Volume 38 | June 2017 | ISSN: 1511-5356

Malaysian Journal of Dermatology

JURNAL DERMATOLOGI MALAYSIA

PERSATUAN DERMATOLOGI MALAYSIA | DERMATOLOGICAL SOCIETY OF MALAYSIA

Indexed in: **Western Pacific Research Index Medicus**

www.dermatology.org.my

ORIGINAL ARTICLE

Low Dermatitis Potential of a Powder-Free, "Accelerator-Free" Non Natural Rubber Latex Gloves Using Modified Draize Study

Maryam Sakinah Jeffrey[1], *MBBS,* Wan Muhamad Aiman Wan Muhamad[2], *MBBS,* Iman Jeffrey[3], *MBBS,* Hanisah Jeffrey[4], *MBBS,* Mardhiah Jeffrey[5], *MBBS,* Muhammad Syafiq Muhammad Isa[4], Said AlGhora[6], *PhD FOM,* Emad Ibrahim Husein Shaqoura[6], *MBBS, Master of anatomy,* Doaa kamal Ibrahim Shaqoura[6], *MBBS, Master of Physiology,* Sharifah Ismail[7], *MD,* Nor Wajihan Muda[7], *Msc.Chem,* Siti Maryam Abdul Jabar[7], *Bsc. Biotech,* Saadiah Sulaiman[7], *MMed*

[1]Hospital Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia
[2]Hospital Selayang, Batu Caves, Selangor, Malaysia
[3]Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[4]Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia
[5]Hospital Duchess of Kent, Sandakan, Sabah, Malaysia
[6]Islamic University of Gaza, Gaza, Palestine
[7]Healthmedic Research Sdn Bhd, Cheras, Kuala Lumpur, Malaysia

Abstract

Introduction:

The escalated demand for protective rubber glove in the healthcare industries has resulted in increased prevalence of glove related skin problem, irritant and allergic contact dermatitis and latex sensitivity. The industry has recently introduced a new nitrile glove product using a novel patented non-sulphur system to effect co-valent bond crosslinking to provide the desired elasticity of the gloves. This glove also has ionic crosslinking provided by the zinc oxide used in the formulation and the carboxylic group of the nitrile latex. The main objective of this study is to prove that residual chemical additives at a level that may induce Type IV allergy in the unsensitized general user population are not present in this rubber glove and to compare it with a powder free latex examination glove.

Methods:

In collaboration with the Islamic University of Gaza, we conduct modified test on a specially formulated and powder free, accelerator free LOW DERMA™ enhanced nitrile rubber glove that has physical properties and barrier integrity similar to that of NRL gloves. This glove does not contain sulphur or sulphur related compound. Two sets of Powder free, accelerator free LOW DERMA™ Nitrile Patient Examination Gloves*, white and blue colour were tested using the modified draize-95' test. Filter paper soaked in normal saline and powder free latex examination glove were used as control.

Results:

A total of 209 subjects, 149 subjects, Caucasian (71.29%), 30 subjects, Afro Caribbean (14.35%) and 30 subjects, Asiatic (14.35%) were recruited. All 209 subjects had a final patch testing scoring of not more than 1.5 during both the induction phase and the challenge phase for both types of Powder Free Nitrile Patient Examination Gloves (white and blue) and to the negative control, normal filter paper and the powder free NRL control glove.

Conclusion:
The skin sensitization test ('Modified Draize-95' Test) of Powder Free Nitrile Patient Examination Gloves (white and blue) and the powder free NRL examination glove were negative. There was no clinical evidence on the presence of residual chemical additives at the level that may induce Type IV allergy in unsensitized general user population for both Powder Free Nitrile Patient Examination Gloves, blue and white colored, non-sterile. Both gloves qualify for "Low dermatitis Claim".

Key words: *Latex, Allergy, Nitrile, Glove*

Introduction

With the practice of universal precaution in response to the AIDS epidemic and the worldwide emergence of fatal influenza A(H1N1), A(H5N1), MERS-CoV, the sporadic epidermic of the deadly ebola virus and many other fatal transmissible diseases, the use of protective glove has become an absolute necessity not only among healthcare professionals but also caregivers.

