p-value
Metformin	21	19	NS
Glibenclamide	5	8	NS
DPP4-group hypoglycemic drugs	2	3	NS
Insulin	5	5	NS
Glimepiride	3	3	NS
Pioglitazone	1	0	NS
Acetylsalicylic acid	4	1	NS
Statins	2	5	NS
Oral anticoagulants	3	0	NS
Digitalis drugs	1	0	NS
ARBs group	33	20	< 0.02
ACEI	17	17	NS
Beta-blockers	11	19	NS
Calcium antagonists	7	20	NS
Thiazides	9	5	NS
Chlortalidone	4	2	NS
Spironolactone	1	2	NS
Furosemide	1	1	NS
Bumetanide	1	2	NS
Total	138	132	

NS: non-significant; ARBs: angiotensin II receptor blockers; ACEI: angiotensin-converting enzyme inhibitors.

Table 2. Chronic diseases and/or drug addictions as a risk factor for the formation of skin ulcers

Risk factor (Sole or multiple) chronic diseases and/or drug addictions	Concerning group	Control group	p-value
Diabetes mellitus	31	30	NS
High blood pressure	58	54	NS
Heart failure	3	4	NS
Coronary heart disease	2	0	NS
Arrhythmias	2	0	NS
Dyslipidemias	2	7	NS
Asthma	2	0	NS
Hypothyroidism	1	2	NS
COPD	1	0	NS
Gout	1	1	NS
Hemolytic anemia	1	0	NS
Prostatic hyperplasia	1	0	NS
Cerebrovascular disease	1	0	NS
Infantile cerebral palsy	1	0	NS
Parkinson's disease	0	1	NS
Smoking	9	4	NS
Alcoholism	2	3	NS
Total pathologies	118	105	

NS: non-significant; COPD: chronic obstructive pulmonary disease.

There were no significant differences among the other variables, such as sex, age, substance abuse, high blood pressure, diabetes mellitus, or any other degenerative chronic diseases, or with the other types of antihypertensive/glucose-lowering drugs, or miscellaneous medication (Table 2).

Discussion

During the search for similar antecedents, no literature was found in the important sources of medical information (Medline, PubMed, and Google Academic) that reported ARA II as a risk factor for severe skin lesions, only one case reports. This work provides information to be considered as such and improve the diagnosis and adjust the integral management of such an issue, and it could shorten long periods of unsuccessful treatment of ulcers of up to 6 years of progression without showing any healing in this series reported (Fig. 1).

The mechanism of ulcer formation turns out to be unknown; nevertheless, more recent studies demonstrate an inflammatory stimulating effect for greater bradykinin accumulation in receptors not blocked by ARBs[12]. In addition, not only does the renin-angiotensin system (RAS) regulate blood pressure at a kidney level, but also plays a local physiological role in other organs, such as the brain, heart, and also in the gastrointestinal tract, such as the liver, pancreas, and bowel, which explain the side effects such as nausea, vomiting, and diarrhea from using ACEI and ARBs[13]. Skin is not free from this physiological regulation. Stecklings

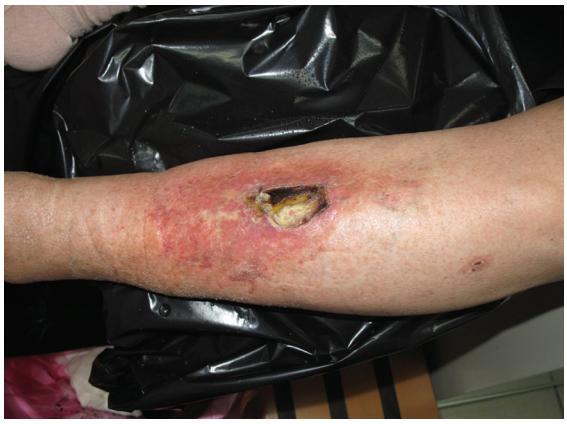

Figure 1. Female patient with a superficial and quite painful skin ulcer, treated with telmisartan and previously treated as a venous ulcer.

demonstrated a very comprehensive review since the mid-1990s, the unequivocal role of angiotensin II receptors in this organ in modulating cellular proliferation[14] influencing the growth and regeneration of skin, a condition that may influence the lack of cicatrization with the blockade of such receptors. Ulcers may also be provoked, like in other medications, such as DPP4-type glucose-lowering drugs[15] and hydroxyurea,[16] by secondary vascular inflammatory processes (vasculitis) to circulating autoimmune complexes[17].

This report may be considered to be a watershed recognizing the role of ARBs as a risk factor in this severe complication and helping encourage to study this more comprehensively, even with histopathological diagnoses, to be able to explain more precisely the mechanism of the injury.

We consider this is one of the first works in demonstrating the relationship in such a risk factor for skin-ulcer formation in the lower limbs, a situation that can be considered in the clinical practice, and to weigh this possibility whenever these drugs are prescribed and also consider to stop and/or change to another type of antihypertensive drugs different than those that influence the RAS as we face the presence of such ulcers not exhibiting any apparent explanations or causes.

Conclusions

ARBs-type drugs are a risk factor for the presence of skin ulcers. This complication should be considered in hardly controlled skin ulcers that do not have any apparent causes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of the data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article.

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