

Clinical Communications

Safety of local anesthesia and prevalence of hypersensitivity reactions in adult patients with clonal mast cell diseases: A retrospective single-center study

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Clinical Implications

- Uniform consensus about local anesthetic management in patients with clonal mast cell diseases is lacking. Local anesthetic procedures should be considered safe, and premedication is recommended only in patients with severe mediator-related symptoms.

Local anesthetics (LAs) cause hypersensitivity reactions, including toxicity, vasovagal reactions, and side effects of concomitant epinephrine administration and allergic reactions, in 2.5% to 10% of cases.^{1,2} The introduction of the amide LA group reduced the number of reactions, but related allergy incidence is unclear, as it ranges from 0% to 5% among different studies.^{1,2}

Mastocytosis represents a heterogeneous group of clonal mast cell diseases (CMDs), characterized by abnormal proliferation and infiltration of mast cells (MCs) in various tissues. Because anesthetic procedures may lead to MC degranulation, they are considered at risk in patients with CMD.³ Nevertheless, few data are available about the incidence of allergic reactions related to LA in patients with CMD.⁴

The aim of this retrospective, single-center study was to evaluate the incidence of LA hypersensitivity reactions in adult patients with suspected CMD, who underwent LA before bone marrow (BM) biopsy.

Between 2012 and 2018, 432 adult subjects with suspected systemic mastocytosis underwent BM biopsies after LA at our multidisciplinary outpatients unit. Before the procedure, an allergological workup including skin prick test (SPT), intradermal test (IDT), and subcutaneous provocation test was performed only in patients with a positive history of LA or multiple and severe drug allergy. The protocol used consisted of SPT with suspected undiluted LA, and IDT with LA at 1/10 concentration followed by provocation test with subcutaneous injection of undiluted LA.⁵ Before BM biopsy, patients received 100 mg of lidocaine ($n = 406$ [94%]) or mepivacaine ($n = 26$ [6%]) LA, without additional vasoconstrictors. Mepivacaine was used for patients with a history of lidocaine allergy or severe drug allergy. Premedication with prednisone (25 mg *by mouth*), ranitidine (150 mg *by mouth*), and diphenhydramine (10 mg intravenous) was given 30 minutes before the procedure only to patients with

a history of severe mediator-related symptoms (ie, vasodilation, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, recurrent unknown anaphylaxis, etc; $n = 7$ [1.6%]). Informed consent was obtained according to the guidelines of the Local Ethics Committee (protocol no. 1828, approved on May 12, 2010).

A comparison of factors was performed using χ^2 test of categorical variables and Fisher exact test. Student t test and median test were used for continuous variables. Statistical analysis was performed using the Statistical Package for Social Sciences version 24 (SPSS Inc).

In the entire cohort, 252 patients (58%) were diagnosed with CMD and 180 (42%) were found to be negative. Final diagnoses of CMDs are presented in Table I. Clinical and allergological data of the 2 groups are reported in Table II. The control group differs significantly for higher female sex ratio and higher frequency of history of an allergy to antibiotics than do patients with CMDs ($P = .003$ and $.026$, respectively). Moreover, the control group received mepivacaine more frequently than did patients with CMD ($P = .034$).

Twelve of 432 patients (2.8%) had a positive history for LA allergies, 5 of whom were in the CMD group (4 to lidocaine and 1 to mepivacaine) and 7 in the control group (2 to lidocaine and 5 to mepivacaine) ($P = .186$). The allergological workup performed before the procedure was negative for all patients. Seven patients received premedication, including 1 with a history of allergy to LA and 5 of them were diagnosed with CMD.

Patients diagnosed with CMD and history of any drug allergy showed a higher probability of positive history for adverse reaction to LA ($P = .035$). Moreover, we found a stronger association between history of antibiotics and LA allergy ($P = .012$). Unfortunately, we had insufficient data to evaluate the association between a positive history of general anesthetics and LA allergy.

