Editorial

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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DOI: 10.4103/0970-9185.155138

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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How to cite this article: Moka E, Argyra E, Siafaka I, Vadalouca A. Chlorhexidine: Hypersensitivity and anaphylactic reactions in the perioperative setting. J Anaesthesiol Clin Pharmacol 2015;31:145-8.
Source of Support: Nil, **Conflict of Interest:** None declared.

Review Article

Perioperative chlorhexidine allergy: Is it serious?

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Abstract

Chlorhexidine is an antiseptic agent, commonly used, in many different preparations, and for multiple purposes. Despite its superior antimicrobial properties, chlorhexidine is a potentially allergenic substance. The following is a review of the current evidence-based knowledge of allergic reactions to chlorhexidine associated with surgical and interventional procedures.

Key words: Allergy, anesthesia, complications, chlorhexidine, perioperative

Introduction

Chlorhexidine is an antiseptic agent, cationic polybiguanide, commonly used, in many different preparations, and for multiple purposes primarily as a skin and wound disinfectant but also in cosmetics and several pharmaceutical products, such as in eye drops, mouthwashes, creams, hand rinses, toothpaste and deodorants.[1,2] Chlorhexidine salts dissociate with release of positively charged chlorhexidine cations at physiological pH. The bacteriostatic and bactericidal actions of chlorhexidine are concentration-dependent, with disruption of the bacterial membrane and cell death occurring at high concentrations. The use of chlorhexidine is recommended in various clinical settings secondary to its activity against a broad range of organisms: Gram-negative and gram-positive as well as facultative aerobes/anaerobes and yeast.[3] Chlorhexidine has been used and recommended as per infection control guidelines and figures on the World Health Organization's list of essential medicines.[4] It is applied and is extremely useful in several poor, underserved areas for disinfection of the umbilical cord in newborns. However, despite its superior antimicrobial properties, chlorhexidine is a potentially allergenic substance. The following is a review of the current evidence-based knowledge of allergic reactions to chlorhexidine associated with surgical and interventional procedures.

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.155140

Review of Studies and Reports

Relevant, peer-reviewed original research articles, reviews and reported cases between 1980 and 2014, as identified in Medline/PubMed using the keywords anaphylactoid, anaphylaxis, and chlorhexidine were reviewed.

During anesthesia, different mediators may be implicated in anaphylactic/anaphylactoid responses such as: IgE in type I hypersensitivity mechanisms, IgA, immunocomplexes, complement activated by an alternative pathway, tryptase, and histamine. Diagnostic methods include skin tests, challenge, histamine release test, human basophil optical degranulation test, and ImmunoCAP.[5] Flow cytometric allergen stimulation tests show promise in differentiating allergic from idiosyncratic pseudo allergic reactions.[6] An increase of tryptase concentration in the serum confirms the diagnosis of an anaphylactic reaction, and triggers may be evaluated and identified by skin tests, intradermal injection, or serologic testing. These tests are useful in eliminating allergens and selecting alternatives during subsequent anesthesia administration, in order to avoid complications, mortality and morbidity.[7]

Chlorhexidine has been reported to cause allergic reactions in sensitized patients. Dermatitis or stomatitis caused by chlorhexidine-containing topical medicaments has

been documented.[8,9] Studies showed that anaphylaxis associated with invasive, interventional and surgical procedures include neuromuscular blocking agents, natural rubber latex, antibiotics, and induction agents as the most common causes. Colloids, opioids, and radio contrast media are less frequent and probably account for <10% of all reactions. The more recent and newer agents used perioperatively, and reported as implicated in anaphylaxis include isosulfan blue and chlorhexidine.[6] A positive patch reaction to chlorhexidine was seen in 36 (0.47%) dermatology patients with suspected contact allergy. Furthermore, four cases of occupational IgE-mediated allergy to chlorhexidine were identified in the UK.[10] Hypersensitivity reactions to chlorhexidine have included allergic contact dermatitis, pruritus, vesicle formation, urticaria, dyspnea, and anaphylactic shock. The precise incidence of chlorhexidine allergic reactions and the associated morbidity and mortality remain unknown. Patch testing using chlorhexidine has revealed positive reactions in more than 2% of patients tested. In eczema patients, the rate may be as high as 5%.[11] Since chlorhexidine is the standard skin disinfectant used before surgery or invasive procedures, the potential for developing allergy to chlorhexidine is significant, especially under anesthesia. Four patients with severe allergic reactions to chlorhexidine associated with surgery and general anesthesia have been reported. Symptoms manifested 20-40 min into the procedure, and all patients required administration of adrenaline. The four patients, subsequently, tested positive for chlorhexidine on skin testing. A history of minor symptoms like rashes in relation with previous invasive procedures or surgeries was present in all of these patients.[12] Another report described six patients who had anaphylactic reactions attributed to chlorhexidine during surgery. These patients were exposed to chlorhexidine in gels, swabs and catheters. On detailed assessment, five of the six patients demonstrated a previous history of reactions on re-exposure to chlorhexidine. All six patients had elevated specific IgE to chlorhexidine. Skin prick test with chlorhexidine was performed in four of the six patients and was found to be positive.[13] A retrospective analysis of patients referred from 2007 to 2011 to a university allergy center with the suspicion of an allergic reaction associated with general anesthesia revealed that a diagnosis of IgE-mediated reaction was established in 63.9% of cases. The most common agents involved were neuromuscular blocking agents (61.8%), antibiotics (14.5%), latex (9.2%) and chlorhexidine (5.2%).[14]

