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Use of Chamomile Infusion to Mitigate Radiotherapy-Induced Dry Desquamation in Head and Neck Cancer Patients

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Abstract

Purpose: To evaluate the effect of using a compress with *Chamomilla recutita* infusion in the regression of dry desquamation and in the prevention of moist desquamation in head and neck cancer patients undergoing radiotherapy. **Methods:** A prospective intervention study was carried out from May 2019 to May 2021. In total, 43 participants were included, who were instructed to apply the compress with the infusion 3 times a day, after occurrence of dry desquamation. Skin evaluation took place daily from initiation of the intervention up to the end of radiotherapy. **Results:** All the participants presented dry desquamation regression, where 65.1% (95% CI 50.1-78.1) had total regression until the end of radiotherapy, with a mean of 9 days of regression. Only 34.9% (95% CI 21.8-49.9) of the participants developed moist desquamation by the end of the radiotherapy sessions, with a mean accumulated dose of ionizing radiation of 50.9 Gy. **Conclusion:** This study highlighted the potential clinical benefits of using *Chamomilla recutita* in the regression of dry desquamation and in the prevention of moist desquamation.

Keywords

radiodermatitis, dry desquamation, head and neck cancer, topical administration, *Chamomilla recutita*, radiotherapy

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Introduction

Radiation dermatitis (RD) is a common skin reaction resulting from exposure to ionizing radiation and affects approximately 100% of the head and neck cancer patients.[1] It can manifest as erythema, dry desquamation, moist desquamation, ulceration, and necrosis.[2]

The clinical manifestations of RD are associated to the cumulative dose of ionizing radiation.[3] Doses above 20 Grays (Gy) may result in the development of dry desquamation in the irradiated region.[2] Dry desquamation is characterized by loss of the damaged epidermal cells, commonly progressing to moist desquamation, caused by subdermal exposure.[3] More severe clinical manifestations such as moist desquamation occur in approximately 36% of the patients who undergo radiotherapy.[4]

Inflammation associated with RD is characterized by cutaneous symptoms, due to the release of activated growth factors and pro-inflammatory cytokines.[2] During the radiotherapy sessions, it is common to report symptoms such as altered sensitivity, dryness, dry skin, itching, pain, physical and psychological discomfort, which negatively affects quality of life.[5]

The recommendations for skin care include daily cleaning of the irradiated area with mild soap.[6] It is also recommended to protect the irradiated area from exposure to the sun, avoiding friction, and temperature extremes.[7] In addition to the recommended care measures, several topical interventions are proposed to minimize RD signs and symptoms in patients with head and neck cancer.[8,9] However, the available

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scientific evidence still does not allow establishing a standardized approach for preventing or treating RD.[8,10]

Chamomilla recutita, also known as *Matricaria chamomilla*, is composed by terpenoids, flavonoids, α-bisabolol, quercetin, apigenin, and coumarins.[11] It is responsible for anti-inflammatory, healing, antimicrobial, antioxidant, hemostatic, lightening, and skin irritation reduction properties.[11,12] The topical action of the *Chamomilla recutita* gel was evaluated for the prevention of RD in a recent study conducted with head and neck cancer patients undergoing radiotherapy. The results showed reduction in RD intensity and delay in the development of the first RD signs, with a protective effect for RD severity.[13]

Dry desquamation requires an intervention that has an anti-inflammatory and, at the same time, moisturizing action. The infusion provides local moisture and allows, through the warm temperature, for the release of sesquiterpenic oils, such as chamazulene, increasing the availability of local anti-inflammatory compounds. This study aimed at evaluating the effect of using a compress with *Chamomilla recutita* infusion in the regression of dry desquamation and in the prevention of moist desquamation in head and neck cancer patients undergoing radiotherapy.

Method

Study Design

A prospective, longitudinal, quantitative, and intervention study.

Locus

The study was carried out at the Radiotherapy Outpatient Clinic of the University Hospital of Brasília (*Hospital Universitário de Brasília*), Brasília, Brazil.

