Chlorhexidine: Hypersensitivity and anaphylactic reactions in the perioperative setting

A short review on "Perioperative chlorhexidine (CHL) allergy: Is it serious" features in this issue of Journal of Anesthesiology Clinical Pharmacology.[1] This short review explores the possible role of CHL as an allergenic during the perioperative period. The most recent literature data are summarized, and the severity of an allergic or anaphylactic reaction to the aforementioned antiseptic substance is emphasized. In the most recent studies and case reports published, the authors aim to enhance readers' understanding in reference to such a critical, perioperative complication. They highlight the issue through their short but concise summary, as well as through their comprehensive literature review regarding CHL hypersensitivity main aspects, basic sensitization pathways, cross-reactivity reactions and new diagnostic laboratory tools available in the clinical setting, in an effort to alarm all clinicians on the rarity, as well as severity of this potential risk.[1]

Chlorhexidine is a synthetic, low molecular weight topical disinfectant, belonging to the family of bis-biguanides that is widely used in medicine, being extensively applied in the surgical environment, especially for antisepsis of operative fields.[1-4] Currently, CHL is highly valued, due to its consolidated bacteriostatic, bactericidal and fungicidal activity, its microbicide properties towards a wide range of microorganisms, but also due to its proven efficacy and low cost.[4] Unfortunately, it may cause hypersensitivity reactions, varying from contact dermatitis to life-threatening anaphylaxis, with its role as an allergen, potentially complicating a perioperative or anesthetic session, still being under-recognized, often undervalued, or occasionally misdiagnosed.[2-4] Taking into account the ubiquitous use of CHL in medical and nonmedical environments, the sensitization rates seem to be low. Various reactions to the agent have been reported, including delayed hypersensitivity reactions, such as contact dermatitis, fixed drug eruptions and photosensitivity reactions.[3-7] Late onset hypersensitivity and eczema regularly occur and are well-documented events. Conversely, immediate hypersensitivity, sometimes taking the form of acute urticaria that can result in anaphylactic shock, is reported to be less common if not rare.[4,7,8] Lately, an increasing number of case reports of immediate-type allergies (contact urticaria, occupational asthma and anaphylactic shock) have started to appear in the literature. The potential risk of anaphylactic reactions, induced by CHL, is well known, with life-threatening consequences, especially when applied to mucous membranes, therefore discouraging such a use, although application at a 0.05% concentration on wounds and intact skin was so far considered to be safe. Very few cases of severe anaphylaxis due to CHL have been reported, being manifested following simple contact with skin or mucosa.[7,8] Related hypersensitivity is rare, but its potential to cause severe anaphylactic shock, with subsequent cardiovascular collapse, is probably underestimated. Out of the 50 case reports of CHL-related anaphylaxis, published worldwide over the past 10 years, 15 occurred during surgery.[8,9] Signs generally appear from 15 to 45 min postinduction of anesthesia. If there is any suspicion of immediate allergy to CHL, prick-tests or even intradermal reaction techniques are highly recommended. In the event of confirmed allergy, strict eviction is required, bearing in mind that over a hundred currently available medicinal products contain CHL. Unfortunately literature on the immune response following CHL application is restricted, and related knowledge is largely derived from case reports, case series, expert opinions and very few retrospective surveys or cohort studies.[8-10] In current routine clinical practice, in case of suspicion of CHL anaphylactic reaction, anesthesiologists actions and interventions are mostly based on the experience regarding the management of similar perioperative allergic events, independently of the initial stimulus. Indeed, although CHL allergic events represent a rare perioperative complication, they should be kept in mind, especially when differential diagnosis as far as the triggering factor is necessary to be performed.[4,8-10]

According to the literature, anaphylaxis during anesthesia is rare and immediate hypersensitivity reactions to anesthetic and associated agents, administered during the perioperative period, are currently reported, albeit with increasing frequency in most developed countries.[11,12] The incidence of perioperative anaphylaxis is estimated between 1 in 10.000 and 1 in 20.000-25.000 cases, mostly being demonstrated by cardiovascular symptoms (73.6%), cutaneous signs (69.6%), and bronchospasm (44.2%), as the most commonly described clinical features.[13] Unfortunately, any drug administered

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in the perioperative period can potentially produce life-threatening, immune-mediated hypersensitivity responses, and as such, allergy and hypersensitivity occurring in the surgical setting remain a major cause of concern for all perioperative physicians. Muscle relaxants are associated with the most frequent incidence of anaphylaxis, and over the last 2 decades, natural rubber latex (NRL, or *cis*-1, 4-polyisoprene) has emerged as the second most common cause of anaphylaxis. However, the incidence of cases of latex anaphylaxis is decreasing as a result of identification of patients at risk and due to the on-time application of preventive measures. Antibiotics and anesthesia induction drugs account for the next group of drugs more likely to lead to an anaphylactic reaction. Serious problems are unusual during surgery (0.4% of cases), but anesthesia contributes to a third of these cases. Allergic reactions are among the major factors that contribute to morbidity and mortality during an anesthetic and to changes in postoperative care.[11,13,15] All serious intraoperative problems and allergy related sequelae have been highlighted in the literature, also suggesting that preventive strategies are mandatory, in order to reduce anaphylaxis derived consequences. Most anaphylactic-hypersensitivity reactions during anesthesia are of immunologic origin (IgE mediated, anaphylaxis) or related to direct stimulation of histamine release (anaphylactoid reactions). Drugs administered during surgery and various anesthetic procedures can elicit two major groups of adverse reactions. The first group includes those that are usually dose-dependent and related to the pharmacological properties of a drug and/or its metabolites. The rest of them are mostly related to hypersensitivity and allergic responses, do not depend on specific pharmacology and in the majority of circumstances are not dose-dependent.[12,15]

