SELF-REPORTED DRUG ALLERGIES IN SURGICAL POPULATION IN SERBIA

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SUMMARY – History of drug allergy is of major concern during perioperative period. Medical records usually lack documents confirming the stated allergy. This study aimed to investigate the prevalence of self-reported drug allergies and their characteristics in adult Serbian surgical population, and to analyze their influence on drug prescription during perioperative period. The study enrolled patients scheduled for general surgery during a one-year period at a tertiary care hospital. They were questioned using a structured questionnaire about the existence of drug allergy and its nature. Medical records were examined after discharge to assess medical prescription during hospitalization. Of 1126 patients evaluated during the study period, 434 (38.5%) reported a total of 635 drug reactions. The most common allergy claim was to antibiotics (68%), nonsteroidal antiinflammatory drugs (16.4%) and iodine (3.9%). Women, urban residents and herbal drug consumers were more likely to state an allergy. The majority of reported reactions were cutaneous (72%) and respiratory (34%), while anaphylaxis was reported by 3.2% of patients. Only 38 (8.7%) patients had previously undergone any allergology testing. Retrospective chart review revealed that 26 (6%) patients were administered the drug to which they had reported allergic reaction in the past, with no adverse effects. Drug allergies are frequently self-reported in surgical population in Serbia, which is in contrast to a very low rate of explored and documented allergies. In order not to deny an effective treatment or postpone a surgery, health care practitioners should pay more attention to an accurate classification of adverse drug reactions.

Key words: Drug hypersensitivity; Hypersensitivity; Drug-related side effects and adverse reactions; Surveys and questionnaires; Surgery department, hospital; Serbia

Introduction

Information regarding the history of allergies is contained in every medical record. It is obtained by almost every health care provider being in contact with patient at any level of health care. Since patients are exposed to a variety of drugs during perioperative period, a history of drug hypersensitivity is of major concern in surgical and anesthetic practice¹.

Drug hypersensitivity reactions (DHR) represent adverse effects of drugs taken at a dose tolerated by normal subjects². DHR comprise approximately 10%-15% of all adverse drug reactions. According to the nomenclature recommended by the World Allergy Organization, drug allergies are defined as hypersensitivity reactions with clearly defined immune background³. Most of the patients are unaware of that fact, so it is clear that they label any unexpected or adverse drug effect as ‘allergic reaction’⁴. Furthermore, medical records usually include only the patient’s statement on the existence of drug allergy and the implicated drug but not details about previous reaction or allergology diagnostic work up, making the reliability of such
data questionable. Literature data reveal that both under-reporting and over-diagnosis of DHR (due to inappropriate use of the term ‘allergy’) are present in clinical practice, which might have consequences on treatment choices and influence the quality of care5,8. Low rate of reporting of adverse drug reactions to pharmacovigilance agencies makes the problem even more difficult to control7,8.

The aim of our survey was to assess the prevalence of self-reported drug allergies in adult surgical population in Serbia, to explore their characteristics and investigate to what degree they influence drug prescription during perioperative period.

Materials and Methods

The survey was conducted during a one-year period (from April 2011 till March 2012) at the Department of Anesthesiology, Clinical Center of Serbia, Belgrade. It enrolled consecutive adult patients scheduled for elective general surgery. Patients were questioned by their anesthetists during routine pre-anesthetic visit whether they had any allergy to report. Anesthetists had to complete a formatted questionnaire based on the European Network of Drug Allergy (ENDA) questionnaire adapted to perioperative needs and Serbian population (Fig. 1)9. The questionnaire contained questions about the nature of previous allergic reactions, previous diagnostic work-up, and also recorded patient demographic and clinical data. An average time for completion of the questionnaire was 5 to 10 minutes. Medical records were examined afterwards to see whether the drugs prescribed conflicted with those self-reported as allergies. The term ‘allergy’ was used deliberately instead of ‘hypersensitivity’ since it is understandable and used by most patients.

Database was created and statistical analyses were performed using the SPSS software version 17.0. The level of statistical significance was set at p<0.05. For descriptive analysis data were expressed as proportions with their 95% confidence interval (CI) or means ± standard deviations. Logistic regression analysis was carried out to determine risk factors for allergy self-reporting.

Results

During the study period, a total of 1126 patients, 627 (55.7%) men and 499 (44.3%) women, age range 19–83 (mean 58.9±15.5) years were evaluated. The majority of patients were residents of urban areas (n=977; 86.8%) whereas 149 (13.2%) were from rural areas. Comorbidities were reported by 885 (78.6%) patients and 663 (58.8%) of them were treated with chronic therapy. In addition, 368 (32.7%) patients reported regular use of various herbal medications or dietary supplements, while 75 (6.7%) patients were diagnosed with a defined allergic disease (such as asthma, allergic rhinitis, chronic urticaria, etc.).