Consequent to this, there is an exponential increase in the demand and usage of protective rubber gloves, both natural and synthetic. This inevitably resulted in the increased prevalence of rubber glove related skin problem mostly contributed by three constituents of rubber gloves, namely the latex protein, chemical accelerators and the powder that is used to ease donning of these gloves.

Three major cutaneous effect of rubber gloves are irritant contact dermatitis, type I allergic reactions and type IV allergic reactions namely allergic contact dermatitis.[1] Irritant contact dermatitis which is non allergenic in nature is most common, affecting any individual and can occur with gloves made from any form of materials.

Type I allergy is an IgE immune-mediated response triggered by exposure to allergenic proteins or polypeptides that occur in latex products. The reaction is immediate and presents typically as direct contact urticaria, less commonly rhinoconjunctivitis and asthma or rarely, systemic in nature, most severe of which is anaphylactic reaction.[2] Chronic occupational exposure to latex results in higher incidence of latex allergy (type I hypersensitivity)[3] affecting 4.32% to 12% of healthcare workers[3-4] and even higher, among atopics with chronic occupational exposure, 43% when compared a prevalence is only 1.4% in the general population.[5]

Type IV reaction is a delayed type hypersensitivity reaction that occurs in response to rubber

Corresponding Author
Dr Saadiah Sulaiman
Healthmedic Research Sdn Bhd, Lot B-G-34, Pangsapuri Sri Penara, Jalan Sri Permaisuri 1, Bandar Sri Permaisuri, 56000 Cheras Kuala Lumpur.
Email: saadiahazim@yahoo.co.uk

chemicals, manifesting also as contact dermatitis which is illicited following usage of rubber glove (24 to 48 hours) in an already sensitised individual. Common causes are residual chemical additives, rubber as accelerators such as dithiocarbamate, tetramethylthiuram disulphide or mercaptobenzothiazoles and antioxidant that was added during the manufacturing of NRL gloves to facilitate cross linking, which is a fundamental process that provide the excellent elastic nature of NRL glove with effective barrier property which can hardly be challenged by synthetic rubber.

Starch powder used to ease donning of rubber glove, increases the allergenic nature of rubber glove as it has the capacity to bind with protein antigens (NRL) and released into the air when the gloves are donned or removed which through inhalation or ingestion can lead to the sensitisation and allergic reactions to NRL.[8-9] Most powdered gloves, powdered surgeon's gloves, powdered patient examination gloves in Germany (1990's) and the United States.[10]

Latex sensitisation which heightened in the 1980s and 1990s has declined dramatically with the combination of safety regulation imposed on latex products, improved education and awareness and with the shift from the use of NRL powdered examination and surgical gloves to the use of powder-free NRL gloves with reduced protein levels and synthetic gloves.[11-17]

Several types of latex-free gloves such as vinyl and nitrile have since been invented to overcome the situation as the demand for glove wearing increased and to provide suitable alternative to individuals with latex allergy. Compared to vinyl, nitrile glove serves greater protective barrier, almost comparable to that offered by latex gloves.[19] However, these synthetic gloves also use the similar cross-linking agent and vulcanisation accelerator with that of NRL glove. Hence, the shift from NRL to synthetic rubber glove did not solve rubber glove related problem. Reports of allergic contact dermatitis to non-latex gloves like nitrile gloves, that used to be far less prevalent than those to NRL gloves, have become more common in recent years.[18]

In order to avoid type IV allergy, it is crucial that synthetic gloves adopt a different formulation or using a different cross-linking system that eliminates the use of chemicals that may cause allergic reactions. The industry has recently introduced a new nitrile glove product using a novel patented non-sulphur system to effect co-valent bond cross linking to provide the desired elasticity of the gloves. This glove also has ionic cross linking provided by the zinc oxide used in the formulation and the carboxylic group of the nitrile latex.