Anaphylaxis is classified among the most severe of immune-mediated adverse responses; it generally occurs following re-exposure to specific antigens and release of pro-inflammatory mediators. The usual early signs and symptoms of an anaphylactic reaction could be overlooked or erroneously interpreted, and nonsevere anaphylaxis could go undetected, with the risk of more severe immunological responses in the future. Using the data registered on the anesthesia chart, it is essential to establish a chronological relationship between drugs and/or substances administered, and the reaction observed. However, anaphylactic reactions cannot be clinically distinguished from nonimmune mediated ones, which account for 30-40% of hypersensitivity responses. Therefore, any suspected anaphylactic event must be extensively investigated, using combined preoperative and postoperative testing to confirm its nature, the suspected drugs that might be responsible and to provide precise recommendations in reference to precautions during future anesthetic procedures. Among currently available investigations, plasma histamine, tryptase and specific IgE antibodies concentration can be determined at the time of the reaction, with subsequent performance of skin tests approximately 6 weeks later. An elevated serum tryptase concentration confirms the diagnosis of an anaphylactic reaction, whereas triggers due to offending substances can be identified by skin prick, intradermal injection, or serologic testing. Nevertheless, such immunologic modalities do not usually give definitive and diagnostic results in the absence of a compromised circulation. Independently, if the slightest suspicion exists, an allergy study should be carried out, preferably between 4 and 6 weeks after the reaction, using a combination of specific IgE, skin and controlled exposure tests (if indicated). Nonetheless, since no specific treatment has been shown to reliably prevent the occurrence of anaphylaxis, allergy assessment must be performed in all high-risk patients. The elimination of triggers during subsequent medical episodes is essential to avoid their recurrence, as well as of critical and paramount importance for the prevention of major mortality and morbidity. However, the need for proper epidemiological studies and the relative complexity of allergy investigation should not be underscored. They indeed represent an incentive for further development of allergiology-anesthesiology clinical networks, to provide expert advice for routine clinical practice.[10,11,14-17]

Chlorhexidine may act as an occupational and patient sensitizer, since it is widely used not only as an antiseptic and disinfectant, in the occupational environment to prevent hospital infections, but also as an adjuvant in oral hygiene substances, as it is present as preservative in toothpaste, mouthwash, nose and eye drops, ointments and personal care products, potentially resulting in airway compromise of both patients and occupationally exposed workers. As the exposure to the agent becomes more widespread, reports of adverse reactions to it are increasing.[4,5,16,18] Allergic contact dermatitis in some cases precedes anaphylaxis. It is imperative that physicians be aware of the many possible sources of contact with this antiseptic and be alert to recognize the potentially debilitating and catastrophic reactions that may occur because of CHL sensitization.[13,16,18] In addition, the role of CHL as an occupational allergen has been confirmed by placebo-controlled specific inhalation challenge tests, monitored by spirometry and analysis of induced sputum (influx of eosinophils after provocation has been observed). Such findings remind clinicians the ability of CHL to cause various hypersensitivity reactions and the potential risk of this widely used antiseptic.

Chlorhexidine may interrupt a surgical procedure, or complicate an anesthetic session, occasionally in an unpredictable way. Since CHL is an underestimated allergen, several anaphylactic

episodes may occur in a patient before it is identified as the responsible allergen. Topical CHL may cause anaphylaxis, especially when applied on mucosal surfaces, with application on even small mucosal areas being sufficiently enough to trigger an IgE mediated anaphylactic response. Multiple authors suggest that such reactions are underreported and as a result alternative noncross-reacting antiseptics are usually not requested, since the underlying sensitization is, unfortunately, unknown or misdiagnosed. Surprisingly, simple contact urticaria, which can be considered as an initial sign of IgE-mediated contact anaphylaxis induced by CHL has been rarely reported.[2-4,16-19]

