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A Comparison of Type IV Hypersensitivity Reaction to Synthetic Polyisoprene Gloves versus Control Gloves Using Modified Draize-95 Test in Normal Individual

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Abstract:

Background: The emergence of epidemics in recent years, such as COVID-19 and monkeypox, has increased the need for protective gloves.

Objectives: This study was performed to provide clinical evidence that no residual chemical additives are present in the powder-free, non-latex, with and without pigment, sterile and non-sterile nitrile, and polyisoprene gloves at a level that may induce type IV allergy in the unsensitized general user population.

Methods and Materials: We conducted the modified Draize-95 test on the GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves (S01) and the GAMMEX® Non-Latex PI Green, sterile powder free synthetic polyisoprene surgical gloves (S02). A quasi-experimental non-equivalent study consisted of 180 healthy unsensitized adult volunteers at the Islamic University of Gaza. Participants were divided into two groups: 150 white subjects and 30 black subjects. Each group divided into two groups, each one contained approximately the same numbers of males and females. We used two sets of different test materials as 2x2 cm pieces of the glove's materials from the inner and outer surfaces mounted on an adhesive patch. For the control groups, we used Nitrile Skin Examination Powder-Free Disposable Gloves (C1) and Aegis Examination Gloves (C2).

Results: None of the participants showed positive reactions to the test materials of equal or greater than 1.5 in the challenge or rechallenge phase, both on the inner and outer surfaces of the GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves (S01), and the GAMMEX® Non-Latex PI Green, sterile powder-free synthetic polyisoprene surgical gloves (S02). Only one white woman showed a reaction to the inner surface of the S02 material in the induction phase.

Three participants showed skin reactions to the second control material, the Aegis Nitrile Examination Gloves (C2). Those three were a white female in the induction phase and two white males in the challenge phase. However, none of them showed any reaction later.

Conclusion: The modified Draize test negative results for the GAMMEX Non-Latex PI, sterile powder-free, synthetic polyisoprene surgical gloves (white and green) support the claim that the chemical sensitization potential of these materials is low and that no residual chemical additives are present in these gloves at a level that could cause type IV hypersensitivity reactions.

Keywords:

Type IV sensitivity, polyisoprene, gloves, nitrile, modified Draize-95 test, skin hypersensitivity, GAMMEX®

Introduction

The emergence of worldwide infectious epidemics, such as the AIDS epidemic in the early 1980s, fatal influenza, MERS-CoV, and recent outbreaks such as COVID-19 and Monkeypox, urges a global need to adopt universal precautionary practices. Such practices include using protective gloves to protect healthcare workers and limit the spread of infection. Therefore, a significant increase in the use of gloves, both natural and synthetic, in healthcare facilities was noticed. Protective medical gloves are made of various materials, including latex, nitriles, polyethylene, polystyrenes, polyvinyl chloride, polyurethane, neoprene, and polyisoprene (**Walsh et al., 2004**). These gloves differ in their characteristics, such as quality, flexibility, durability, fit, comfort, level of barrier, and allergen content. Due to their durability and low cost, latex and nitrile gloves are usually preferred. However, with the increasing awareness of chemical allergy and the push toward powder-free gloves because of the powder-release related issues for patients and healthcare workers, powder-free and synthetic gloves are gaining favor (**Brehler et al., 1998; Bardorf et al., 2016; Edelstam et al., 2002**).

Latex is the material of standard gloves. It fits well and provides comfort, strength, and moderate protection. Vinyl gloves offer reduced protection and are susceptible to tears, breakage, and pinholes. Nitrile gloves have excellent durability and chemical resistance , but are more expensive than vinyl gloves. Polyisoprene gloves are "latex-like" synthetic gloves that offer better comfort, tear and puncture resistance, and tactile sensitivity. However, it is more expensive than other synthetic gloves **(Chen et al., 2020**). With all types of gloves, allergen content has been an important criterion to check on. Many skin problems have been reported, including irritant contact dermatitis, irritant contact dermatitis, type IV reaction of delayed hypersensitivity, and type I reaction of immediate hypersensitivity (**Alenius et al., 2002**).