The main objective of this study is to prove that residual chemical additives at a level that may induce Type IV allergy in the unsensitized general user population are not present in this rubber glove and to compare it with a powder free latex examination glove. This study is also designed to meet the requirements for claim, "where this product must demonstrate reduced potential for sensitizing users to chemical additives as described in "Guidance for Industry and FDA Staff - Medical Glove Guidance Manual. Supporting Test Data: A negative skin sensitization test (Modified Draize-95 Test)" on a minimum of 200 non-sensitized human subjects.

Materials and Methods

In collaboration with Islamic University of Gaza, we conducted a modified test on a specially formulated and powder free, accelerator free LOW DERMA™ enhanced nitrile rubber glove that has physical properties and barrier integrity similar to that of NRL gloves, made from acryclonitrile-butadiene. This glove does not contain sulphur or sulphur related compound.

Ethical Consideration

This study was conducted in compliance with the Helsinki Declaration and a written informed consent from the subject was obtained prior to recruitment and filed with the subject's records. The ethical approval were obtained from Islamic University of Gaza (Ethics approval number: PHRC/HC/46/14) and Healthmedic Research Ethics Committee (HMREC) (Ethics approval number: HMREC-HMR-12-2016-B).

Materials

Two sets of Powder free, accelerator free LOW DERMA™ Nitrile Patient Examination Gloves, white and blue colored that have undergone primary skin irritation test and guinea pig sensitisation studies and have been tested negative for rubber chemical accelerators using chemical analytical technique were tested. Filter paper soaked in normal saline were used as negative control and powder free latex examination glove were used as control. The nitrile gloves are produced from a patented

manufacturing process No. US 2013/0198933 A1 and are provided provided by the sponsor (Kossan International Sdn. Bhd.).

Selection and recruitment of study subjects

A total of 209 non-sensitized healthy adult human subjects with no skin problem or previous type 1 or type IV allergy, aged between 18 to 65 years were recruited into the study.

The study comprised of 3 weeks induction phase, 2 weeks rest period followed by challenge phase. During the induction phase, a total of 10 test patches that consists of 2cm by 2cm of tests and control materials were patched onto the skin on each working day. The test patches were removed and replaced with a new one at the same site every 48 hours, for a total of 10 changes. Patches applied before the weekend were removed the next working day, ie 72 hours later.

During the challenge phase, two samples of the same test material were applied consecutively to a virgin site for 48 hours each. The test sites are evaluated for cutaneous reaction at the time of each patch removal and for the challenge patch, the test sites are again evaluated 2 to 4 days after removal of the second patch.

Scoring Criteria

Patch Testing Scoring criteria are based on standard scoring of the North American Contact Dermatitis Research Group (NACDRG).[19] The intensity of reactions were scored as basic and supplemental score according to the criteria listed in table 1a and 1b.

Table 1a. 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 1b. Scoring Criteria (Supplemental Score)

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

Skin reaction during the patch testing were observed and labelled using the scoring criteria provided. For skin reactions (basic score) that occur together with the described signs (supplemental score), both of the scores were added to produce the final score as the final result.

In order to qualify for the claim of a reduced sensitization potential, all the subjects completing the study should exhibit score value of no more than 1.5 based on the scoring criteria describe above.

Results

A total of 209 subjects, 149 Caucasian subjects (71.29%), 30 Afro Caribbean subjects (14.35%) and 30 Asiatic subjects (14.35%) were recruited and completed the study. Age range of the study subjects were between 18 – 58 years (25.29± 9.13). One hundred and five subjects were females (50.24%) and 104 subjects were males (49.76%).

All 209 subjects had a final score of not more than 1.5 during both the induction phase and the challenge phase for both types of Powder Free Nitrile Patient Examination Gloves (white and blue) and to the negative control, normal filter paper and the powder free NRL glove. The results of the final score are summarized in the table 2 while table 3 summarizes the percentage of positive reaction in the duration of induction and challenge test.

