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The Optimal Reading Time for Patch Testing: A Retrospective, Cross-sectional, Single Center Study Over 8 Years from Turkey

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ABSTRACT

Background: Controversy still exists concerning the optimal reading time of patch testing, and the lack of analysis after day seven might result in missing late positive reactions in rare cases. We aimed to describe our experience with patch test reading and the frequency of early and late positivity, with particular attention to detecting delayed reactions.

Material and Methods: This is a retrospective study on 791 patients who were consecutively patch tested with the extended European baseline series and gold salts, between January 2004 and December 2012. Test sites were evaluated on day D2, D3, and D4, and since 2010, on D7 as well, according to the European Society of Contact Dermatitis patch-test guideline. Positivity on D2 or D3 was identified as early reaction, and on D4, D7 and later as late reaction.

Results: Of the total 791 patch-tested patients, 773 (97.7%) had at least one positive patch test reaction of which 651 (84.2%) were classified as early (on days 2 or 3), and 122 (15.8%) were classified as late (on day 4 or later). The early and late reaction groups were similar in terms of age, sex and atopy; however, metal hypersensitivity was significantly more frequent in the late reaction group. The substance with the most number of late positive tests was nickel sulfate (16.3%). In terms of relative frequency of positivity on D7 or even later, the most notable substances included neomycin sulfate, gold salts, epoxy resin and polyethylene glycol.

Conclusion: The results of our study promote the value of an additional late patch test reading on D4 and D7 or even later in the presence or suspicion of allergy caused by nickel sulfate, cobalt chloride, gold salts, epoxy resin, polyethylene glycol, and neomycin.

Keywords: Patch test, Allergic contact dermatitis, Late reactions, Reading time, Delayed, Early

Introduction

Patch testing is a routinely used standardized protocol for investigation of contact allergy resulting from type IV hypersensitivity [1,2].

The European baseline series (EBS) of contact allergens is preferred throughout Europe as a standard patch test screening [3]. According to the European Society of Contact Dermatitis (ESCD) guidelines, the results of diagnostic patch testing is advised to be assessed through at least two readings which may be performed on day D2, D3 or D4, and around D7, after application. A reading at D3 or D4 is considered obligatory [4]. The morphological criteria for visual assessment has been described by the International contact dermatitis research group (ICDRG) [5].

It has been previously shown that approximately 30% of negative results at the D2 reading became positive at D4, which has denoted that D4 may be an optimal time-point for the second reading [6].

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Late readings between D7-D10 is accepted to be optional, but it is known that some allergens, such as corticosteroids, antibiotics and some metals, may manifest late reactions on D7 and later. Lack of late readings might cause that 7-30% of positive reactions are missed [7]. On the contrary, some authors have concerns on late readings. Saino et al. [8] found that there was a 3% increase in the number of positive reactions after D3 and they suggested that patch-test evaluation after D3 would be too time-consuming to be used routinely. It is well-known that some allergens are "late reactors", or delayed reactions may be sensitized from the patch test itself (patch test sensitization, active sensitization), or they might be a result of the varying reaction characteristics of different individuals [9].

Controversy still exists with regard to the optimal reading time of patch testing. Such inconsistencies would inevitably affect correct interpretation of patch test results, and therefore, the detection of allergens associated with late positive reactions. In this study, we aimed to define the optimal reading time for patch testing, especially to detect late positive reactions.

Materials and Methods

Study Group

We conducted a retrospective analysis on patch test data from January 2004 to December 2012, which included 791 consecutive patients meeting the inclusion and exclusion criteria who had undergone routine patch testing in the Allergy Unit of the Department of Dermatology and Venereology, Istanbul Faculty of Medicine. Ethics committee approval of this study was carried out by Istanbul Faculty of Medicine Ethics Committee (07.06.2013/2013/700). All tests had been conducted via the same method as described below, with our extended EBS allergens and gold sodium thiosulfate.

Informed oral/written consent was obtained from all patients (or the parents or legal guardians of children) before their inclusion in the study. Any patients using prescribed medications that could affect patch testing, those who had applied topical corticosteroids/calcineurin inhibitors to the test site within 4 weeks and those with excessive sun exposure within 4 weeks were excluded.

