

Orthopedic Surgeons' Knowledge and Approach to Hypersensitivity Reactions to Commonly Prescribed Nonsteroidal Anti-inflammatory Drugs

Ortopedi Hekimlerinin Sıkça Reçetelendirilen Nonsteroidal Anti-inflamatuar İlaçlara Bağlı Gelişen Aşırı Duyarlılık Reaksiyonlarına Yaklaşımları ve Bilgi Seviyeleri

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ABSTRACT

Objective: To investigate the knowledge level about NSAIDs hypersensitivity of orthopedic surgeons who very commonly prescribe NSAIDs in their clinical practice and their approach in case of development of hypersensitivity reactions (HRs) to NSAIDs in their patients.

Method: Participants were asked to complete a structured online survey which contained questions about demographic features of them and knowledge level and attitude about NSAIDs HRs.

Results: One-hundred-nine orthopedic surgeons were included in the study. The mean age of the participants was 40.53±7.88 years and they have been working on orthopedic field for the mean 15.02±8.28 years. The physicians examined median (min-max) 30 (2-130) patients and prescribed median (min-max) 10 (1-60) NSAIDs per day. Forty-eight (44%) participants observed hypersensitivity reactions to NSAIDs in their patients. 32.1% of them suggested to stop the culprit NSAID and consulted to an allergist and 28.6% of them suggested to stop the culprit NSAID and recommended different treatment modalities, respectively. In the comparison of the groups of well- and poor-approach, regarding the duration of working on orthopedic field, academic degree, types of trained for orthopedic and currently worked hospital, the presence of pediatric or adult allergy clinic in medical faculty of medicine, trained and currently worked hospital, no association was observed ($p>0.05$). Only 4 and 1 physicians correctly answered the questions about underlying mechanism and classification.

Conclusion: The present study indicated that among orthopedic surgeons the knowledge level about NSAID HRs was low and approach to the patients whom NSAID HRs developed was inadequate among orthopedic surgeons.

Keywords: Nonsteroidal anti-inflammatory drugs, hypersensitivity reactions, knowledge level, appropriate approach

ÖZ

Amaç: Çalışmanın amacı ortopedi hekimlerinin günlük pratiklerinde sıkça reçetelendirdikleri nonsteroidal anti-inflamatuar ilaçlara (NSAİİ) bağlı gelişen aşırı duyarlılık reaksiyonları (ADR) ile ilgili bilgi seviyelerini ve hastalarında reaksiyon gelişmesi durumunda yaklaşımlarını araştırmaktır.

Metod: Katılımcılardan demografik özellikleri ve NSAİİ ADR ile ilgili bilgi seviyelerini ve tutumlarını değerlendiren soruları içeren bir anketi çevrimiçi olarak doldurmaları istendi.

Bulgular: Yüz-dokuz ortopedist çalışmaya dahil edildi. Katılımcıların ortalama yaşı 40.53±7.88 yıldır ve ortalama 15.02±8.28 yıldır ortopedi alanında çalışmaktaydılar. Hekimler günde medyan (min-max) 30 (2-130) hasta görmek ve 10 (1-60) NSAİİ reçetelendirmektedir. Katılımcıların %44'ü hastalarında NSAİİ ilişkili ADR geliştiğini belirtmiştir. %32,1'i suçlu NSAİİ kullanmayı bırakmasını önererek alerjiye konsülte ettiğini ve %28,6'sı da suçlu NSAİİ bırakarak NSAİİ dışı bir tedavi önerdiğini bildirmiştir. Uygun ve uygun olmayan yaklaşım gösterenlerin özellikleri karşılaştırıldığında, ortopedi alanındaki çalışma süresi, akademik derecesi, ortopedi eğitimi aldığı ya da çalıştığı kurumda ve eğitim aldığı tıp fakültesinde pediatrik ya da erişkin alerji kliniği bulunup bulunmaması ile ilişkili olmadığı görülmüştür ($p>0.05$). Sadece 4 ve 1 hekim sırasıyla altta yatan mekanizma ve sınıflama sorularına doğru cevap vermiştir.

