Review Article

Local Anesthesia in Complex Dermatological Diseases: Adverse Reactions and Clinical Considerations

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Abstract

Local anesthesia is fundamental to dermatologic and dermatosurgical practice, enabling effective pain control while facilitating minimally invasive procedures across a wide spectrum of skin diseases. Its use becomes particularly complex in patients with inflammatory, autoimmune, genetic, and systemic dermatological disorders, in whom altered skin physiology and immune dysregulation can significantly influence anesthetic efficacy and safety. Amide-type local anesthetics, such as lidocaine and bupivacaine, are preferentially used due to their chemical stability and lower allergenic potential, acting primarily through inhibition of voltage-gated sodium channels, with additional membrane-mediated and nociceptive modulatory effects. However, pharmacokinetic and pharmacodynamic behavior is highly dependent on the local tissue environment. Barrier dysfunction, increased vascularity, chronic inflammation, fibrosis, and immune activationcommonly observed in conditions such as psoriasis, atopic dermatitis, epidermolysis bullosa, and connective tissue diseasescan impair anesthetic diffusion, reduce analgesic effectiveness, and increase systemic absorption. Certain

dermatological conditions are associated with higher anesthetic risk due to multisystem involvement, comorbidities, and heightened inflammatory responses, necessitating individualized anesthetic planning. Although adverse reactions to local anesthetics are infrequent, they encompass a broad clinical spectrum, ranging from vasovagal and psychogenic responses to hypersensitivity reactions and the rare but potentially life-threatening local anesthetic systemic toxicity. Accurate clinical evaluation and differential diagnosis are essential to distinguish anesthetic-related reactions from disease flares or other drug-induced events. Diagnostic tools, including plasma anesthetic level measurement, cutaneous testing, and structured causality algorithms, support appropriate management and future risk reduction.

Key words

Pharmacokinetics; immunological dysregulation; inflammatory dermatoses; risk stratification; anesthetic safety; clinical management.

Introduction

Local anesthesia plays a central role in dermatology and dermatosurgery, as it enables effective pain control during a wide range of procedures while allowing for precise and minimally invasive interventions. Its use is particularly fundamental in techniques such as Mohs micrographic surgery and skin grafting, where adequate analgesia is essential to ensure procedural accuracy and patient comfort [1, 2]. In parallel with its established applications, ongoing innovations have sought to optimize anesthetic delivery and patient experience. Among these advances, dissolvable microneedles loaded with lidocaine hydrochloride have been developed to improve transdermal penetration, achieving a rapid onset of action and effective analgesia that surpasses conventional topical anesthetic gels [3]. In addition to novel delivery systems, modifications of traditional techniques have also demonstrated clinical benefit. Buffering local anesthetics with sodium bicarbonate has been shown to significantly reduce injection-related pain, thereby enhancing patient comfort during procedures such as Mohs surgery [1].

Within this therapeutic context, the use of local anesthesia is particularly relevant in the management of complex dermatological diseases. This group encompasses conditions such as skin cancers, hypertrophic scars, keloids, and calcinosis cutis, which frequently require surgical or minimally invasive interventions as part of their treatment strategy [2, 4]. These disorders often necessitate technically demanding procedures, including bone burring under local anesthesia in cases of skin cancer with periosteal involvement, an approach that has been shown to be well tolerated by patients while remaining cost-effective [2]. Similarly, in non-oncologic conditions such as primary palmar hyperhidrosis, local anesthesia is routinely employed to mitigate procedural pain during interventions like botulinum toxin injections, thereby improving tolerability and adherence to treatment [5].

Despite its widespread use and favorable safety profile, the potential for adverse reactions to local anesthetics represents a clinically relevant concern. Systemic toxicity remains one of the most significant complications, with manifestations that may involve both the central nervous system and the cardiovascular system, underscoring the importance of vigilance during dermatological procedures. In this regard, monitoring plasma concentrations of local anesthetics can be a valuable tool for the identification and confirmation of systemic toxicity, contributing to timely diagnosis and enhanced patient safety [6]. Nevertheless, available evidence indicates that when topical and intralesional anesthetics are administered at appropriate doses, serum concentrations remain

well below toxic thresholds. This supports their continued use as effective analgesic agents in dermatological practice, as they provide adequate pain relief without clinically significant systemic absorption [7].

The objective of this article is to examine the use of local anesthesia in complex dermatological diseases, emphasizing adverse reactions and key clinical considerations to support safe and effective dermatologic practice.