Table 2. Final Score of the skin reaction induced by the test patches during the challenge phase for non-sensitized subjects for inner surface of both types of Powder Free Nitrile Patient Examination Gloves (white and blue).

Sample	Total Score	Number of Subject
Powder Free Nitrile Patient Examination Gloves, **White Colored**, Non-sterile, Low Dermatitis Potential Claim (inner surface).	Score less than 1.5	209
	Score more than 1.5	0
Powder Free Nitrile Patient Examination Gloves, **Blue Colored**, Non-sterile, Low Dermatitis Potential Claim (inner surface).	Score less than 1.5	209
	Score more than 1.5	0

Table 3. Summary of percentage of positive reaction during the induction phase and the challenge phase for the test material and the control sample.

Description	Number of subject	Percentage of positive reaction in non sensitized subjects	
		Induction	Challenge
Test material:			
Powder Free Nitrile Patient Examination Gloves, **White Colored**, Non-sterile, Low Dermatitis Potential Claim (inner surface).	209	0%	0%
Powder Free Nitrile Patient Examination Gloves, **Blue Colored**, Non-sterile, Low Dermatitis Potential Claim (inner surface).	209	0%	0%
Negative control:			
Filter paper	209	0%	0%
Control glove:			
NRL glove	209	0%	0%

Discussion

These nitrile gloves are manufactured from a co-polymer of acrylonitrile and butadiene synthetic latex, (carboxilic nitrile rubber latex) instead of NRL, using a patented method. It is the best alternative and to a certain extent almost equal to latex glove, in terms of performance.[18] The patented method eliminates the usage of sulfur as crosslinking agent and sulfur containing compound as crosslinking accelerator, specifically, dithiocarbamate, tetramethyltiuram-disulfide (TMTD) or mercaptobenzothiazole (MBT)[19] which are among the commonest sensitizers detected in patients with contact dermatitis (Type IV) and suspected glove allergy[21-22]. It serves as one of the best option for synthetic rubber latex and does not contain latex protein, which is a known cause of Type 1 allergy.

Patch testing, chosen for this study to evaluate the presence of and the potential effects of the sensitizers is universally regarded as the best method to identify these allergens. It is used to simulate and exaggerate the everyday situations of product application on the skin. None of the volunteers showed positive reaction towards the gloves sample. The results can be interpreted as the non-existence of allergen causative agent or perhaps it exists in a very low amount that has no clinical effects on the skin of the study subjects, thus, provides more than 95% confidence that the chemical sensitization potential in the user population is expected to be less than 1.5%.

NRL glove which uses the chemical accelerators that was used as control in this study also gave similar result. In this case the chemical accelerators in this NRL gloves maybe present in very small quantity that is lower than the threshold for sensitisation hence also qualify for claim of low dermatitis potential.

Changes in glove technology and a dramatic decrease in the prevalence of NRL allergies after interventions, technological advances and education justify the revisit of glove restriction policies of the use of devices made of NRL in healthcare that has been practised as precautionary measures against the perceived risk of NRL allergy.

The introduction of powder-free gloves has been associated with reductions in protein content and associated allergies. The use of low-protein, low-allergenic, powder-free gloves is associated with a significant decrease in the prevalence of type I

allergic reactions to NRL among healthcare workers. Given the excellent barrier properties and physical characteristics, dramatically reduced incidences of allergic reactions, competitive costs, biodegradable in nature[23-25] and naturally derived environmental friendly material, the restriction of usage of NRL gloves within the hospital environment warrants reappraisal. Nevertheless, low-protein, low-allergenic, powder-free gloves does totally eliminate problem relating to NRL allergy, hence there is still a need for non NRL glove especially among high risk individuals.

Although most patients can be treated effectively for type IV and type I reactions without clinical sequelae, major allergy may prevent them from pursuing certain careers, using many household and workplace objects, and seeking timely medical care. Moreover, those with underlying atopy and sensitive skin may well be sensitised with prolonged exposure. Type 1 allergy eg contact urticaria[26] can directly impair barrier function through swelling of the skin surface or indirectly, through scratching, predispose to type IV allergy even with very small quantity rubber chemical.