The increased demand and use of protective gloves increased these skin problems. In 2020, coincided with the COVID-19 epidemic, the prevalence of skin problems related to glove use was reported to be between 17 and 55% (**Alluhayyan et al., 2020**). A high prevalence of latex glove allergy was reported at a rate of 9.1%, including latex protein allergy and contact dermatitis. In **Sakkaravarthi et al** study, irritant contact dermatitis was

the most common manifestation of latex glove allergy (68.6%) (**Sakkaravarthi et al., 2022**). Rising concerns about latex protein allergy have led several healthcare facilities to seek alternatives to synthetic gloves. However, the shift to synthetic gloves did not solve gloves' skin-related problems. It contains no latex proteins, although it contains chemical accelerators. Thus, it may help reduce the possibility of glove-related latex protein sensitization.

To clinically prove that polyisoprene gloves do not contain additives that could result in hypersensitivity reactions, we used the negative skin sensitization test (Modified Draize-95 Test). This test assesses if a product demonstrates a reduced potential for sensitizing users to chemical additives as described in Guidance for Industry and FDA Staff - Medical Glove Guidance Manual 9 (**Health, 2020**). The test evaluates whether residual chemical additives are present in a finished rubber-containing medical device at a level that may induce Type IV allergy in the unsensitized general user population.

This study was performed to provide data using the Modified Draize-95 test to support the claim that GAMMEX Non-Latex PI, sterile powder-free Synthetic Polyisoprene Surgical gloves (S01) and GAMMEX® Non-Latex PI Green, Sterile Powder-Free Synthetic Polyisoprene Surgical Gloves (S02) compared to the control Nitrile Skin Examination Powder-Free Disposable Gloves (C1) and Aegis Examination Gloves (C2).

Subjects and Methods

Study population and sample size

A quasi-experimental, non-equivalent study was conducted using the modified Draize-95 test from June 22 to August 12, 2021, at the Islamic University of Gaza on 180 female and male volunteers aged between 15 and 56 years old. The sample size calculation was done using the free OpenEpi software version 2.3.1, with the prevalence of the exposure group set at 2.3% (**Wan & Lue, 2006**). The power of the study is set at 90% with a confidence interval of 99% and an additional 20% of respondents for rejected samples due to exclusion criteria, resulting in a minimum of 165 samples to be included. Ultimately, and without exception, 180 participants were included.

Study design

The participants were divided into "black and white" groups according to their skin colors. The black group consisted of 30 volunteers (15 males and 15 females), but the white group consisted of 150 participants (90 males and 60 females). On the other hand, the black male volunteers were randomly divided into two groups: group 1 (n = 8) and group 2 (n = 7). The black female volunteers were also randomly divided into groups 1 (n = 7) and 2 (n = 8). The white male volunteers were randomly divided into two groups: 1 (n = 45) and 2 (n = 42). The white female volunteers were also randomly divided into groups 1 (n = 29) and 2 (n = 34). All participants were given sequential numbers for easy tracking. Group 1 received a set containing S01 inner and outer surfaces and S02 inner surfaces, plus the control materials (C1 and C2). Group 2 received a set that contains S02 inner and outer surfaces and S01 inner surfaces plus the control (C1 and C2) (Figure 1).

Inclusion and exclusion criteria

Healthy individuals were included in the present study if they granted documented informed consent and did not participate in another voluntary test in the previous 30 days. All participants were excluded from the study if they had any visible skin disease, a history of frequent skin irritation, or a history of type I or type IV allergy to natural rubber chemical additives. In addition to other exclusion criteria such as a recent history of using immunosuppressive drugs, prolonged exposure to the sun, and a history of using corticosteroids, whether systematically or topically, at the sites of the test two weeks before the study, all pregnant and lactating women were excluded.

Ethical Consideration

Ethical approval was obtained from the Research Ethics Committee at the Palestinian Health Research Council (Ethics number: PHRC/HC/46/14) and institutional board review from the Islamic University of Gaza. After a thorough explanation of the study procedures, its purpose, and the potential risk of participation, written informed consent was obtained from all participants prior to recruitment in this study. The data were collected anonymously, i.e., without any identifying information. Participants were informed of their ability to withdraw at any time during the study.

Description of material	Group 1	Group 2	Description of material	Negative control	Description of material
S01- inner:			S01- inner:		C1-Control
S01-outer			S02-outer		C2-Control
S02- inner			S02- inner		

Figure 1: The study's test and control materials among groups 1 and 2.

