Clinical Commentary Review

Surgery-Related Contact Dermatitis: A Review of Potential Irritants and Allergens

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Surgical procedures utilize an increasing number of medical products including antiseptics, anesthetics, gloves, suture materials, tissue adhesives, topical antibiotics, and bandages. Many of these products have irritant potential. Allergic contact dermatitis has also been reported. This review covers preoperative, operative, and postoperative exposures that may result in contact dermatitis. Testing with standard patch panels such as T.R.U.E. Test and the North American Contact Dermatitis Group 65 allergen series does not evaluate for all relevant contactants. A thorough understanding of potential exposures is vital to effectively evaluate a patient with surgery-related contact dermatitis. A systematic approach is needed to ensure that standard patch panels and supplementary patches adequately address each encountered contactant. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)**

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The early years of surgery were defined by frequent complications in the absence of anesthesia and antisepsis. Surgery was often considered a last resort with anticipated pain and frequent surgical site infections.[1] Over the last century significant improvements have been made in antiseptics, anesthetics, surgical instruments, and methods of surgical wound closure. A variety of new products continue to improve and refine these areas. Although surgical outcomes and infection rates have improved,[1] a number of these products have been implicated in surgery-related contact dermatitis.[2,3] Many of these products, such as natural rubber latex (NRL), have been implicated in type I immediate hypersensitivity reactions as well. This review will focus on type IV delayed hypersensitivity related to surgical exposures.

Contact dermatitis related to surgical exposures is typified by delayed onset pruritus and a papulovesicular rash manifesting 48 to 96 hours after surgery.[3] Inflammatory mechanisms may include a direct irritant effect or a delayed hypersensitivity reaction resulting in allergic contact dermatitis.[4] Both may result in poor wound healing and, in some cases, wound dehiscence.[5] In the case of allergic contact dermatitis, inflammation may persist for weeks after discontinuation or removal of the offending contactant.[4] Inflammation around the surgical site may sometimes be confused with cellulitis, leading to unnecessary antibiotics and delay in definitive management.

Even when contact dermatitis is suspected, it may be difficult to determine the causative agent. However, because surgical procedures are conducted in a highly systematic fashion, it is possible to identify all the products that were used. This includes preoperative application of antiseptics and anesthetics, operative intervention using sterile metallic instruments, and postoperative wound closure and aftercare. Each step involves exposure to potential irritants and allergenic contactants. Evaluation of surgery-related contact dermatitis requires a thorough understanding of potential exposures and a history detailing all encountered contactants. Complete evaluation may then be conducted by patch testing with contactants and their ingredients. With a growing number of surgical indications and approaches, it has become increasingly important to identify the causative agent of contact dermatitis and to identify acceptable alternative products when available, to recommend for future surgeries to avoid recurrence.

PREOPERATIVE CONTACTANTS

Antiseptics

Antiseptics are applied topically to areas within the planned surgical field to reduce the risk of infection. Many of the first antiseptics contained high levels of elemental iodine. Use of these preparations was limited by a short duration of action and high irritant potential.[6] Newer preparations utilize an iodophor, a preparation containing iodine complexed with a solubilizing agent such as povidone, which aids in product dispersion and reduces exposure to free iodine. Betadine branded products contain 7.5% to 10% povidone-iodine. The concentration of free iodine in povidone-iodine is highest in its liquid form, with lesser irritant potential on drying.[6] Thus, the greatest risk of irritant contact dermatitis stems from pooling of iodine containing antiseptics beneath a patient, which may be obscured by a surgical drape.[7] Although irritant reactions are not uncommon, povidone-iodine has also rarely been implicated as a cause of allergic contact dermatitis.[8-12] Irritant potential must be considered when patch testing. One study patch-tested 500 patients with 1% povidone-iodine aqueous diluted in water. Fourteen patients tested positive, although only 2 of the 14 reacted during repeat open application testing. From this the authors concluded that patch testing with aqueous povidone-iodine may lead to false positives.[13] Repeat open application testing ensures clinical relevance, an important consideration

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Abbreviations used
NACDG 65- North American Contact Dermatitis Group 65 allergen series
NRL- Natural rubber latex
PABA- Para-aminobenzoic acid

when known irritants are being tested under occlusion.[4] Patch testing with dried 10% povidone-iodine solution has also been advocated to reduce false-positive results.[14]

Another commonly used antiseptic is chlorhexidine. Chlorhexidine demonstrates broad antibacterial activity against both gram-negative and gram-positive organisms. It has been utilized since the 1970s in a wide variety of products including consumer handwash and mouthwash, as well as in medical products such as vascular catheters, sponge dressings, and topical surgical preparations.[15] Surgical preparations such as ChloraPrep and Hibiclens contain 2% to 4% chlorhexidine. These preparations have become increasingly favored in the operating room with demonstrated reduction in surgery-related infections when compared with iodophors.[16] Chlorhexidine also carries the potential for irritant reactions,[17] but is also rarely reported as a cause of patch test-proven allergic contact dermatitis.[18-20]