Sample Selection

The target population of this study consisted in head and neck cancer patients undergoing radiotherapy, who presented dry desquamation in the irradiated area. Recruitment took place between May 2019 and May 2021.

The eligibility criteria were as follows: patients aged 18 years old or more, diagnosed with head and neck cancer, and who presented dry desquamation in the irradiated area during radiotherapy. Patients with previous hypersensitivity or adverse reaction to *Chamomilla recutita* or to any plant from the *Asteraceae* or *Compositae* family were excluded.

The participants underwent radiotherapy with elective bilateral nodal irradiation, using linear accelerator-type devices, one from manufacturer VARIAN® (Palo Alto, CA, USA), CLINAC CX model, and the other by SIEMENS® (Concord, CA, USA), PRIMUS model, using 3D-CRT conformational planning.

Recruitment and Data Collection

During daily nursing monitoring, the head and neck cancer patients who developed dry desquamation in the irradiated area were identified and recruited.

The participants received individualized and pre-packaged portions of the *Chamomilla recutita* flower heads and were instructed to perform the infusion at a concentration of 2.5% (10 g of flower heads in 400 mL of water), a value established through a previous study.[14] To perform the compress, the participants were instructed to leave the infusion warm and subsequently moisten a clean cloth with approximately 40 cm^2 of the infusion and apply it for 20 minutes to the region with dry desquamation. Additionally, they were instructed to repeat this process 3 times a day.

On the day of the first radiotherapy session, all the participants received information about radiotherapy and self-care guidelines. The guidelines on skin care were delivered in the format of a previously elaborated and validated manual.[15,16] The recommendations consist of the usual institutional care and encompass cleaning the skin with a neutral moisturizing soap (Dove®, Valinhos, SP, Brazil), provided to the participants, and care measures to minimize heat and friction in the irradiated region.

The participants were monitored daily from the first day of occurrence of dry desquamation occurrence until the end of radiotherapy. To classify RD, the Acute Radiation Dermatitis Graduation (GRAL) Scale was used,[7] which classifies the grades into: 0 (no change), 1 (hyperpigmentation), 2 (erythema), 3 (skin dryness), 4 (dry desquamation located in one or more separate points), 5 (dry desquamation disseminated in one or more adjacent points), 6 (local moist desquamation and/or in folds), 7 (disseminated moist desquamation), 8 (bleeding and/or ulceration), and 9 (Necrosis). To document the irradiated area, photographs of the regions (frontal region, right cervical region and left cervical region) were taken on alternate days. The photographs were taken using the camera of an ASUS Smartphone, ZenFone Max Shot ZB634KL, triple camera, (São Paulo, SP, Brazil). All photographs were standardized observing conditions such as background color, distance from the patient to the camera and ambient lighting.

The sociodemographic and clinical data collected were as follows: age (in complete years old), gender, schooling, phototype defined as skin type when exposed to the sun, collected according to the Fitzpatrick Scale[17] measured with a Doctor Skin Phototype device (Hangzhou, China). The other variables collected were the following: smoking and drinking status, occupational exposure to the sun, skin disease, diabetes, and Body Mass Index. The clinical variables collected that were associated to the treatment were diagnosis, staging, histopathology, current treatment (exclusive radiotherapy and/or chemotherapy), number of sessions, total dose, fractionated dose, and type of energy (photons and/or electrons).

The primary outcome was dry desquamation regression until the end of radiotherapy. Dry desquamation regression was judged by 3 nurse evaluators through the photographs that recorded the monitoring and evolution of dry desquamation on the participants' skin. Dry desquamation regression was classified as total regression (absolute dry desquamation regression), partial regression (when there were still areas of dry desquamation—grade 4) or no regression (when the entire irradiated area still presented dry desquamation—grade 5, and had not changed with the intervention).