Methodology

This manuscript was developed as a narrative review focused on the clinical use of local anesthesia in complex dermatological diseases, with particular emphasis on adverse reactions and practical considerations that influence patient safety and procedural outcomes. Rather than following a rigid methodological sequence, the review was structured around clinical reasoning, prioritizing how pharmacological, dermatological, and immunological factors intersect during real-world dermatologic and dermatosurgical practice.

To maintain conceptual coherence across these domains, artificial intelligence–assisted tools were used as supportive resources for thematic organization and for mapping relationships between local anesthetic pharmacology, altered skin pathophysiology, and mechanisms underlying adverse reactions. These tools were applied exclusively for content structuring and synthesis and did not influence the interpretation, selection, or weighting of the scientific evidence.

Following the definition of the conceptual framework, relevant literature was consulted to substantiate the narrative discussion. Peer-reviewed articles published between 2021 and 2026 and indexed in PubMed, Scopus, and Web of Science were selectively included based on their relevance to local anesthetic use in dermatology. Priority was given to studies addressing pharmacological properties of local anesthetics, clinical applications in complex dermatological conditions, adverse reactions and toxicity, immunological mechanisms, and strategies for prevention and management. Non–peer-reviewed sources, redundant data, and publications without direct clinical relevance were excluded.

This narrative approach allowed for an integrative and flexible synthesis of current evidence, highlighting the interaction between disease-specific skin alterations and anesthetic response, and supporting a clinically oriented perspective aimed at optimizing the safe and effective use of local anesthesia in complex dermatological settings.

Pharmacological Principles of Local Anesthetics

Local anesthetics used in dermatology are primarily classified into amide and ester types. Amide anesthetics, such as lidocaine and bupivacaine, are the most employed agents in dermatologic practice due to their greater chemical stability and lower allergenic potential when compared with ester compounds such as procaine. This favorable safety profile has positioned amide anesthetics as the preferred choice for a wide range of cutaneous and dermatosurgical procedures. In addition to conventional formulations, quaternary lidocaine derivatives have been investigated for their rapid onset and prolonged duration of action, characteristics that are particularly advantageous in dermatological settings where sustained analgesia is desirable [8].

The anesthetic effect of these agents is mediated through well-defined mechanisms at both the cutaneous and neural levels. Local anesthetics primarily exert their action by inhibiting voltage-gated sodium channels, thereby preventing the initiation and propagation of action potentials along nerve fibers and resulting in reversible loss of sensation [9]. Beyond this canonical mechanism, local anesthetics also interact with the physical properties of cellular membranes, inducing membrane-mediated effects that

influence a variety of receptors and ion channels. These alterations can further modulate nerve impulse transmission and contribute to the overall anesthetic effect [10]. In parallel, local anesthetics have been shown to modulate transient receptor potential channels, which are integral to nociceptive signaling, a mechanism that may enhance analgesic efficacy, particularly in the context of inflammatory skin conditions [9].

Pharmacokinetic and pharmacodynamic factors play a critical role in determining the clinical performance of local anesthetics in diseased skin. The onset of anesthesia is largely governed by diffusion through extracellular spaces rather than transmembrane transport, a process that is highly sensitive to local tissue pH. Acidic environments, which are common in inflamed or infected skin, can reduce drug accumulation and diminish anesthetic efficacy [11]. To address these limitations, advances in transdermal delivery systems, such as dissolvable microneedles, have been developed to enhance cutaneous penetration, achieving rapid onset and effective pain control that is particularly well suited to dermatological applications [3]. The duration of anesthetic action is another key consideration, with extended-release formulations, including liposomal bupivacaine, designed to prolong analgesia. Nevertheless, their higher cost and variable clinical effectiveness continue to represent important limitations [12]. From a safety perspective, topical administration of agents such as lidocaine and bupivacaine has been shown to provide effective analgesia while maintaining minimal systemic absorption, thereby reducing the risk of toxicity when used appropriately [7].

Skin Pathophysiology and Its Impact on Local Anesthesia

Alterations of the skin barrier and vascularity represent key factors influencing the behavior of local anesthetics in complex dermatological diseases. Conditions such as psoriasis and atopic dermatitis are characterized by significant skin barrier dysfunction, which can directly affect anesthetic penetration and efficacy. In psoriasis, aberrant keratinocyte differentiation and hyperproliferation disrupt the structural integrity of the epidermal barrier, potentially modifying the absorption and clinical performance of local anesthetics [13, 14]. Similarly, atopic dermatitis is associated with reduced filaggrin expression and alterations in epidermal lipid composition, resulting in a weakened barrier that can interfere with predictable anesthetic delivery and action [15, 16].