Study Design, Patch Testing and Data Analysis

Test allergens were provided by Chemotechnique Diagnostics (Vellinge, Sweden), Brial Allergen (Greven, Germany), and AllergEAZE (Calgary, Canada), and in the earlier years by Hal-Brial (Leiden, The Netherlands). The allergens were applied on the upper part of the back using IQ chambers (Chemotechnique Diagnostics) for 48 hours under occlusion. Patients' files were evaluated with regard to demographic features (gender, age, atopy), history of metal hypersensitivity, patch test findings, and the strength of reaction. Patients who had been diagnosed with atopic dermatitis according to the criteria put forth by Eichenfield et al. [10] and those with mucosal atopy or atopic skin diathesis were recorded as atopic.

The readings were made by the International ICDRG criteria, after awaiting 20-30 minutes following removal of patch test plasters [4,11]. Test sites were assessed by experienced dermatologists on day D2, D3, and D4, and since 2010, on D7 as well. Weak (+), strong (++) and extreme (+++) patch test reactions were categorised as positive reactions. In addition to definite negative results (-), reactions classified as irritant, or doubtful were also counted as negative [12].

According to the onset of positive patch test reactions, patients were divided into "early and late" reaction groups. The early reaction group included patients in whom positive reactions were observed at D2 or D3. Patients whose positive reaction started at D4 or later were included in the late reaction group. For patients with a positive reaction beyond D7, a second patch testing was performed to differentiate between late positive reaction and active sensitization. Early positive patch test reaction on D2 or D3 in the second patch testing indicated an active sensitization with the suspected allergen.

Statistical Analysis

All analyses were performed on Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS, Inc., an IBM Company, Chicago, Illinois). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables, depending on the normality of distribution. Quantitative variables were compared using the independent samples t-test (parametric) or the Mann-Whitney U test (non-parametric), and qualitative variables were compared using chi-square tests, including McNemar's test or Fischer's exact test. $P<0.05$ values were accepted as statistically significant results.

Results

A total of 791 patients (416 females, 375 males, mean age 37.7 years) who had undergone patch testing with the 27 allergens of the extended EBS and gold salts were included in this study. Patients' demographics are shown in Table 1.

Out of these 791 patients, 773 (97.7%) had at least one positive patch test reaction. Among these, 478 reactions occurred on D2, 173 occurred on D3, 80 occurred on D4, 28 occurred on D7 and 14 occurred after D7. Therefore, among the overall number of positive tests, 651 (84.2%) were classified as early reaction, and 122 (15.8%) were classified as late reaction (Table 1). The early and late reaction groups were similar for age, sex, atopy ($p>0.05$). Nevertheless, the frequency of metal hypersensitivity in the history was significantly higher among patients with late reaction ($p=0.001$). In addition, subjects with a positive reaction on D7 or later ($n=42$) were similar

Table 1. The demographic characteristics of the patch tested patients between 1996-2012

		Overall (n=791)
Age, mean ± SD		37.7±15.8
Sex, n (%)	Female	416 (52.6%)
	Male	375 (47.4%)
Atopy (atopic dermatitis/ atopic skin diathesis/allergic rhinoconjunctivitis), n (%)	Yes	159 (20.1%)
	No	420 (53.1%)
	No data	212 (26.8%)
Year of patch testing, n (%)	2004	110 (13.9%)
	2005	88 (11.1%)
	2006	98 (12.4%)
	2007	98 (12.4%)
	2008	118 (14.9%)
	2009	32 (4%)
	2010	67 (8.5%)
	2011	104 (13.1%)
	2012	76 (9.6%)
Onset of positive patch test reactions	Early	651 (82.3%)
	Late	122 (15.4%)
	None	18 (2.3%)
Metal hypersensitivity in the history, n (%)	Yes	732
	No	451
	No data	426

to those with a positive reaction on D4 regarding age, sex, atopy and metal hypersensitivity (n=80) (p>0.05).