Chlorhexidine allergy is IgE-mediated and measurement of specific IgE and histamine release are good adjuncts to skin testing to support the diagnosis of chlorhexidine allergy in patients with clinical history suggesting sensitivity to chlorhexidine.[15] Investigations of allergic reactions during anesthesia ranging from mild to severe would follow a standard step-by-step protocol of skin testing and *in vitro* testing. Blood samples for tryptase analysis are drawn at the time of the allergic reaction, and a control sample is drawn together with samples for specific IgE analysis 2-4 weeks after the allergic reaction. Subsequent skin testing comprises both prick tests and intradermal tests in most cases. Patients are tested with all potential allergic substances exposed to, including antibiotics, colloids, latex and chlorhexidine.[16] The incidence of anaphylaxis to vital dyes and chlorhexidine has been reported as increasing.[17] In the presence of an allergic reaction, investigation should include screening for chlorhexidine in all patients as exposure to both these agents is common and allergic reaction to this substance may be overlooked.[18]

In a study including patients with leg ulcers, patch testing to chlorhexidine performed with chlorhexidine gluconate aq., and chlorhexidine acetate 1% aq., reported that 39/297 of patients showed positive reactions to one of these compounds or to both, 36 positive reactions to chlorhexidine acetate were observed, in contrast to 18 reactions to chlorhexidine gluconate. In 22 of the 39 patients with positive reactions, the results were considered relevant, since these patients had developed an eczematic reaction in the area where a chlorhexidine compound was used, and discontinuing chlorhexidine resulted in improvement of the reaction. It is of note that in 10 of these 22 symptomatic patients, the diagnosis would have been missed if the gluconate was the only compound used for testing, while the chlorhexidine acetate test failed to diagnose two patients. In patients without leg ulcers, inconclusive patch test readings (i.e., irritant reactions or weak positive reactions) were found in 17% with chlorhexidine acetate 1% aq., compared to 5% with chlorhexidine gluconate 1% aq., implying a high degree of irritant potential of the acetate 1% aq. Some positive reactions would be lost if chlorhexidine gluconate 1% aq., only is used for patch testing, therefore, the authors suggested that further testing with chlorhexidine acetate 1 and 0.5% aq., should be performed, in parallel with chlorhexidine gluconate 1% aq., in order to establish appropriate test concentration.[19]

On a molecular basis, two molecules of chlorguanide form the symmetrical molecule of chlorhexidine while the interior structure of alexidine (that is excluding the terminal 2-ethylhexyl groups) is identical to part of the chlorhexidine molecule. Chlorguanide and alexidine, the structures of which each comprise part of the chlorhexidine molecule, showed significant inhibition of the binding of IgE antibodies to chlorhexidine; however, neither compound was as potent an inhibitor as chlorhexidine itself. It

seems that the whole chlorhexidine molecule is complementary to the IgE antibody combining sites and that the 4-chlorophenol, biguanide and hexamethylene structures together comprise the allergenic determinant. [20]

Recommendations

The true incidence of chlorhexidine allergic reactions and their associated morbidity and mortality remains unknown. It is recommended that centers investigating patients with reactions during anesthesia and surgery should routinely include testing for chlorhexidine allergy. [13, 21] Anaphylaxis during surgical and interventional procedures may be difficult to evaluate because of the rapid, successive use of multiple drugs. A detailed history, and careful analysis of anesthetic records and diagnostic tests such as determination of chlorhexidine specific IgE, mast cell tryptase and skin tests may be performed to ensure a complete evaluation. Any suspected hypersensitivity reaction during anesthesia must be extensively investigated to confirm the nature of the reaction, to identify the responsible drug, and to provide recommendations for future anesthetic procedures. Tryptase assay at the time of the reaction has to be implemented by thorough investigations carried out weeks later: Prick tests and intradermal tests, quantification of specific IgE, histamine release test or cytometric analysis of basophile activation.[17] An informed guess is not a reliable way of determining the cause of a supposed allergic reaction during anesthesia and may put a significant number of patients at unnecessary risk. Some patients may be labeled with a wrong allergy, leading to unnecessary warnings against harmless substances, and some patients may be put at risk of subsequent re-exposure to the real allergen. Patients with suspected allergic reactions during anesthesia should be referred for investigation, whenever possible.

Conclusion

Hypersensitivity reactions to chlorhexidine are diverse and comprise allergic contact dermatitis, pruritus, vesicle formation, urticaria, dyspnea, and anaphylactic shock. [15] Principal sources of chlorhexidine contact sensitization are chlorhexidine-containing corticosteroid creams, skin disinfectants and oral hygiene products. There are many reports of allergic reactions, including anaphylaxis, following exposure to chlorhexidine. Reactions may occur via contact with the skin and mucous membranes or from catheters treated with an antibacterial agent. In the surgical patient, allergy to chlorhexidine may be more prevalent [12] with possibility of underreporting of cases due to the lack of suspicion toward this substance.

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How to cite this article: Abdallah C. Perioperative chlorhexidine allergy: Is it serious?. J Anaesthesiol Clin Pharmacol 2015;31:152-4.
Source of Support: Nil, **Conflict of Interest:** None declared.