Clinical trials

We used two sets of different types of test material as pieces of coded rubber gloves. Each was a 2x2 cm piece mounted on an adhesive patch. The types of materials of the gloves used include GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves, white (S01) and green (S02), and control materials: Nitrile Skin Examination Powder-Free Disposable Gloves (C1) and Aegis Examination Gloves (C2). These gloves are labeled as non-latex and have excellent chemical resistance, a soft grip, comfort, and effortless donning. The test was done on the inner and outer surfaces of each material. The test materials for the gloves were provided by Healthmedic Research Sdn. Bhd., Malaysia.

Procedures

The study consisted of three main phases: a 3-week induction phase, a 2-week resting phase, and a challenging phase, in addition to a possible fourth rechallenge phase under some conditions, the study phases are detailed below. After a detailed explanation, informed consent was obtained, and inclusion criteria were checked, participants proceeded to the study as follows:

Induction phase

The induction phase involved applying 2x2 cm patches of the inner and outer surfaces of the glove's material and the control for both groups as detailed above. The patches were applied on the left upper back skin of the participants, which is secured on the edges with a nonreactive adhesive tape to ensure continuous and adequate skin.

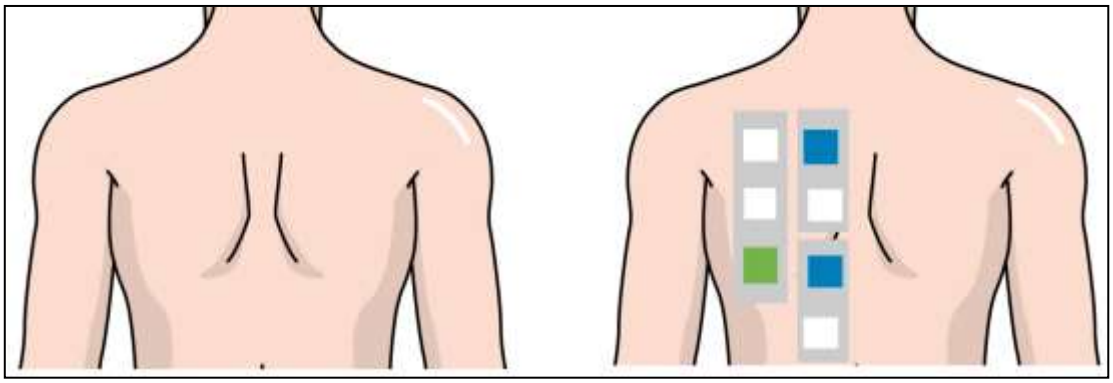

Figure2 : Induction phase; before (left) and after (right) application of the patch for group 1 (S01 inner and outer surface, S02 inner and control material) on the back of the left shoulder.

Ten patches of each type of glove were applied on ten working days: each Saturday, Monday, and Wednesday. Every 48 hours, the patches were removed and a fresh one replaced at the same location, making a total of ten alterations. The patches applied on Wednesday were removed on Saturday, i.e., 72 hours later. The participants were observed for skin reactions, and data was recorded upon removal of each patch on a case record form.

The interpretation of any reactions was determined according to the standard scoring criteria of the North American Contact Dermatitis Research Group (NACDRG). The participant is considered a pre-sensitized individual for any reaction at the initial induction test patch. Any reaction observed after the placement of the second patch in the induction phase will be considered an irritation. In addition, for any local irritation caused by the occlusion material, the occlusion tape will be replaced with the non-irritating one, and the induction patching will be continued. No further patching was done for any case that developed a positive reaction (a score value of 1.5) to chemicals or showed signs of irritation after patch applications. Later, after a minimum of 3 weeks of rest, participants received a challenging patch to confirm the observed reaction as either preexisting sensitivity or an irritant reaction. All such cases were recorded and reported.

Resting phase

At the end of the induction phase and with the removal of the last patch, participants were provided with a 3-week resting period during which no patches were applied.

Challenge Phase

During the challenge phase, two samples of the same test sets of the induction phase were applied simultaneously at the right upper back skin (a virgin site). The test site was evaluated for skin reactions at the time of each patch removal and again two to four days after the removal of the second patch (Figure 3).