The secondary outcome was occurrence of moist desquamation (yes or no) in the irradiated region. Additionally, the symptoms reported by the participants were recorded weekly by means of a checklist, contained in the GRAL scale, which allows assessing symptoms such as local heat, burning, itching, dry skin, and pain.[7]

Data Analysis

For data analysis and sample characterization, descriptive statistics were used, with calculation of mean, frequency, odds ratio, and confidence interval. The data were analyzed using the *Statistical Package for Social Science* (IBM SPSS®, Endicott, New York, USA) software, version 26 for Mac, and in the *Open Source Epidemiologic Statistics for Public Health* (OpenEpi®, Atlanta, GA, USA), software, version 3.

Ethical Aspects

The patients who agreed to participate in the research expressed their acceptance by signing the Free and Informed Consent Form and the imaging authorization form. The study was approved by the Research Ethics Committee of the Health Sciences School, University of Brasília.

Results

A total of 43 participants with dry desquamation in the cervical region during radiotherapy were recruited, included and monitored. There was no loss related to monitoring during the evaluation period. No patient presented adverse events related to using the compress containing the *Chamomilla recutita* infusion.

The participants were predominantly male (90.7%). As for location of the tumor, (44.1%) of the participants had oral cavity cancer, followed by laryngeal cancer in 27.9% of the cases. Most of the participants (86%) had a histopathological type of squamous cell carcinoma and IVA staging (58.1%). Regarding the current treatment, 32.6% were undergoing exclusive radiotherapy and 67.4%, chemoradiotherapy with a mean duration of 5 weeks. All the participants received photons and 18.6% received electrons. The participants' sociodemographic and clinical characterization is shown in Table 1.

Table 1. Sociodemographic and Clinical Characteristics of the Participants.

Sociodemographic and clinical characteristics	n = 43
Age in years old, mean (SD)	60.9 (13.4)
Median (min-max)	61 (19-105)
Male, n (%)	39 (90.7)
Schooling, n (%)	
Illiterate	9 (20.9)
Incomplete elementary school	19 (44.2)
Complete elementary school	4 (9.3)
Incomplete high school	3 (7.0)
Complete high school	7 (16.3)
University education	1 (2.3)
Phototype, n (%)	
II	2 (4.7)
III	5 (11.6)
IV	25 (58.1)
V	11 (25.6)
Smoker, n (%)	
Never	5 (11.6)
Discontinued for more than 6 months	16 (37.2)
Discontinued in the last 6 months	14 (32.6)
Current smoker	8 (18.6)
Drinker, n (%)	
Never	4 (9.3)
Discontinued for more than 6 months	21 (48.8)
Discontinued in the last 6 months	12 (27.9)
Current drinker	6 (14)
Occupational exposure to the sun, yes, n (%)	36 (83.7)
Skin disease, yes, n (%)	4 (9.3)
Diabetes, yes, n (%)	3 (7)
BMI, n (%)	
Underweight <18.5	5 (11.6)
Eutrophic ≥ 18.5 and <24.9	29 (67.4)
Overweight ≥ 25 and <29.9	5 (11.6)
Obesity ≥ 30.0	4 (9.3)
Location of the tumor, n (%)	
Oral cavity	19 (44.1)
Oropharynx	4 (9.3)
Larynx	12 (27.9)
Hypopharynx	3 (7)
Nasopharynx	4 (9.3)
Paranasal sinuses	1 (2.3)
Staging, n (%)	
I	2 (4.7)
II	4 (9.3)
III	6 (14)
IVA	25 (58.1)
IVB	5 (11.6)
Not identified	1 (2.3)
Number of sessions, mean (SD)	34.0 (1.8)
Total dose (Gy), mean (SD)	68.1 (3.4)
Fractionated dose (Gy), mean (SD)	2.0 (0.0)

Table 2. Dry Desquamation Regression and Occurrence of Moist Desquamation in the Participants.