Among 122 patients with a late reaction, 28 (23%) had a positive reaction on D7 and 14 (11.5%) after D7. The strength of positive patch test reactions was (+) in 85 (69.7%), (++) in 34 (27.9%), and (+++) in 3 (2.5%). One hundred and twenty-two late positive reactions consisted of: nickel sulfate 16.3%, cobalt chloride 9%, thimerosal 8.2%, both neomycin sulfate and palladium chloride 7.3%, polyethylene glycol 6.6%, potassium dichromate 4.9%, and other less frequent allergens. On the other hand, if the ratio of late positivity (reacting on D4 and/or D7) according to the total number of positive reactions for each allergen was determined as "relative incidence", the following rates were obtained: budesonide (100%, 1/1), neomycin sulfate (69.2%, 9/13), gold sodium thiosulfate (50%, 2/4), epoxy resin (42.9%, 3/7) and polyethylene glycol (42.1%, 8/19). Contact allergens with the greatest "relative incidence" regarding positive reactions on D7 or later were budesonide (100%), neomycin sulfate (38.5%), gold sodium thiosulfate (25%), lanolin alcohols (22.2%), epoxy resin (14.3%), Euxyl® K400 (14.3%), cobalt chloride (12.5%), polyethylene glycol (10.5%), and thimerosal (10.2%). Only one patient showed late reactions to methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) on D7, not reacting on D4. Additional patch testing to ascertain whether active sensitization had occurred was performed on 14 subjects out of the 42 individuals with a late positive reaction on D7 or later. Among them, two patients (14.3%) were found to have active sensitization (one to cobalt chloride, the other to p-phenylenediamine). Any late positive reaction was reacted with benzocaine, clioquinol/quinoline mix, mercapto mix, 4,4'-diaminodiphenylmethane, quaternium-15, carba mix, toluene sulfonamide formaldehyde resin (TSF), hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®), methyl dibromo glutaronitrile, zinc diethyldithiocarbamate.

Discussion

Determination of the optimal reading time is essential for patch testing, both in terms of the reliability of the patch test results and the accuracy of detecting allergens yielding late-positive reactions. In the current study, 97.7% of patients had at least one positive patch test reaction of which 651 (84.2%) appeared as early positive reactions and 122 (15.8%) as late positive reactions. Findings of the present study show that the great majority of patients with a positive reaction can be detected on days 2 and 3. However, our data showed that if D3 was designated as the final analysis time point, 15.8% of the positive reactions would have been missed. That underlined the necessity of readings on D4 and later. Moreover, if D7 and later readings had not been performed, 5.4% of the positive reactions would have been missed.

It is difficult to compare our results with those of other studies because different "reading time" protocols have been used for patch testing of contact allergens. Moreover, the assigned days for "late" reading may vary considerably. Late readings are commonly characterized as occurring after D3 or D4 in certain research based on late patch-test reactions [13]; while the delayed reading period is defined as beginning at D7 in other [14,15].

Van Amerongen et al. [16] reported that, in patients tested with T.R.U.E. Test® panel 1 and 2 (including additional allergens), 13.5% of positive reactions could not be detected if D7 reading had not been performed, supporting the value of an additional late patch test reading on D7. Geier et al. [17] reported that, when compared to D3 readings, the rate of new positive reactions was 14.8% at D4 and 22.7% at D5. However, readings on days 3 and 5 may be problematic as at least one of the reading days would be on the weekend. In another study, the rate of new positive reactions (compared to D3 and D4) was found to be 13.5% at the second reading on days 6 or 7 [18]. In an interesting analysis by Wolf et al. [19] it was suspected that very late reactions could be associated with active sensitization caused by the patch test, or could reflect a slow response with respect to individual reaction patterns. In the present study, active sensitization was found to have been present in two of the 14 subjects who had undergone a second patch testing. Despite the fact that this is a small ratio, we must note that only 14 of the 42

Table 2. Positive patch test results obtained with the baseline series and gold salts between 2004-2012