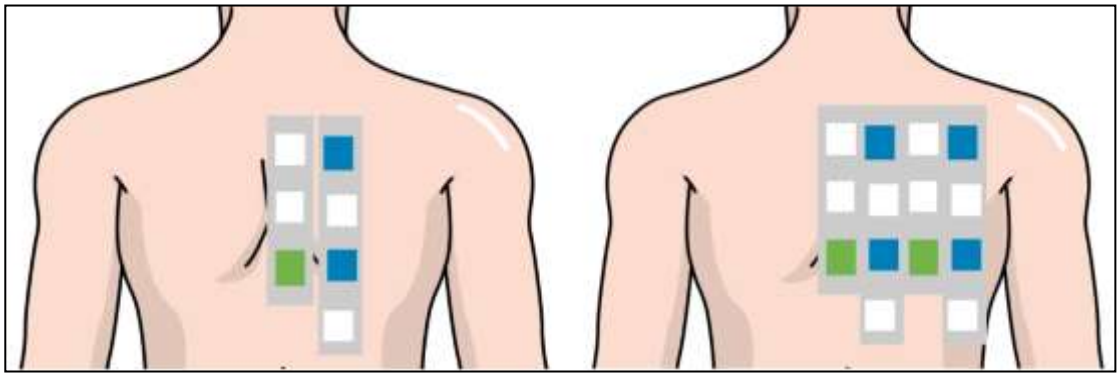

Figure 3 : Two samples of the sample test are applied in the challenge phase on the back of the right shoulder.

Re-challenge phase

The rechallenge phase is carried out if the participants experience skin reactions with score values equal to or higher than 1.5 in the scoring system. The same procedures of the challenge phase were repeated for the rechallenge phase, and the skin was observed.

Scoring criteria

The scoring criteria used in this study are based on those of the North American Contact Dermatitis Research Group (NACDRG) (**DeKoven et al., 2018**). The intensity of reactions was scored as a basic and supplemental score, as shown in Tables 1 and 2. The supplemental scores were added to the basic score if the reactions included the described symptoms. The final score is the sum of the basic and supplemental score values, e.g., 3.5 BS, in the presence of a strong reaction with bullae.

Table 1: Scoring Criteria (Basic Score)

Basic score	Description
0	No visible reaction
0.5	Doubtful or negligible erythema reaction
1.0	Mild or just perceptible macular erythema reaction in a speckled/follicular, patchy or confluent pattern (slight pinking)
2.0	Moderate erythema reaction in a confluent pattern (definite redness)
3.0	Strong or brisk erythema reaction that may spread beyond the test site

Table 2: Scoring Criteria (Supplemental Score)

Supplemental scores	Description	Label
0.5	Edema	E
0.5	Papules	P
0.5	Vesicles	V
0.5	Bullae	B

All subjects who successfully completed the study should have displayed a score value of no more than 1.5 based on the scoring criteria given above. This will qualify the claim that the study material has a reduced sensitization potential when using these gloves.

Results

In this study, the induction phase started on either June 22 or 24 for white volunteers and June 26 for males and females in the black groups. The induction phase finished on July 12 and 14 for white subjects and July 16 for blacks. After that, the challenge phase started on 1, 3, and 5

August and finished on 12 August for all groups. Only 178 volunteers completed this study. One white female from group 1 tested positive for pregnancy after six patches and dropped from the study. Another old white male from group 1 dropped out as he had medical problems and tested COVID-19 positive after five patches. In the induction phase, only two participants scored 1.5 in group 1 of white females. The first scored 2 with the first test material (S02 inner), and the second scored 1.5 with the second control material (C2 control). The patches were removed from another site, and no reaction was seen. None of the two scored 1.5 or more in the challenge phase. In the challenge phase, two white male volunteers from groups 1 and 2 scored 1.5 with the second control material (C2 control) after removing the second patch on the third working day of the challenge phase. There was no scoring of 1.5 for any volunteers during the re-challenge phase. Many volunteers complained of itching or redness related to the adhesive plaster. There were also complaints about the number of patches applied in the study. A summary of the final scores of the study is provided in Table 3, and Table 4 summarizes the percentage of positive reactions in the study phases.

Table 3 Final Score of the skin reaction after the patch testing during the challenge phase for the inner surfaces of both types of GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves (white and green)

Sample	Total Score	Number of Subject
GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves, inner surface, white (S01)	Score less than 1.5	178
	Score more than 1.5	0
GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves, inner surface, green (S02)	Score less than 1.5	177
	Score more than 1.5	1

Table 4 Summary of percentage of positive reaction during the induction phase, the challenge phase, and the rechallenge phase for the test material and the control sample