Sonuç: Bu çalışma ortopedistlerin NSAİİ ADR ile ilgili bilgi düzeylerinin düşük ve NSAİİ ilişkili ADR gelişmesi durumundaki yaklaşımlarının da yetersiz olduğunu göstermiştir.

Anahtar Kelimeler: Nonsteroidal anti-inflamatuar ilaçlar, aşırı duyarlılık reaksiyonları, bilgi düzeyi, uygun yaklaşım

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used medications due to their anti-inflammatory, anti-pyretic and analgesic effects [1]. Hypersensitivity reactions (HRs) to NSAIDs is a challenging problem for clinicians. Because, they are the one of the most common causes of the drug HRs and drug-induced anaphylaxis [2-6]. Furthermore, they can lead to various kind of HRs with a wide range from mild to life-threatening reactions in severity (from itching, rhinorrhea to anaphylaxis and death) by different mechanisms including immunologic (allergic): IgE and T cell mediated and non-immunologic: cyclooxygenase-1 (COX-1) inhibition. The clinical presentation is similar in both immunologic and non-immunologic reactions but the management differs [7]. Therefore, to facilitate the diagnosis and management of HRs to NSAIDs, a classification of the HRs to NSAIDs was proposed by Expert Committee of the European Academy of Allergy and Clinical Immunology (EAACI) in 2011 and revised in 2013 [7,8]. The classification includes five different groups depending on the underlying mechanisms, clinical entity, interval between drug intake and onset of the HR, the presence of underlying chronic skin or respiratory diseases and the cross-reactivity [7]. The groups are; 1. NSAID-exacerbated respiratory disease (NERD) in which respiratory symptoms such as rhinorrhea, nasal congestion, dyspnea or asthmatic attacks develop after ingestion of NSAIDs in the patients with underlying chronic respiratory diseases, 2. NSAID-exacerbated cutaneous disease (NECD) which leads to episodes of urticaria and/or angioedema in patients with underlying chronic spontaneous urticaria (CSU), 3. NSAID-induced urticaria and angioedema (NIUA) in which urticaria and/or angioedema occurs after ingestion of chemically different NSAIDs in the patients without any underlying chronic respiratory or cutaneous diseases, 4. Single NSAID-induced urticaria, angioedema and/or anaphylaxis (SNIUAA) develops with only one or more chemically related NSAIDs with good tolerance to other chemically different NSAIDs in patients without underlying chronic diseases, 5. Single NSAID-induced delayed reactions (SNIDR) that cause a large range of non-immediate type HRs from maculopapular rash (MPR) to severe cutaneous

reactions such as Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) after ingestion of chemically related NSAIDs with well tolerance to other NSAIDs [7,8]. However, some authors showed that chemically unrelated NSAIDs can lead to anaphylaxis so the third group, NIUA is most commonly accepted as NSAID-induced urticaria, angioedema and anaphylaxis (NIUAA). Furthermore, some authors draw attraction to blinded reactions [9, 10].

Since of the complexity in underlying mechanism and clinical presentation and lack of exact diagnostic tests, HRs to NSAIDs should be evaluated by an expert allergist. However, NSAIDs are prescribed by all the clinicians and they can experience the occurrence of HRs in their patients at first. The appropriate management of the NSAIDs related HRs can prevent the future undesirable reactions before admission to an allergist. However, the knowledge level and attitude of clinicians other than the allergists about HRs to NSAIDs is not well known. Therefore, the aim of the study was to assess the knowledge levels about NSAIDs hypersensitivity of orthopedic surgeons who very commonly prescribe NSAIDs and their approach in case of development of HRs to NSAIDs in their patients.