This powder free, accelerator free LOW DERMA™ rubber glove provides reasonable alternative to NRL rubber glove and further advantage over NRL rubber glove among atopic individuals, high risk group and latex sensitised individuals and elimination of possible future latex sensitisation even though both meets the criteria of low dermatitis potential.

Conclusion

The skin sensitization test ('Modified Draize-95' Test) of Powder Free Nitrile Patient Examination Gloves (white and blue) and the powder free NRL examination glove is negative. There was no clinical evidence of the presence of residual chemical additives at the level that may induce Type IV allergy in the unsensitized general user population in the Powder Free Nitrile Patient Examination Gloves, Blue and white Colored, Non-sterile, Low Dermatitis Potential Claim. Powder free, accelerator free LOW DERMA™ provides for the continuing requirement for synthetic gloves with low dermatitis potential for known latex-allergic patients and staff and those who are high risk of latex sensitisation.

Conflict of Interest Declaration

Authors declare no affiliation or significant financial involvement in any organizations or entity with a direct financial interest in the subject matter or materials discussed in the manuscript on this page. Kossan International Sdn. Bhd sponsored the study material - nitrile gloves (US 2013/0198933 A1).

Acknowledgement

The authors would also like to thank the Director General of Health, Malaysia for permission to publish this paper.

References

1. Cohen DE, Scheman A, Stewart L, Taylor J, Pratt M, Trotter K, Prawer S et al. American Academy of Dermatology's position paper on latex allergy. J Am Acad Dermatol 1998;39:98–106.
2. Ownby DR, Tomlanovich M, Sammons N, McCullough J: Anaphylaxis associated with latex allergy during barium enema examinations. AJR Am J Roentgenol 1991;156:903–8.
3. Bousquet J, Flahault A, Vandenplas O, Ameille J, Duron JJ, Pecquet C et aI. Natural rubber latex allergy among health care workers: a systematic review of the evidence. J Allerg Clin Immunol 2006;118:447–54.
4. Occupational Safety and Health Administration. Latex Allergy. US Department of Labor. Available at http://www.osha.gov/SLTC/latexallergy/index.html. Accessed: June 28, 2013.
5. Köse S, Mandiracioğlu A, Tatar B, Gül S, Erdem M. Prevalence of Latex Allergy Among Healthcare Workers in Izmir (Turkey), Cent Eur J Public Health 2014;22:262–5.
6. Galindo MJ, Quirce S, Garcia OL. Latex allergy in primary care providers. J Investig Allergol Clin Immunol. 2011;21:459-65.
7. Smith DR, Smyth W, Leggat PA, Wang RS. Prevalence of hand dermatitis among hospital nurses working in a tropical environment. Aust J Adv Nurs 2005;22:28-32.
8. Moriber-Katz S, Goldstein S, Ferluga D, Greenstein SM, Miller AS, Schwartz AB et al. Contamination of Perfused Donor Kidneys by Starch from Surgical Gloves. Am J Clin Pathol 1998;90:81-4.
9. Edelstam G, Arvanius L, Karlsson G. Glove powder in the hospital environment – consequences for healthcare workers. Int. Arch. Environ. Health 2002;75:267-71.
10. "FDA proposes ban on most powdered medical gloves." fda.gov. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491466.htm (accessed April 5, 2017).
11. Timo Palosuo Latex Medical Gloves: Time for a Reappraisal, Int Arch Allergy Immunol 2011;156:234– 46.
12. Allmers H, Schmengler J, Skudlik C. Primary prevention of natural rubber latex allergy in the German health care system through education and intervention. J Allergy Clin Immunol 2002;110:318–23.
13. Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. J Allergy Clin Immunol. 2004;114:347–51.
14. Reunala T, Turjanmaa K, Alenius H, Reinikka-Railo H, Palosuo T. A significant decrease in the incidence of latex-allergic health care workers parallels with a decreasing percentage of highly allergenic latex gloves in the market in Finland. J Allergy and Clin Immunol. 2004;113:60.