Variables	Mean dose in Gy, mean (SD)	Time in days between dry desquamation and regression, mean (SD)	n = 43, n (%)
Dry desquamation regression			
Total regression	59.5 (6.2)	9 (3.8)	28 (65.1)
Partial regression	59.8 (6.6)	8 (3.7)	15 (34.9)
No regression	—	—	0 (0)
Occurrence of moist desquamation, yes	50.9 (4.1)	—	15 (34.9)

From using the compress with *Chamomilla recutita* infusion, all the participants presented some type of dry desquamation regression during monitoring (Table 2). More than half of the participants, 65.1% (95% CI 50.1-78.1), presented total dry desquamation regression and 34.9% (95% CI 21.8-49.9) had partial dry desquamation regression until the end of radiotherapy. It is also noted that no participant was classified in the category without regression.

The participants presented total dry desquamation regression with the mean dose of 59.5 Gy. Considering the total mean radiotherapy dose of 68.1 Gy, the participants were free from dry desquamation before the end of radiotherapy, showing the benefits of using the infusion for dry desquamation regression.

With the use of the compress with *Chamomilla recutita* infusion, partial dry desquamation regression took a mean of 8 days to occur and total dry desquamation regression required a mean of 9 days, with the participants continuing to receive ionizing radiation daily, which reiterates the action of the pharmacological properties of *Chamomilla recutita*.

Dry desquamation regression was accompanied by an improvement in skin appearance and by a reduction in the dry desquamation area and the intensity of the erythema and/or hyperpigmentation in the irradiated region, as shown in Figure 1.

Only 34.9% (95% CI 21.8-49.9) of the participants developed moist desquamation, with the mean accumulated dose of ionizing radiation of 50.9 Gy, with the possibility of inferring that using a compress with *Chamomilla recutita* infusion delayed the occurrence of moist desquamation.

Regarding some risk factors to develop or increase RD severity, we observed that 8 (18.6%) of the current smokers developed moist desquamation. The univariate analysis by logistic regression showed an odds ratio of 1.15 (95% CI 0.23-5.65) for current smokers and of 3.70 (95% CI 2.17-6.28) for patients with a smoking history that had partial regression.

The symptoms reported by the participants were evaluated weekly from the beginning of compress use (time of dry desquamation occurrence) until the end of radiotherapy (Figure 2). All the symptoms reported regressed from 50 Gy of mean dose with the use of the *Chamomilla recutita* infusion, allowing the participants to present an improvement in the symptoms even with the radiotherapy sessions in progress and daily receiving more ionizing radiation doses, which shows the benefits of using a compress with *Chamomilla recutita* infusion also in reduction of the symptoms. One patient was not included in the analysis for not being able to report the symptoms, considering that he was subjected to radiotherapy sessions under sedation. The number of patients differs each week, considering the week in which the patient was recruited and due to the difference in the number of radiotherapy sessions prescribed for each participant.

Discussion

This study showed dry desquamation regression with the use of the *Chamomilla recutita* infusion, in which all the participants presented dry desquamation regression, with 65.1% presenting total regression until the end of radiotherapy. Dry desquamation occurs due to the local inflammation that results in loss of the skin barrier and destruction of the sebaceous glands by ionizing radiation.[18,19] Its regression, demonstrated in this study, highlights the benefit to the patient due to non-evolution of RD severity and to the improvement in skin appearance even with the radiotherapy sessions in progress.

The risk for developing more severe RD grades is related to several factors, such as smoking and chemoradiotherapy, which predispose to greater severity,[5] relevant characteristics in the sample. In this study, being a current smoker or having a smoking history increase the chance to develop moist desquamation and to have partial RD regression. Although the radiotherapy techniques have been advancing with the objective of minimizing adverse effects, such as Intensity-Modulated Radiotherapy (IMRT) and proton beam therapy, patients with head and neck cancer are at a higher risk of developing severe RD as they have the skin very close to the target volumes.[20]

The presence of moist desquamation considered a severe RD grade causes suffering to the patient, as it is accompanied by symptoms such as pain and discomfort, in addition to increasing the risk of infection.[21] After the occurrence of any RD skin change, the skin exposed to ionizing radiation