Description	Number of subjects	Percentage of positive reaction in non-sensitized subjects		
		Induction	Challenge	rechallenge
GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves, inner surface, white (S01)	178	0%	0%	0%
GAMMEX® Non-Latex PI, sterile powder-free synthetic polyisoprene surgical gloves, inner surface, green (S02)	178	0.5%	0%	0%
Control group (C1)	178	0%	0%	0%
Control group (C2)	178	0.5%	1%	0%

Discussion

Our study was performed on 180 healthy, non-sensitized adult volunteers. None of the participants reacted positively to the glove's materials on the inner and outer surfaces. These results can be interpreted as support for the claim that the test material's chemical sensitization potential is low and contains no chemical additives at a level that could cause type IV hypersensitivity reactions. The modified Draize-95 test used in this study on human subjects provides more than 95% confidence that the chemical sensitization potential of the tested GAMMEX Non-Latex PI, sterile powder-free synthetic polyisoprene rubber-containing medical device in the user population is expected to be less than 1.5%. The low sensitivity potential of this type of surgical glove provides an excellent alternative to latex gloves with comparable characteristics.

These latex-like gloves offer similar functions to latex gloves in establishing asepsis, provide comfort and durability, and have low skin problem potential. This alternative is timely considering the increased demand for precautions related to healthcare workers and the general population in times of epidemic emergence, which necessitated the use of gloves in many settings to protect people and prevent the spread of infections. This is especially

important for high-risk groups, atopic individuals, and latex-sensitized people at risk of serious sensitivity reactions with prolonged use. Although most afflicted individuals can be treated without experiencing any long-term effects, type I and type IV reactions may negatively affect their quality of life and interfere with their ability to perform daily tasks at home and at work, or possibly prevent them from performing those tasks altogether. (Kersh et al., 2018). Our study provides clinical evidence to bridge the gap in the literature due to the low number of studies using the modified Draize test-95. This patch test is considered one of the best tests to detect allergies and has more sensitivity than the skin-prick test in diagnosing allergies and detecting contact dermatitis (Strömberg, 2002). A similar study used the modified Draize test-95 to prove the "low dermatitis claim" for a modification of rubber nitrile gloves. The powder-free, accelerator-free LOW DERMA^{TM} Nitrile Examination Gloves showed no clinical evidence of a level of chemical additives that could cause sensitization in the general population (Jeffrey et al., 2017). Our study included 100% participants from the Caucasian race, white and black. We noticed no reaction for the black group of participants compared to the white group, whether for the polyisoprene gloves or the control. This is against what is found in some studies for different races. For example, African American/black people are more susceptible to sensitization than white people (Wegienka et al., 2013; Brunner & Guttman-Yassky, 2019). However, remarkably little high-quality data explains the role of race in developing hypersensitivity reactions to allergens, including gloves. Though our study is not explicitly designed to test racial disparities' role in hypersensitivity reactions to gloves, it provides some insight into this field, concluding the low sensitivity of Caucasians, white and black, to polyisoprene gloves. Similarly, there is no significant difference between males and females in developing sensitization.

Our study has many limitations. For example, the limited number of black participants compared to white participants, in addition to not taking the age of participants into account when dividing people into groups, The allocation of participants to groups was not randomized, either. Despite these limitations, it has many strengths, such as the standardized interventional method of study, the use of controls, and the ideal sample size with very few dropped and withdrawn cases.

We recommend further studies of different designs to provide more robust evidence of the low sensitization risk of using polyisoprene gloves. We recommend different

methodologies to study the risk in addition to the real-world data, such as using cross-sectional or cohort studies in different populations and races with different occupations and durations of use.

Our study showed promising results for using polyisoprene gloves regarding the development of hypersensitivity reactions. Gammex non-latex PI, sterile powder-free synthetic polyisoprene surgical gloves are a reasonable alternative to latex gloves with similar physical properties and a safer profile regarding allergic skin reactions.

Conclusion

The negative results in our study using the Modified Draize-95 test on the GAMMEX® Non-Latex PI, Sterile Powder-Free Synthetic Polyisoprene Surgical Gloves (white and green) and the control gloves support the claim that these materials have a reduced potential to cause skin reactions and that they contain no residual chemical additives and show no clinical signs of type IV allergy in unsensitized individuals. This evidence is encouraging to use these gloves with low dermatitis potential in healthcare settings, especially for individuals known for latex allergies or at high risk of sensitization.

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Conflict of interest: The author declares no conflicted interest, whether affiliation or financial benefits in any entity that directly has a financial interest in the subject materials tested in the study.

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