Method

A cross-sectional questionnaire study was conducted between 2021 and 2022. A total of 178 orthopedic surgeons were randomly contacted via physician-focused social media groups. They were asked to fill a structured questionnaire which contained questions about demographic features of them and knowledge level and approach about NSAIDs hypersensitivity. Among them, 109 surgeons agreed to complete the survey, which was sent to them via e-mail. The response rate was 61.2%, which is considered acceptable for this type of study. One question for assessment of their approach (Q11d) was used and its answers as categorized as well-approach including the answers A1 and A2 and poor-approach including the answers A3 and A4. Two questions were asked to evaluate the level of knowledge (Q12 and Q13) were asked (Table 1).

At first, a consent form was sent to participants by e-mail and they were asked to signed and sent

it back. After that, the link of questionnaire which was prepared in Survey Monkey® was sent to participants via e-mail and asked to complete the survey. Then the results were analyzed.

The study was approved by ethic committee in İstanbul Atlas University Non-invasive Scientific Research Ethics Committee (Approval number: E-22686390-050.01.04-10396) and conducted in accordance with the Declaration of Helsinki.

Statistical analysis

The statistical analyses of data were performed with SPSS version 21.0 (Chicago, IL, USA). Descriptive statistics which were presented as number and percentage or mean±standard deviation (SD) or median (minimum-maximum) according to type or distribution of the data were used to evaluate the characteristics. Continuous variables were compared with independent or nonparametric t-test and categorical data were compared by χ^2 or Fisher's Exact tests depending on the distribution of the data. P values less than 0,05 were considered statistically significant.

Results

The mean age of the participants was 40.53±7.88 years. The majority of the participants were specialist (n=65, 59.6%) and 15.6% (n=17), 11% (n=12), 11% (n=12) and 2.8% (n=3) were resident, doctoral lecturer, associated professor and professor respectively. They have been working on orthopedic field for the mean 15.02±8.28 years. Most of the physicians got the orthopedics training in university hospital (n=83, 76.1%) and the remaining was trained in training and research hospital. There were adult and/or pediatric allergist in the university which they were graduated and hospital which they got orthopedic training in 94.5% and 91% of the participants, respectively. The types of clinics they worked were private hospital (n=30, 27.5%), university hospital (n=25, 22.9%), training and research hospital (n=25, 22.9%), government hospital (n=16, 14.7%) and private clinic (n=13, 11.9%). The participants examined median (min-max) 30 (2-130) patients and prescribed median (min-max) 10 (1-60) NSAIDs per day. The most and least commonly prescribed NSAIDs were ibuprofen (48.6%) and paracetamol (0.9%), respectively (Figure 1).

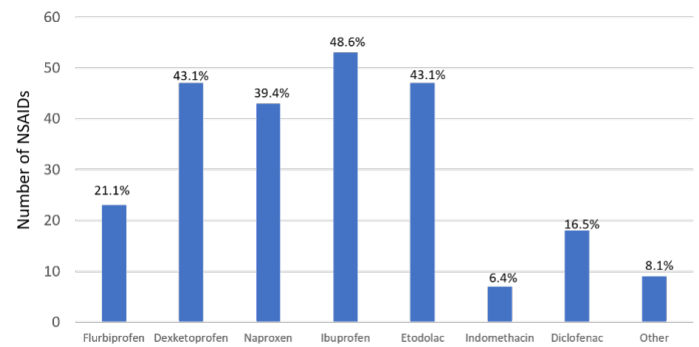


Figure 1: The number of NSAIDs most commonly prescribed and responsible for the hypersensitivity reactions observed by the participants in their patients.