In the perioperative environment, anaphylaxis symptoms generally appear immediately, within the first 15-45 min after anesthesia induction. Initial symptoms are often underestimated (simple acute urticarial) or not recognized due to surgical draping of the patient. Nonetheless, generalized urticaria may develop rapidly up to systemic anaphylaxis, characterized by multiple signs and symptoms, including tachycardia, bronchospasm, and hypotension. Without proper and rapid treatment the cascade may evolve to severe anaphylactic shock due to cardiovascular collapse and cardiac or respiratory arrest. Sometimes delayed-type reactions, such as allergic contact dermatitis and immediate-type reactions may coexist in the same patient, whereas CHL-induced eczema may precede the development of CHL-induced anaphylaxis by years, suggesting that patients with CHL-induced contact dermatitis are prone to IgE sensitization. Therefore, in patients with allergic CHL-contact delayed-type hypersensitivity, further use of CHL or CHL-coated catheters should be avoided to prevent IgE sensitization.[2-4,16-20]

In reference to perioperative CHL anaphylactic episodes, in most of the case reports published, patients ended up in experiencing at least two episodes of perioperative anaphylaxis, despite the fact that CHL had been correctly identified as the responsible allergen and avoided in disinfectants during the second anesthesia session. Researchers speculated that it might be possible that CHL hypersensitivity, carefully reported by the patient, has been probably undervalued by anesthesiologists during central venous catheter (CVC) line placement or patients' perioperative care.[16,18-19]

Recently, studies involving cohorts of patients with CHL-induced anaphylactic reactions following the placement of urethral catheters or CVC, have been published, suggesting either an increased attention to the problem from anesthesiologists or an augmented use of CHL in medical devices. Furthermore, in most of the patients with CHL induced anaphylaxis, some previous mild reactions following CHL exposure could be retrospectively identified in their clinical history. These symptoms were undervalued or misdiagnosed, being attributed to a vaso-vagal reaction or to a nonallergic erythematous urticarial rash, due to drugs with histamine-releasing effects. During anesthesia, it is imperative that every procedure and drug administration should be recorded and annotated step by step in the patient's clinical chart: that may help to identify the causative agent in case of perioperative anaphylaxis. Importantly, CHL is not documented as a drug administered by anesthesiologists because skin disinfection and peripheral venous catheter insertion performed by nursing staff, in the majority of cases, are considered as routine preoperative activities.[18-20]

Chlorhexidine hypersensitivity seems to be more frequent than initially estimated and an increasing attention is dedicated to this disinfectant as potential allergen, complicating general anesthesia, despite the fact that the real incidence of immediate-type adverse reactions is still unknown and underestimated. When allergic tests to latex after perioperative anaphylaxis remain negative, anesthesiologists' and allergiologists' attention should be focused on CHL as a hidden allergen, because diagnostic tools as skin tests and serum specific IgE assay for accurate identification are indeed available, but a first prerequisite is the necessity to suspect correctly the allergen involvement.[2,3,13,18,20]

Additionally, although recent anesthesia guidelines suggest letting the skin applied with disinfectant to be completely dry before beginning an invasive procedure, the cutaneous absorption or the possibility to introduce CHL with CHL-coated catheters through mucosal or intravenous route neutralizes that precaution.

Nevertheless, more studies are still needed to further address the problem and sequentially establish the predictive value of skin tests in patients reporting potential risk factors for CHL hypersensitivity as:

1. A CHL induced contact dermatitis;
2. A professional exposure to disinfectants;
3. Previous invasive medical procedures in patient's clinical history.

The identification of specific serum IgE in allergy testing to CHL is a reliable tool (high specificity and sensitivity). Inhalation challenge tests with assessment of clinical symptoms, spirometry changes and cellular changes in induced sputum or nasal lavage play a significant role in the diagnosis of CHL allergy (mainly for compensation for occupational disease).[2,3,13,18-21]

In conclusion, occupational and perioperative severe anaphylaxis to CHL has been estimated to be rare, but in reality percentages may be higher than reported. Its extensive use to reduce hospital-acquired infections has the potential to sensitize a small proportion of patients, leading to life-threatening anaphylaxis on subsequent exposure. Such a potential necessitates vigilance of physicians and nursing personnel involved in patients

perioperative care and should also prompt occupational health and safety services to improve health risk management towards effective implementation of preventive measures.[2,3,5,7,13,18-21]

Anaphylaxis, especially due to CHL, is generally an unanticipated severe allergic reaction, often explosive in onset that may occur during a surgical procedure, when multiple drugs are administered for the conduction of an anesthetic. Because patients are under drapes and mostly unconscious or sedated, the early cutaneous signs of anaphylaxis are often unrecognized, leaving bronchospasm and cardiovascular collapse as its first recognized signs. Although CHL anaphylaxis is a rare intraoperative event, it should always be kept in mind of anesthesiologists, in case the triggering factor is unknown. Unfortunately, documentation of anaphylaxis is often lacking because the cause and effect relationship is often hard to prove and because the diagnosis is not easy to be made with the patient under anesthesia. Furthermore, only a minority of patients get referred for allergy testing to confirm the offending drug. Prevention is the most important component to decrease the incidence of anaphylaxis. Documentation of anaphylaxis during anesthesia, referral to an allergiologist for identification of the causative drug and appropriate labeling of the patient are essential to avoid similar episodes in the future.

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