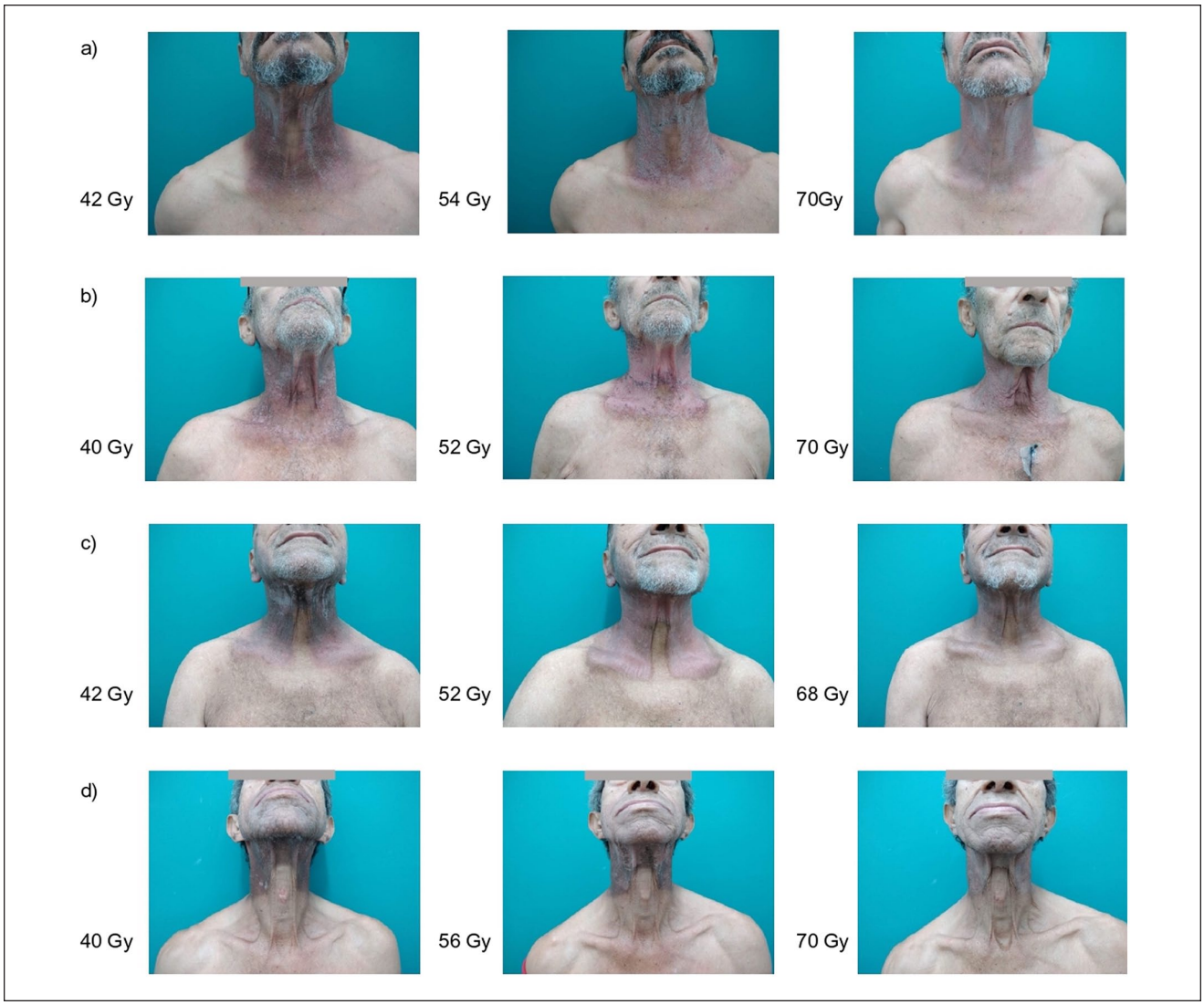

Figure 1. Follow-up of dry desquamation regression of the participants with the use of the compress with *Chamomilla recutita* infusion according to the accumulated dose of ionizing radiation.

tends to evolve to moist desquamation without the use of interventions for its management. With the use of a compress infused with *Chamomilla recutita*, only 34.9% of the participants developed moist desquamation, with a mean accumulated dose of ionizing radiation of 50.9 Gy. According to the literature, with doses of 30 to 40 Gy, dry desquamation is expected to evolve into moist desquamation.[18,21] Considering the participants' mean fractionated dose of 2 Gy, there was a mean delay of 5 to 10 days for the occurrence of moist desquamation when compared to the literature, reinforcing the effect of *Chamomilla recutita* on delaying the occurrence of moist desquamation.