	Number of tested patients	Total number of positive reactions	Total number of early reactions	Onset of early reactions		Total number of late reactions		Onset of late reactions			P***
Allergen	N	n (%)	n (%*)	D2, n	D3, n	n, (%*)	%**	D4, n	D7, n	>D7, n	
Potassium dichromate, 0.5% pet.	785	63 (8)	57 (90.5)	49	8	6 (9.5)	0.8	3	2	1	0.125
p-phenylenediamine (PPD), 1.0% pet.	779	34 (4.5)	31 (91.2)	26	5	3 (8.8)	0.4	2	0	1	1.000
Thiuram mix, 1.0% pet.	782	41 (5.2)	39 (95.1)	33	6	2 (4.9)	0.3	2	0	0	0.500
Neomycin sulfate, 20.0% pet.	788	13 (1.6)	4 (30.8)	1	3	9 (69.2)	1.1	4	2	3	**0.004**
Cobalt (II)chloride hexahydrate, 1.0% pet.	786	40 (5)	29 (72.5)	23	6	11 (27.5)	1.4	6	3	2	**0.001**
Benzocaine, 5.0% pet.	788	6 (0.7)	6 (100)	4	2	–	-	-	-	-	1.000
Nickel (II) sulfate hexahydrate, 5.0% pet.	786	160 (20.3)	140 (87.5)	109	31	20 (12.5)	2.5	18	2	-	**0.000**
Clioquinol 5.0%/Quinoline mix, 6.0%, pet.	774	5 (0.6)	5 (100)	3	2	–	-	-	-	-	1.000
Colophonium, 20.0% pet.	788	24 (3)	18 (75)	14	4	6 (25)	0.8	4	1	1	**0.03**
Paraben mix, 16.0% pet.	781	3 (0.4)	2 (66.7)	2	-	1 (33.3)	0.1	1	-	-	1.000
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD), 0.1% pet.	774	6 (0.8)	5 (83.3)	5	-	1 (16.7)	0.1	1	-	-	1.000
Lanolin alcohol, 30.0% pet.	780	9 (1.2)	6 (66.7)	3	3	3 (33.3)	0.4	1	1	1	0.250
Mercapto mix, 2.0% pet.	780	8 (1)	8 (100)	8	-	–	-	-	-	-	1.000
Epoxy resin, 1.0% pet.	783	7 (0.9)	4 (57.1)	4	-	3 (42.9)	0.4	2	1	-	0.250
Peru balsam (myroxylon pereirae resin), 25.0% pet.	788	32 (4)	27 (84.4)	20	7	5 (15.7)	0.6	2	2	1	0.063
4-tert-Butylphenolformaldehyde resin (PTBP), 1.0% pet.	783	7 (0.9)	5 (71.4)	3	2	2 (28.6)	0.3	2	-	-	0.500
2-Mercaptobenzothiazole (MBT), 2.0% pet.	787	12 (1.5)	11 (91.7)	7	4	1 (0.8)	0.1	1	-	-	1.000
4,4'-Diaminodiphenylmethane, 0.5% pet.	787	17 (2.2)	17 (100)	10	7	–	-	-	-	-	1.000
Fragrance mix I, 8.0% pet.	789	35 (4.4)	32 (91.4)	27	5	3 (8.6)	0.4	1	2	-	0.250
Sesquiterpene lactone mix, 0.1% pet.	775	10 (1.3)	7 (70)	6	1	3 (30)	0.4	3	-	-	0.250
Quaternium-15, 1.0% pet.	760	4 (0.5)	4 (100)	2	2	–	-	-	-	-	1.000
Carba mix, 3.0% pet.	545	22 (4)	22 (100)	17	5	–	-	-	-	-	1.000
Toluenesulfonamide formaldehyde resin (TSF), 10.0% pet.	788	9 (1.1)	9 (100)	9	-	–	-	-	-	-	0.125
Mercury (II) amidochloride, 1.0% pet.	781	25 (3.2)	21 (84)	16	5	4 (16)	0.5	3	1	-	0.125
Palladium (II) chloride, 2.0% pet.	789	54 (6.8)	45 (83.3)	24	21	9 (16.7)	1.1	6	3	-	**0.004**
Thimerosal, 0.1% pet.	788	49 (6.2)	39 (79.6)	18	21	10 (20.4)	1.3	5	2	3	**0.002**
Euxyl K 400, 0.5% pet.	654	14 (2.1)	10 (71.4)	7	3	4 (28.6)	0.6	2	2	-	0.125
Fragrance mix II, 14.0% pet.	176	5 (2.8)	4 (80)	3	1	1 (20)	0.6	1	-	-	1.000