In parallel with barrier disruption, inflammatory skin diseases frequently exhibit marked changes in vascularity. Increased angiogenesis has been documented in conditions such as psoriasis and recessive dystrophic epidermolysis bullosa, leading to enhanced blood flow within affected tissues. These vascular alterations can influence both the distribution and clearance of locally administered anesthetics, thereby affecting their duration of action and systemic exposure, and may necessitate adjustments in dosing strategies to maintain efficacy while minimizing risk [17, 18].

Beyond structural and vascular changes, inflammation, fibrosis, and immune activation further modify the local tissue environment in ways that are clinically relevant for anesthetic management. Chronic inflammation, as observed in psoriasis and atopic dermatitis, alters nociceptive signaling through the release of inflammatory cytokines and infiltration of immune cells, which can modify nerve sensitivity and pain perception and complicate the achievement of adequate anesthesia [14, 15]. In fibrotic conditions such as localized scleroderma, excessive collagen deposition and tissue stiffening impede anesthetic diffusion, reducing effectiveness. The presence of inflammatory fibroblast subclusters adds further complexity to the tissue milieu, potentially influencing anesthetic action at the local level [19]. Autoimmune activation also plays a significant role in disorders such as

epidermolysis bullosa acquisita, where immune-mediated inflammation can alter nerve function and exacerbate pain. In this context, the contribution of scratching and mechanical irritation underscores the intricate interaction between immune responses and anesthetic requirements [20].

Collectively, these disease-related alterations have important implications for both anesthetic efficacy and safety. The modified skin environment associated with inflammation, barrier dysfunction, and altered nerve signaling can lead to reduced anesthetic effectiveness, sometimes requiring higher doses or alternative delivery methods to achieve adequate analgesia, particularly in atopic dermatitis and psoriasis [16]. At the same time, increased vascularity and inflammatory activity may enhance systemic absorption of local anesthetics, thereby raising the risk of toxicity. For this reason, careful patient assessment, dose adjustment, and monitoring are essential to ensure safe anesthetic use in complex dermatological settings [17, 18].

Dermatological Diseases Associated with Higher Anesthetic Risk

Autoimmune and inflammatory dermatoses represent a particularly challenging group of conditions in the context of local anesthetic management, as their underlying immunological dysregulation and frequent systemic involvement can significantly influence anesthetic response and safety. Sarcoidosis, a chronic inflammatory disease with potential cutaneous manifestations, exemplifies this complexity, as its clinical presentation may overlap with disorders such as psoriasis and eczema. This overlap, combined with the immunological heterogeneity inherent to these conditions, necessitates individualized anesthetic strategies aimed at minimizing risk while ensuring adequate analgesia [21]. Atopic dermatitis further illustrates the need for careful consideration, as it extends beyond a purely cutaneous disorder and is associated with an increased prevalence of cardiovascular, autoimmune, and metabolic comorbidities. These systemic associations can complicate anesthetic management, underscoring the importance of thorough pre-procedural assessment and tailored peri-procedural planning [22]. Similarly, lichen planus is frequently linked to other autoimmune conditions, including systemic lupus erythematosus and Sjögren's syndrome, which may heighten anesthetic risk and require comprehensive evaluation to ensure safe anesthetic administration [23].

Chronic inflammatory and pigmentary disorders also pose distinct challenges due to their systemic immunological components. Psoriasis, in particular, is characterized by persistent systemic inflammation that can affect multiple organ systems. In severe cases, the need for systemic therapy and the presence of associated comorbidities can further complicate anesthetic decision-making, necessitating careful coordination to prevent additional complications during dermatologic procedures [24, 25]. In parallel, pigmentary and hair disorders such as vitiligo and alopecia areata share overlapping immune-mediated mechanisms with psoriasis. These shared pathways may have systemic implications that influence anesthetic response and warrant heightened awareness during anesthetic planning [25].

Genetic and systemic diseases with cutaneous involvement represent an additional layer of complexity. Epidermolysis bullosa is characterized by extreme skin fragility and frequent multiorgan involvement, creating substantial anesthetic challenges even for minor procedures. Safe management in these patients requires meticulous planning, strict avoidance of mechanical trauma to the skin, and careful airway management to reduce the risk of peri-procedural complications [26]. Likewise, lupus erythematosus may present as a systemic disorder with prominent cutaneous manifestations, and its potential involvement of multiple organs can significantly affect anesthetic safety. In such cases, accurate diagnosis and individualized anesthetic

approaches are essential to address both cutaneous and systemic considerations and to optimize patient outcomes [27].