Severe RD grades affect the patient's quality of life, due to the associated local symptoms and changes in body image.[22] Pain is one of the most severe symptoms

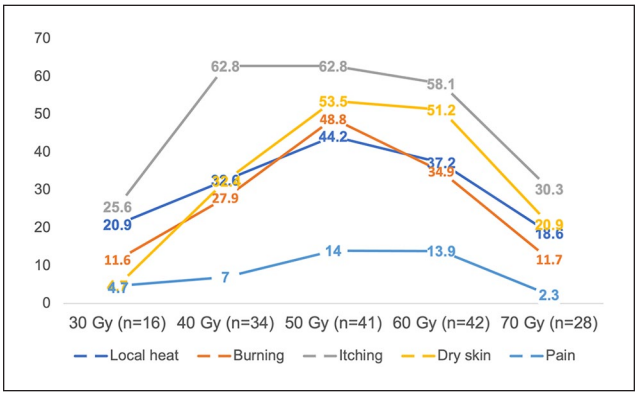

Figure 2. Proportion of participants who reported symptoms due to the mean accumulated dose of ionizing radiation.

associated with RD.[5] All the symptoms reported in this study had a gradual reduction from 50 Gy of mean accumulated dose; and pain was the symptom least reported by the participants, highlighting the effect of *Chamomilla recutita* on the reduction of local symptoms.

The cutaneous cellular response resulting from exposure to ionizing radiation is regulated by different cytokines and chemokines, such as IL-1, IL-6, TNF-α, TGF-β, and IL-8a. For this reason, inhibition of pro-inflammatory cytokines, such as IL-1α/β, TNF-α, IL-6, MCP-1, TGF-β1, and COX-2 can improve tolerance of the skin tissue to radiotherapy.[19] Several studies carried out with *Chamomilla recutita* demonstrate its anti-inflammatory effect, through its inhibitory action on COX-2.[23] Also, the confirmation of the reduced production of TNF-α observed in mice treated with apigenin,[24] and measurement of the levels of inflammatory cytokines IL-1β, IL-6, and TNF-α after treating macrophages with flavonoids.[25]

Mankind has used herbal medications to manage wounds for centuries. Natural products are being increasingly employed due to their effectiveness, accessibility, and improved scientific evidence.[26] The anti-inflammatory effect of *Chamomilla recutita* on the relief of RD suggests a promising topical intervention in the management of moist and dry desquamation. In addition, the compress with *Chamomilla recutita* infusion is low-cost, being an accessible strategy for patients with head and neck cancer undergoing radiotherapy.

The absence of a control group stands out as a limitation of this study, which precluded comparative analyses on the effectiveness of the compress with *Chamomilla recutita* infusion in RD management. However, this study shows the potential clinical benefits when using a compress with *Chamomilla recutita* infusion on dry desquamation regression and on the prevention of moist desquamation, which can be explored in future comparative studies.

Conclusion

The compress with *Chamomilla recutita* infusion showed total dry desquamation regression in most of the participants, demonstrating its clinical benefit. One third of the participants developed moist desquamation until the end of the radiotherapy sessions; most of them were current smokers or had a smoking history.

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Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by AGM and PSMB. Data analyses and interpreted data outcomes were performed by AGM, EBF, ENSG, and PEDR. The first draft of the manuscript was written by AGM and all authors critically reviewed the manuscript's drafts and approved the final version.

Declaration of Conflicting Interests

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Ethics Approval

The study was approved by the Research Ethics Committee of the Health Sciences School, University of Brasília, no. 04223118 .0.0.0000.0030.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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