15. Filon FL, Radman G. Latex allergy: a follow up study of 1,040 healthcare workers. OccupEnviron Med 2006;63:121–5.
16. LaMontagne AD, Radi S, Elder DS, Abramson MJ, Sim M. Primary prevention of latex related sensitisation and occupational asthma: a systematic review. Occup Environ Med 2006;63:359-64.
17. Vandenplas O, Larbanois A, Vanassche F, François S, Jamart J, Vandeweerdt M et al. Latex-induced occupational asthma: time trend in incidence and relationship with hospital glove policies. Allergy 2009;64:415–20.
18. Patel HB, Fleming GJP, Burke FT. A preliminary report on the incidence of pre-existing pinhole defects in nitrile dental gloves. British dental journal 2003;195:509-12.
19. North American Contact Dermatitis Research Group (NACDRG). Am. J. Contact Dermatitis 1991;2:122-9.
20. Khoo SH, Lim LST, Lee SP, Enomoto M (2013). United States Patent Application Publication. US20130198933A1.
21. Nettis E, Assennato G, Ferrannini A, Tursi A. Type I allergy to natural rubber latex and type IV allergy to rubber chemicals in health care workers with glove-related skin symptoms. Clin Exp Allergy. 2002;32:441-7.
22. Geier J, Lessmann H, Uter W, Schnuch A. Occupational rubber glove allergy: results of the Information Network of Departments of Dermatology (IVDK), 1995–2001. Contact Dermatitis 2003;48:39-44.
23. Yip E, Cacioli P. The manufacture of gloves from natural rubber latex. J Allergy Clin Immunol 2002;110:S3–S14.
24. Berekaa MM, Linos A, Reichelt R, Keller U,Steinbüchel A: Effect of pretreatment ofrubber material on its biodegradability by various rubber degrading bacteria. FEMSMicrobiol Lett 2000;184:199–206.
25. Yikmis M, Arenskötter M, Rose K, Lange N, Wernsmann H, Wiefel L et al. Secretion and transcriptional regulation ofthe latex-clearing protein, lcp, by the rubber-degrading bacterium Streptomyces sp.Strain K30. App Environ Microbiol 2008;74:5373–82.
26. Turjanmaa K, Laurila K, Mäkinen-Kiljunen S, Reunala T. Rubber contact urticaria: allergenic properties of 19 brands of latex gloves. Contact Dermatitis. 1988;19:362–7.

ACKNOWLEDGEMENT
June Issue 2017

The Editorial Board of The Malaysian Journal of Dermatology gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Assoc Professor Dr Adawiyah Jamil
2. Assoc Professor Dr Adrian Yong Sze Wai
3. Dr Agnes Heng Yoke Hui
4. Datin Dr Asmah Johar
5. Dr Azura bt Mohd Affandi
6. Dr Ch'ng Chin Chwen
7. Dr Chan Lee Chin
8. Dr Chang Choong Chor
9. Dr Chong Yew Thong
10. Dr Dawn Ambrose
11. Assoc Professor Dr Felix Yap Boon Bin
12. Dr Henry Foong Boon Bee
13. Dr Khor Yek Huan
14. Dr Kwan Zhenli
15. Mr. Lim Yang Kwang
16. Dr Leong Weng San
17. Dr Lo Kang Shang Chit
18. Dr Ma Soot Keng
19. Dr Ng Ting Guan
20. Dato' Dr Noor Zalmy Azizan
21. Assoc Professor Dr Norashikin bt Shamsudin
22. Dr Norazirah Md Nor
23. Dr Priya Gill
24. Mr Regunathan A/L Villanayer
25. Dr Rohna Ridzwan
26. Dr Sabeera Begum
27. Dr Tan Wee Ping
28. Dr Tang Jyh Jong
29. Dr Tang Min Moon
30. Dr Tarita bt Taib
31. Dr Tey Kwee Eng