Adverse Reactions to Local Anesthesia

Adverse reactions to local anesthetics encompass a spectrum of clinical manifestations ranging from mild, self-limited events to rare but potentially life-threatening complications. Among these, local anesthetic systemic toxicity represents the most severe form, characterized by neurological and cardiovascular involvement. Although uncommon, this condition may present with central nervous system symptoms such as agitation and seizures, progressing in severe cases to cardiovascular instability and cardiac arrest [28, 29]. The risk of systemic toxicity is influenced by multiple factors, including the administration of high doses, rapid systemic absorption, and patient-related variables such as extremes of age, underlying organ dysfunction, and pregnancy, all of which can alter anesthetic metabolism and distribution [28, 30]. Lidocaine, one of the most widely used local anesthetics in dermatology, is frequently implicated in reports of systemic toxicity, with clinical manifestations ranging from early central nervous system disturbances to marked cardiovascular depression in more advanced cases [31, 32]. Consequently, preventive strategies play a critical role in clinical practice and include the use of the minimal effective dose, aspiration prior to injection, and, when applicable, the use of ultrasound guidance to reduce inadvertent intravascular administration [28, 29].

In contrast to toxic reactions, true allergic responses to local anesthetics are considerably less common. Immunoglobulin E–mediated hypersensitivity reactions have been reported infrequently, with an estimated prevalence of approximately 4.3% in pediatric populations, and typically manifest as mucocutaneous symptoms rather than severe systemic reactions. Identified risk factors include a personal history of anaphylaxis or urticaria, as well as a family history of atopic disease, which may predispose certain individuals to allergic responses [33]. In patients with unclear or suspected allergy histories, structured allergy testing can be instrumental in de-labeling false diagnoses, thereby permitting the safe use of local anesthetics when clinically indicated [34].

Vasovagal and psychogenic responses constitute another important category of adverse events and are often misattributed to the anesthetic agent itself. Vasovagal reactions, typically characterized by transient hypotension, bradycardia, and syncope, are frequently triggered by procedural anxiety or pain rather than by the pharmacological effects of the anesthetic. Similarly, psychogenic reactions, including anxiety-induced symptoms such as dizziness or palpitations, are common in clinical settings and generally respond well to reassurance and supportive measures without the need for pharmacological intervention [31].

From an epidemiological perspective, adverse reactions to local anesthetics occur at a low overall incidence; however, certain populations exhibit increased vulnerability. Children and pregnant women have been identified as higher-risk groups due to physiological differences that influence drug pharmacokinetics and pharmacodynamics [30, 35]. In addition, procedural factors such as the specific anesthetic agent used, administered dose, and anatomical site of injection significantly affect the likelihood of adverse events [29, 33]. Although severe reactions remain rare, their potential consequences underscore the necessity for ongoing vigilance, appropriate risk stratification, and preparedness among healthcare providers involved in dermatologic and dermatosurgical care [36].

Immunological Mechanisms and Hypersensitivity

Hypersensitivity reactions to local anesthetics can be broadly categorized into immediate and delayed forms, each mediated by distinct immunological mechanisms and presenting with

different clinical characteristics. Immediate hypersensitivity reactions typically occur within minutes to hours following exposure and are most often immunoglobulin E–mediated, involving mast cell degranulation. Clinically, these reactions may manifest as urticaria, angioedema, or, in severe cases, anaphylaxis. In the setting of local anesthetic use, immediate-type reactions are relatively uncommon but have been documented, particularly in pediatric populations, where skin prick testing has confirmed true allergic sensitization in a small proportion of patients [33].

In contrast, delayed hypersensitivity reactions develop hours to days after exposure and are primarily mediated by T lymphocytes rather than antibodies. These reactions are more commonly associated with other drug classes, such as beta-lactam antibiotics, and involve complex immune pathways that remain incompletely understood. When they occur in relation to local anesthetics, delayed reactions may present with cutaneous findings that can complicate clinical interpretation, particularly in patients with underlying inflammatory or autoimmune skin diseases [37].

Beyond the active anesthetic compounds themselves, excipients, preservatives, and vasoconstrictors contained within anesthetic formulations play a relevant role in hypersensitivity reactions. Excipients such as polysorbate 80, commonly used as stabilizing agents, have been implicated in hypersensitivity responses. This is illustrated by reports of immediate contact urticaria associated with polysorbate 80 exposure in patients receiving biologic therapies, highlighting the need to consider non–active ingredients as potential triggers in suspected allergic reactions. Similarly, preservatives and vasoconstrictors included in local anesthetic preparations have been associated with hypersensitivity phenomena, although specific evidence regarding their contribution in dermatological settings remains limited [38].