Many chlorhexidine-based antiseptics contain isopropyl alcohol. For instance, ChloraPrep and Hibiclens contain 70% and 4%, respectively. Isopropyl alcohol can also be found in presoaked alcohol swabs used at IV insertion sites, injection sites, and for minor dermatologic procedures. Historically, isopropyl alcohol has been cited as a mild skin and eye irritant with little known allergenic potential. However, a large case series of patients with various eczematous skin lesions and a history of isopropyl alcohol exposure demonstrated sensitization by patch testing in 3%.[21] This suggests that allergic contact dermatitis to isopropyl alcohol is more common than previously thought, although case reports remain rare.

Skin pen markers

Skin pen markers are often used preoperatively to mark the planned surgical site and to provide orienting landmarks. A few cases of contact dermatitis have been reported due to these pens, and have identified dye and other components as the offending allergens.[22,23] The relative paucity of cases may reflect the rather minimal surface area of exposure to the ink and typical removal after surgery.

Anesthetics

Local anesthetics may be applied topically and/or injected into the soft tissues near the surgical site. Both methods may result in an allergic contact dermatitis in sensitized patients.[24-30] IgE-mediated immediate hypersensitivity reactions have also very rarely been reported.[31,32] Local anesthetics are typically grouped into structural classes. Para-aminobenzoic acid (PABA)-based anesthetics are commonly referred to as esters, whereas non-PABA anesthetics are referred to as amides.[4] Amide anesthetics are felt to be uncommon sensitizers,[33] whereas benzocaine, an ester, is the most prevalent anesthetic causing allergic contact dermatitis.[34] Anesthetics within each structural group demonstrate some cross-reactivity[35] (Table I). Therefore, it is recommended that patients experiencing allergic contact dermatitis to a particular anesthetic should avoid all structurally related anesthetics.[4]

TABLE I. Local anesthetics by the structural group

Esters	Amides
Benzocaine	Bupivacaine
Chloroprocaine	Dibucaine
Cocaine	Lidocaine
Procaine	Mepivacaine
Tetracaine	Ropivacaine

Lidocaine is the most commonly used anesthetic in the surgical setting[27,31] and is available in an assortment of topical products as well as injectable forms. Lidocaine containing topical products include EMLA (Astra Pharmaceuticals, Wilmington, Del), BLT (Wedgewood Pharmacy, Swedesboro, NJ), LMX-4 (Ferndale laboratories Inc., Ferndale, Mich), and Topicaine (Ebsa Laboratories, Jupiter, Fla) amongst others. Many of these products are now available over the counter. Fortunately, the prevalence of lidocaine sensitization is less than 1%.[34]

OPERATIVE CONTACTANTS

Gloves

Protective gloves are a common cause of allergic contact dermatitis in the wearer, but rarely in the surgical patient. Gloves are considered a mandatory component of universal precautions and serve to protect the surgeon from blood borne pathogens and to prevent transmission of microorganisms from the surgeon to the surgical site. NRL gloves became popular in the 1980s[36] with increasing use spurred by the emergence of HIV. Immediate hypersensitivity reactions became increasingly prevalent with the use of NRL products.[37] More recently, regulations for lower protein content in NRL gloves, as well as the use of non-powdered gloves, have reduced rates of NRL sensitization.[38] These reactions are due to IgE-mediated sensitization to NRL. Contact dermatitis due to rubber gloves, however, occurs by a different mechanism that does not involve the latex component. Instead, delayed hypersensitivity reactions are due to sensitization to rubber accelerants, including mercapto compounds, thiurams, thioureas, and carbamates, that improve elasticity of rubber products and prevent fracturing.[39]

Because of increased risk of NRL sensitization in health care workers relative to the general population, there is now a mandate for latex-free alternatives. Nitrile gloves have become an increasingly popular substitute. Notably, production of nitrile gloves also requires the use of many of the same accelerants.[40] Carbamates are the most common accelerants used in both nitrile and latex gloves, although thiurams are regarded as the most common causes of allergic contact dermatitis due to protective gloves.[41] Accelerant-free gloves may be used in sensitized patients.

Metals

There is much debate regarding the potential role of metal allergy in orthopedic implant failures. Weight bearing orthopedic implants are typically composed of cobalt-chromium alloys (may contain small amounts of nickel) or titanium-aluminum alloys.[42] Static hardware such as plates and screws may utilize stainless steel made of chromium-iron and nickel.[43] Although nickel is the most common metal sensitizer, followed by cobalt and chromium,[41] there is currently an evolving and unclear link with