Approach of participants in case of NSAID HRs development

Forty-eight (44%) participants observed hypersensitivity reactions to NSAIDs in their patients. Any of these patients died due to NSAID hypersensitivity. The most commonly observed hypersensitivity reaction was urticaria (n=26, 23.4%) and the most common culprit NSAIDs were naproxen (n=12, 11%) and flurbiprofen (n=12, 11%) and 12 participants did not recall the culprit agents (Figure 1). Forty-eight participants were further asked how did they continue to the treatment in their patients who developed an NSAID-induced hypersensitivity reaction (Table 1). 32.1% of them suggested to stop the culprit NSAID and consulted to an allergist and 28.6% of them suggested to stop the culprit NSAID and recommended different treatment modalities (other than NSAID) while 37.5% and 1.8% of them suggested to stop the culprit NSAID and prescribed another NSAID and added an antihistamine to his/her treatment, respectively (Figure 2). The number of participants classified in the well-approach group (suggested to stop the culprit drug and suggested treatment modalities other than NSAIDs or consulted to an allergist when an NSAID HR developed in their patients) was 24. In the comparison of the groups of well- and poor-approach, regarding the duration of working on orthopedic field, degree (being professor or associated professor or not), types of trained for orthopedic and currently worked hospital, the presence of pediatric or adult allergy clinic in university, trained and currently worked hospital, no association was observed ($p>0.05$).

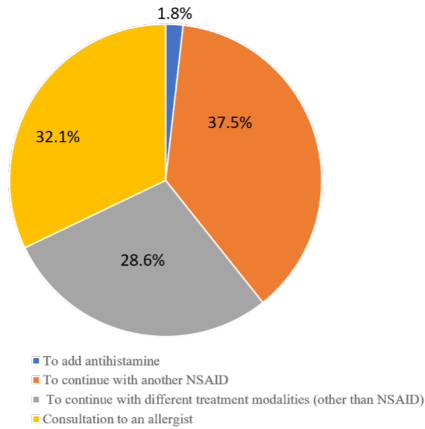


Figure 2: The approaches of participants in continuing the treatment of patients who developed hypersensitivity reactions to NSAIDs.

Table 1: The survey applied to participants

Questions
1. Age
2. Which university did you graduate from?
3. Which clinic did you get your orthopedic training from?
4. How long have you been working on orthopedic field?
5. What kind of hospital do you work?
University hospital
Government Hospital
Training and Research Hospital
Private Hospital
Private clinic
6. What is your title?
Resident
Specialist
Doctoral lecturer
Associated Professor
Professor
7. Is there an allergist in the hospital/clinic you work?
8. How many patients do you see on average per day?
9. How many nonsteroidal anti-inflammatory drugs (NSAIDs) do you prescribe on average per day?
10. Which of the followings NSAIDs do you prescribe most frequently? (you can tick more than one option)
Flurbiprofen
Dexketoprofen
Naproxen
Ibuprofen
Etodolac
Indomethacin
Diclofenac
Metamizole
Others (Please specify)

Table 1. Continued...
11. Have your patients developed an allergic reaction to NSAIDs?
11a. What kind of allergic reaction(s) did develop in your patient(s)? (you can tick more than one option)
Anaphylaxis
Urticaria
Angioedema
Rhinitis/dyspnea
Maculopapular eruptions
Steven-Johnson syndrome/Toxic epidermal necrolysis
Others (please specify)
11b. Which of the following NSAIDs was/were the culprit agent(s)? (you can tick more than one option)
Flurbiprofen
Dexketoprofen
Naproxen
Ibuprofen
Etodolac
Indomethacin
Diclofenac
Metamizole
Others (Please specify)
I do not remember
11c. Have you ever had a patient who died due to an NSAID-induced allergic reaction?
11d. How did you continue to the treatment in your patient who developed an NSAID-induced allergic reaction?
A1. I added an antihistamine to his/her treatment
A2. I suggested to stop the culprit NSAID and prescribed another NSAID
A3. I suggested to stop the culprit NSAID and recommended different treatment modalities (other than NSAID)
A4. I suggested to stop the culprit NSAID and consulted to an allergist
Other (please specify)
12. What kind of mechanism do NSAIDs cause an allergic reaction by? (you can tick more than one option)
IgE mediated
T cell mediated
By COX-1 inhibition
By MGPRX2 activation
I have no idea
Other (please specify)
13. On which of the followings does current classification of NSAIDs allergic reactions depend? (you can tick more than one option)
Underlying mechanism
Reaction type
Presence or absence of cross-reactivity
Onset time of reaction
NSAID chemical groups
I have no idea
Others (please specify)