Cross-reactivity among local anesthetic agents represents an additional clinical concern, particularly when selecting alternative drugs for patients with suspected hypersensitivity. Cross-reactivity is more likely to occur within the same chemical class; however, true immunoglobulin E–mediated cross-reactivity among local anesthetics appears to be rare. In pediatric cohorts, cross-reactivity has been observed only in a minority of cases, suggesting that while it is possible, it is not a frequent occurrence [33]. From a mechanistic perspective, cross-reactivity is often attributed to shared structural components between compounds, analogous to the role of common side chains in beta-lactam antibiotics, a principle that may also apply to anesthetics with similar chemical structures [37].

Clinical Evaluation and Differential Diagnosis

Adverse reactions to local anesthetics may present with a wide range of cutaneous and systemic manifestations, reflecting the underlying mechanism and severity of the reaction. Local anesthetic systemic toxicity represents one of the most serious systemic complications and is characterized by variable involvement of the central nervous and cardiovascular systems. Neurological manifestations may include altered mental status and seizures, while cardiovascular effects can range from arrhythmias to cardiovascular collapse and cardiac arrest, underscoring the potential severity of this condition despite its low incidence [6, 29]. In contrast, hypersensitivity reactions to local anesthetics are uncommon and typically manifest as immediate-type responses, presenting with urticaria, angioedema, or, in rare cases, anaphylaxis. In these situations, diagnostic tools such as skin prick tests and intradermal testing can assist in identifying true allergic sensitization and guiding future anesthetic selection. More severe cutaneous adverse reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, represent rare but critical entities that require prompt recognition and careful differentiation from other drug-

induced or disease-related dermatologic reactions [33, 39].

Accurately distinguishing anesthetic-related adverse reactions from exacerbations of underlying dermatological disease is a crucial component of clinical assessment, particularly in patients with complex skin disorders. A comprehensive pre-procedural evaluation is essential, as exemplified by conditions such as epidermolysis bullosa, where extreme skin fragility may not only complicate anesthetic administration but also mimic or mask adverse reactions [26]. Inflammatory dermatoses may also exhibit flares that resemble drug-induced reactions, making differential diagnosis challenging. For instance, disease exacerbations such as those observed in Sweet syndrome can be triggered by external stimuli, including vaccinations, and may be incorrectly attributed to anesthetic exposure if not carefully evaluated [40].

A structured diagnostic approach supported by targeted investigations is therefore necessary to clarify the etiology of suspected adverse reactions. Measurement of plasma concentrations of local anesthetics can provide objective evidence in cases of suspected systemic toxicity, supporting the clinical diagnosis of local anesthetic systemic toxicity [6]. In the context of suspected hypersensitivity, cutaneous testing modalities, including patch tests, prick tests, and intradermal tests, are valuable tools for identifying the causative agent and informing safer anesthetic choices for future procedures [39]. In more complex drug reactions, such as drug reaction with eosinophilia and systemic symptoms, the use of structured causality assessment tools, including algorithms such as ALDRESS, can enhance diagnostic accuracy by systematically attributing causality to specific medications, thereby aiding both acute management and prevention of recurrent reactions [41].

Conclusions

Local anesthesia remains a cornerstone of dermatologic and dermatosurgical practice; however, its pharmacological behavior is significantly influenced by skin pathophysiology, particularly in complex dermatological diseases. Alterations in skin barrier integrity, vascularity, inflammation, and immune activation can modify anesthetic diffusion, efficacy, and systemic absorption, underscoring the need for individualized anesthetic selection, dosing, and delivery strategies.

Patients with autoimmune, inflammatory, genetic, and systemic dermatological disorders represent a higher-risk population for anesthetic complications due to underlying immunological dysregulation, multisystem involvement, and altered nociceptive signaling. These factors necessitate thorough pre-procedural assessment, careful risk stratification, and heightened clinical vigilance to balance effective analgesia with patient safety.

Although adverse reactions to local anesthetics are uncommon, their potential severityranging from systemic toxicity to hypersensitivity reactionshighlights the importance of preventive measures, accurate differential diagnosis, and structured diagnostic approaches. Integrating pharmacological knowledge, disease-specific considerations, and appropriate monitoring is essential to optimize anesthetic outcomes and minimize complications in complex dermatological settings.

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