Table 2. continued

	Number of tested patients	Total number of positive reactions	Total number of early reactions	Onset of early reactions		Total number of late reactions		Onset of late reactions			P***
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®), 5.0% pet.	181	3 (1.7)	3 (100)	2	1	–	-	-	-	-	1.000
Budesonide, 0.01% pet.	183	1 (0.5)	–	-	-	1 (100)	0.5	-	1	-	NA
Methyl dibromo glutaronitrile (MDBGN), 0.5% pet.	256	3 (1.2)	3 (100)	1	2	–	-	-	-	-	1.000
Methylisothiazolinone/ Methylchloroisothiazolinone -, 0.01% aq.	779	11 (1.4)	10 (90.9)	8	2	1 (9.1)	0.1	-	1	-	1.000
Formaldehyde, 2.0% aq.	747	11 (1.5)	9 (81.8)	4	5	2 (18.1)	0.3	2	-	-	NA
Gold sodium thiosulfate, 0.5% pet.	109	4 (3.7)	2 (50)	2	-	2 (50)	1.8	1	-	1	0.500
Zinc diethyldithiocarbamate, 1.0% pet.	265	3 (1.1)	3 (100)	3	-	–	-	-	-	-	1.000
Polyethylene glycol, 100%	515	19 (3.7)	11 (57.9)	4	7	8 (42.1)	1.6	6	2	-	**0.008**
Propylene glycol, 5.0% pet.	514	4 (0.8)	3 (75)	1	2	1 (25)	0.2	1	-	-	1.000
Total number		773 (100)	651	478	173	122		80	28	14	

*: Percentage with respect to all positive reactions to the substance, **: Percentage of positivity with respect to patients tested for the substance, *** Statistical significance of late positive reactions (McNemar analysis) †: Euxyl K 400: methyldibromo glutaronitrile/phenoxyethanol, NA: Not applicable

patients with a late reaction had undergone this analysis. Therefore, future studies could benefit from performing this analysis in all subjects with late positivity beyond D7.

In the current study, consistent with the literature reports, metals were the most common allergens leading to late-positive reactions, including nickel sulfate, cobalt chloride, palladium chloride and gold salts [7,14,20,21]. Jonker and Bruynzeel [21] had also come upon the conclusion that the most common allergen leading to late positive reaction was nickel sulfate.

Chaudhry et al. [7] showed that a patch-test reading after D7 is particularly useful to assess reactions to metals, specific preservatives and the topical antibiotic neomycin. For other patients, a patch test schedule concluding with a D5 reading was reported to be able to identify reactions to most allergens, with the inclusion of topical corticosteroids that are known to manifest delayed reactions [7]. D6 readings were found to be particularly useful by other researchers due to the higher frequency of newly positive reactions to nickel, colophonium, and potassium dichromate [22]. A total 607 patients reacted positively to nickel sulfate in another cohort study, with 104 (17.1%) of these reactions being new positive D7 reactions [16]. However, some authors reported no late reactions with nickel sulfate [23]. In the present study, among a total of 160 positive reactions with nickel sulfate, 18 (11.3%) had developed after D4, and 2 (1.3%) after D7 (Table 2).

Our results showed that other contact allergens associated with late positive reactions were thimerosal, neomycin, polyethylene glycol and colophonium. Madsen and Andersen [18] reported a high rate of late positive reactions to neomycin (57%) which was in accordance with the results of the current study, since 9 reactions out of the 13 positive reactions to neomycin (69.2%) were detected after D4, while 5 of them (38.5%) were detected on D7 or later. According to the literature, neomycin sulfate has been the most frequently reported allergen related to new positive reactions at late readings [7,24]. Macdonald and Beck [25] reported slow local absorption of neomycin entirely the skin and slow local immunological reactivity as contributors to late positivity, while the possibility of neomycin storage in the epidermis for a long time was also suggested as a factor causing the late manifestation of positivity. Furthermore, similar to our findings, thimerosal and colophonium have also been reported to be allergens causing late positivity [21].

In the present study, polyethylene glycol was responsible for 6.6% of 122 late-positive patch test reactions. In agreement with our results, Özkaya and Kılıç [26], in their retrospective study, showed that more than one-third of the patients (34.3%, n=12) with polyethylene glycol sensitivity showed late positive patch test reactions starting on D4 or later. They concluded that late positive reactions on D7 are frequent and that late readings are essential to accurately detect positive patch test reactions.