None of the patients in the control group had an LA reaction during the BM procedure. Only 1 patient affected by CMD (0.4%) developed a hypersensitivity reaction to LA. He was a 58-year-old man, with maculopapular cutaneous mastocytosis, with no history of LA or other drug allergies or mediator-related symptoms. The serum basal tryptase level was 20 ng/mL. He underwent BM biopsy after lidocaine without premedication. A few minutes after the administration of lidocaine, during the BM aspiration, he complained of discomfort and flushing, and a blood pressure measurement showed severe hypotension. The procedure was interrupted, and he rapidly recovered after intravenous hydrocortisone and antihistamine. Unfortunately, tryptase level during the anaphylactic period was not determined. Because we could not proceed to the BM biopsy, the diagnosis of indolent systemic mastocytosis with skin involvement was based on the presence of 3 minor criteria (1) $>25\%$ of BM MCs, 2) CD25 positives MCs, and 3) D816V KIT mutation). The allergological workup for LA, performed after 1 month and including SPT, IDT, and challenge test with lidocaine, was negative, thus suggesting the non-immune-mediated pathogenesis of the hypersensitivity reaction.

TABLE I. Final diagnosis of 252 patients with CMD

Diagnosis	n (%)
Cutaneous mastocytosis	6 (2.4)
Clonal MC activation syndrome	9 (3.6)
Indolent systemic mastocytosis (ISM) without skin involvement	155 (61.5)
ISM with skin involvement	75 (29.8)
Aggressive systemic mastocytosis	1 (0.4)
Systemic mastocytosis with an associated hematological neoplasm	6 (2.4)

TABLE II. Clinical and allergological characteristics of patients

Characteristic	Total cohort (n = 432 [100%])	Clonal MC disease group (n = 252 [58%])	Control group (n = 180 [42%])	P value
Male/female, n (%)	246 (56.9)/186 (43.1)	158(62.7)/94 (37.3)	88 (48.9)/92 (51.1)	
Sex ratio	1.32	1.68	0.95	.003
Age (y), median (range)	52.9 (17-86)	52 (18-80)	55 (17-86)	.064
History of LA hypersensitivity, n (%)	12 (2.8)	5 (1.9)	7 (3.9)	.235
Lidocaine	6 (1.4)	4 (1.6)	2 (1.1)	
Mepivacaine	6 (1.4)	1 (0.4)	5 (2.8)	
History of drug allergy, n (%)	99 (22.9)	47 (18.6)	52 (28.9)	.46
Antibiotics	56 (13)	25 (9.9)	31 (17.2)	.026
NSAIDs	39 (9)	20 (7.9)	19 (10.5)	.349
General anesthesia	4 (0.9)	2 (0.8)	2 (0.5)	.734
History of food allergy, n (%)	30 (6.9)	19 (7.5)	11 (6.1)	.583
Severe mediator-related symptoms, n (%)	7 (1.6)	5 (2)	2 (1.1)	.502
LA used before BM biopsy, n (%)				
Lidocaine	406 (94)	242 (96)	164 (91.1)	.034
Mepivacaine	26 (6)	10 (4)	16 (8.9)	
Premedication before BM biopsy, n (%)	7 (1.6)	5 (2)	2 (1.1)	.502
Allergic reaction after LA, n (%)	1 (0.2)	1 (0.4)	0 (0)	

NSAID, Nonsteroidal-anti-inflammatory drug.

There is little information on LA reactions in patients with CMD. A retrospective study of the Spanish Network on Mastocytosis reported good tolerance to epidural amide-type LA in pregnancy.⁶ In 2015, the same group found an incidence of perioperative MC-related symptoms of 1% (6 of 591) in adult patients with CMD who underwent local or epidural anesthetic procedures, despite the fact that most of them (87%) had previously received prophylactic antimediation treatment (PAT).⁴

In our knowledge, this is the first and largest study reporting on the safety of LA without PAT in adult patients with CMD. Only 1 patient (0.4%) developed a hypersensitivity reaction during BM biopsy, thus indicating a similar prevalence with that reported either in healthy subjects or in patients with CMD receiving PAT.

Our study suggests that LA should be considered safe in patients with CMD, despite a positive history for drug or LA allergy. In fact, we did not find any significant association between a positive history for drugs, food, or anesthetics allergy and LA hypersensitivity reactions, but further studies are needed to confirm these results.

The use of PAT before LA procedures is still under debate.^{4,7} On the basis of our experience, we do not recommend PAT, except for patients with severe mediator-related symptoms,

though the number of patients with mastocytosis and severe MC-related symptoms in our study was limited.

In conclusion, our study demonstrates that LA administration in patients with CMD is to be considered a safe clinical practice as it is in the general population.⁸ PAT might be considered as a precaution only in patients with severe mediator-related symptoms. Screening allergy tests are not recommended for patients with CMD without a history of hypersensitivity to LA.⁹

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