Knowledge level of participants about NSAID HRs

45.9% of the participants reported that they have no idea about the underlying mechanism which NSAIDs cause hypersensitivity reactions while 41.3%, 20.2% and 15.6% stated that the mechanism was IgE mediated, T cell mediated and due to COX inhibition, respectively. Four physicians answered as the NSAID hypersensitivity could occur by IgE, T cell mediated or COX inhibition ways. 12 participants stated that NSAID hypersensitivity could develop due to IgE or T cell mediated ways while 5 of them thought that it could occur IgE mediated or COX inhibition ways. Almost half of the participants (49.5%) did not have any idea about the current classification of NSAID hypersensitivity. 24.8%, 24.8%, 16.5%, 18.3% and 4.6% of them answered as the classification depended on underlying mechanism, reaction type, presence of cross-reactivity among chemically different NSAIDs, chemical groups which culprit NSAIDs belong to and onset time of reaction, respectively. Only 1 physician stated that the classification depended on the underlying mechanism, reaction type, onset time of reaction and presence of cross-reactivity.

Discussion

In our knowledge the current study was the first one which indicated the low knowledge level about NSAID HRs and inappropriate approach in case of NSAID HR development among the orthopedic surgeons who commonly prescribe NSAIDs.

NSAIDs which are widely used medications are the one of the leading causes of drug HRs [2-6]. Since of unpredictability and mortality and morbidity risk, drug HRs gain importance and make the NSAID induced HRs significant problems for the physicians especially who are not trained specifically for this issue. To prevent the recurrent reactions and to decrease the mortality and morbidity, knowledge and attitude of physicians other than allergist are important. There are a few numbers of studies which evaluated this subject. Çeliksoy et al. reported that the knowledge of primary care physicians about management of drug HRs was insufficient [11]. In line with their findings Güvenir et al. also found that the knowledge and attitude of pediatrics and family

physicians were not satisfactory [12]. In another study which conducted on the various health care professionals, drew attention to importance of this issue as well [13]. When we think that the drug HRs are seen with considerable frequency, the urgent need to increase the understanding of physicians about drug HRs is obvious and more specific studies are necessary to determine the gap in the knowledge and approach.

In the present study, it was observed that almost 40% of the orthopedic surgeons who experienced HRs in their patients did not know how to manage. When we compared the participants with well- and poor-approach in case of NSAID triggered HRs we did not observe any relationship between the factors including types of hospital either they worked or were trained for orthopedic, being professor or associated professor, duration worked on orthopedic field and the presence of an allergist in their hospital (worked or trained) and faculty of medicine. Furthermore, we showed that the knowledge level about NSAID HRs mechanisms and classification was very low among orthopedic surgeon. To know the underlying mechanism and classification of NSAID HRs facilitate the understanding of the problem and result in appropriate management of the reactions.

This study has some limitations that should be considered when interpreting its findings. Firstly, the sample size was relatively small, which may limit the generalizability of the results. Secondly, the absence of a control group—specifically, physicians from different specialties—restricts the ability to compare knowledge levels across diverse medical fields. To mitigate these limitations, we compared our findings with those from previous studies that assessed the knowledge levels of physicians in other specialties.

To conclude, the current study showed that the knowledge level about NSAID HRs was low and approach to the patients whom NSAID HRs developed was unsatisfactory among orthopedic surgeons. To increase the knowledge level and to correct the physicians' approach to NSAIDs HR recurrent training program on drug HRs could be a choice of solving this problem.

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