Budesonide and tixocortol are known as late allergens which are suggested to mask the clinical signs of a positive patch test reaction due to their anti-inflammatory activities. As this effect diminishes over time, the test site becomes eczematous at subsequent readings [27]. In the present study, budesonide was positive in only one patient presenting with a late positive reaction after D7. Although the value of these extended readings was limited, some studies reported delayed reactions to corticosteroids [28,29]. However, Higgins and Collins [14] found no additional positive corticosteroid reactions in late readings in their study of 203 patients. Despite the fact that only 183 patients had been tested for budesonide, the relative incidence of late reactivity for budesonide was identified as %100 (a single case). Other late-positive allergens exhibiting a high relative incidence were neomycin sulfate, gold salts, epoxy resin and polyethylene glycol. A comparative analysis with prior studies focusing on late reactivity to patch testing is given in Table 3. In a recent study, Ozkaya et al. [30] reported two late positive reactions in 77 positive reactions with MCI/MI.

Table 3. An overview of previous studies evaluating late positivity in patch testing

	Macfarlane et al. (24)	Geier et al. (17)	Jonker and Bruynzeel (21)	Davis et al. (20)	Madsen and. Andersen (18)	Present study
Publication year	1989	1999	2000	2008	2012	
Number of patients	403	1096 (Group I) 1243 (Group II) 1136 (Group III)	760	372	9997	791
Allergen	Neomycin, potassium dichromat, cobalt chloride	European baseline series	European baseline series	European baseline series, metal and corticosteroid series	European baseline series	Extended European baseline series allergens and gold salts
Time of late positivity	4th day and after	4. day (Group I) 5. day (Group II) 6. day (Group III)	6th or 7th day and after	5th day and after	6th or 7th day and after	4th day and after
Number of late positive reactions	Not available	255 (Group I) 355 (Group II) 279 (Group III)	77	30 817	881	122
Percent of late positive reactions	Not available	12.9 (Group I) 18.5 (Group II) 15.2 (Group III)	Not available	Not available	13.5	15.8
Percent of patients with a late positive reaction	7.2	12.9 18.5 15.2	8.2	Not available	Not available	12.6
Contact allergens with a late positive reaction among all tested patients	Neomycin sulfate Potassium dichromat Cobalt chloride	Nickel sulphate Neomycin sulfate Cobalt chloride Thimerosal Peru balsam	Nickel sulphate Neomycin sulfate Tixocortol-21-pivalate PTBF-FR Methylisothiazolinone/ Methylchloroisothiazolinone Potassium dichromate	Gold sodium thiosulfate Dodecyl gallate Palladium chloride Neomycin sulfate	Not available	Nickel sulphate† Gold sodium thiosulfate Polyethylene glycol Cobalt chloride Neomycin sulfate
Contact allergens with a late positive reaction among positive patch test reactions					Neomycin sulfate Budesonide Hydrocortisone Tixocortol-21-pivalate Thimerosal	Budesonide Neomycin sulfate Gold sodium thiosulfate Epoxy resin Polyethylene glycol

†: Nickel sulphate was tested at 2.5 concentration. PTBP: 4-tert-Butylphenolformaldehyde resin

Study Limitations

The retrospective nature is one of the limitations of this study. It is difficult to compare publications on delayed positive patch test reactions due to differences in terminology and day of the patch test reading (which may vary from D5 to D9). Also, test materials and concentrations do not always match in comparable studies. Some evidence also suggests that the positive reactions on D7 or later may be related to the vehicle used, rather than the primary allergen itself.

Conclusion

The results of our study supported the importance of an additional late patch test reading on D4 and D7 or later, particularly for metals such as nickel sulfate, cobalt chloride, palladium chloride, and neomycin. Therefore, we would recommend to perform a D4 and D7 reading routinely and later patch test readings for those with suspect of contact sensitivity to aforementioned substances.

Ethics

Ethics Committee Approval: Ethics committee approval of this study was carried out by Istanbul Faculty of Medicine Ethics Committee (approval number: 700, date: 07.06.2013).

Informed Consent: Informed oral/written consent was obtained from all patients (or the parents or legal guardians of children) before their inclusion in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.Ö.A, E.Ö., Concept: T.Ö.A, E.Ö., Design: T.Ö.A, E.Ö., Data Collection or Processing: T.Ö.A, E.Ö., Analysis or Interpretation: T.Ö.A, E.Ö., Literature Search: T.Ö.A, E.Ö., Writing: T.Ö.A, E.Ö.

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