We found that 434 (38.5%) patients considered themselves allergic to at least one drug and they reported a total of 635 reactions. The most frequently implicated drugs were antibiotics, being responsible for 68% of the reported adverse events. Penicillins were involved in 302 (47.6%) reactions and they were by far the most commonly addressed allergens. Other antibiotics to which allergic reactions were frequently reported were sulfonamides (14.3%), cephalosporins (12.9%), macrolides (5.0%), tetracyclines (1.9%), and others (such as vancomycin or quinolones, 2.4%). Regarding other drugs designated as responsible for allergic reaction, nonsteroidal antiinflammatory drugs (NSAIDs) were involved in 104 (16.4%) reactions, iodine in 25 (3.9%), contrast medium in 13 (2.1%), angiotensin-converting enzyme (ACE) inhibitors in 7 (1.1%), atropine in 4 (0.7%), calcium antagonists in 5 (0.8%), local anesthetics in 2 (0.3%), and latex in 3 (0.5%) reactions. Two patients reported allergic reaction to an undetermined anesthetic and it was not possible to identify whether the implicated event was to an intravenous anesthetic, muscle relaxant, an opioid, or some other drug (Fig. 2). These patients were referred for preoperative allergology testing (skin-prick tests), which revealed no allergy to the tested battery of agents for use during general anesthesia and perioperative period.

Logistic regression analysis revealed that women (OR=4.3, 95%CI=2.8–6.2), patients from urban areas (OR=1.8, 95%CI=1.3–2.9) and those regularly taking
herbal drugs (OR=3.2, 95%CI=2.6-4.9) were significantly more likely to claim a drug allergy (Table 1).

The most common clinical manifestations recalled by patients were cutaneous (72%), respiratory (34%), cardiovascular (18%) and gastrointestinal (11%), all of them being rather mild than severe. Anyway, 36 (3.2%) patients reported previous anaphylactic reaction with various presentations (Table 2).

Out of 635 self-reported allergic reactions, 80 (12.6%) occurred during the past year, 58 (9.1%) during the past 10 years, 208 (32.7%) reactions occurred 10-20 years before, while in the majority of cases (n=289; 45.5%) the claimed allergic reaction had occurred more than 20 years before.

Oral administration of drug preceded self-reported allergic reaction in 152 (23.9%) cases, while 483 (76.1%) reactions followed the parenteral route of drug administration. According to the patients’ answers, 432 (68.0%) reactions occurred at a healthcare institution, whereas 203 (32.0%) took place at home, usually after oral administration of the drug.

Almost 98% of study subjects (425/434) had completely avoided the suspected agent thereafter. Only 38 of 434 (8.7%) patients with self-reported drug allergy underwent further allergology investigation and in 12 patients, the reported allergy was confirmed by allergology testing.

Questionnaire analysis showed that in 42.5% (270/635) of cases, anesthesiologists judged the reported drug allergy to be certain or probable, which was based on the responses about previous diagnostic work-up or reported symptoms highly suggestive of an allergy. The remaining self-reported allergies were associated with lower probability (possible, doubtful, unrelated) of a true allergic reaction as estimated by the attending anesthesiologist. The self-reported history of allergy was noted in the official anesthesia chart, irrespective of this estimation.

Medical records after patient discharge revealed that 26 (6.0%) patients were administered a drug to which they claimed to be allergic during their hospital stay, with no adverse reactions. Antibiotic prophylaxis with cephalosporins was administered to 82% of the patients with reported allergy to penicillin and to 86% of those without reported allergy (p>0.05), with no adverse events recorded.

**Discussion**

The prevalence of self-reported drug allergy in our survey was 38.5%. Most studies performed in inpatients showed a higher incidence of self-reported allergies, ranging from 25% to 39%, than surveys conducted in the general population, where the prevalence was 7.8%-9.7%10-11.

<table>
<thead>
<tr>
<th>Severity grade</th>
<th>Clinical manifestation</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Itching on the skin</td>
<td>287 (45.2)</td>
</tr>
<tr>
<td>(skin and/or subcutaneous</td>
<td>Skin rash, urticaria</td>
<td>231 (36.4)</td>
</tr>
<tr>
<td>tissue only)</td>
<td>Erythema</td>
<td>140 (22.1)</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>76 (12.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Sneezeing or nose secretion</td>
<td>76 (12.0)</td>
</tr>
<tr>
<td>(respiratory, cardiovascular</td>
<td>Itching or secretion of eyes</td>
<td>64 (10.1)</td>
</tr>
<tr>
<td>or gastrointestinal</td>
<td>Throat tightness</td>
<td>95 (15.0)</td>
</tr>
<tr>
<td>involvement)</td>
<td>Dyspnea</td>
<td>64 (10.1)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>10 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Wheezing</td>
<td>52 (8.2)</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
<td>70 (11.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>Hypotension</td>
<td>38 (6.0)</td>
</tr>
<tr>
<td>(hypoxia, hypotension,</td>
<td>Tachycardia</td>
<td>53 (8.3)</td>
</tr>
<tr>
<td>neurologic symptoms)</td>
<td>Loss of consciousness</td>
<td>21 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td>16 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Collapse</td>
<td>29 (4.6)</td>
</tr>
</tbody>
</table>

n (%) = number (%) of reported reactions

Table 2. Frequency of clinical manifestations reported by patients and their severity grading
**Fig. 1. History of allergy questionnaire used in the survey (translation from Serbian language).**

**ALLERGY QUESTIONNAIRE**

Protocol No: ___________ Date: ___________

**PATIENT:**
Name______________________ Date of birth:______________________Age:_____________years
Sex: ☐M ☐F Residence: ☐Urban ☐Rural Occupation: __________________________

**PERSONAL HISTORY:**
Diagnosis:______________________ Comorbidities: ☐Y ☐N __________________________
Chronic therapy: ☐Y ☐N __________________________ ASA:__________
Herbal medication or dietary supplement consumption: ☐Y ☐N
Allergic diseases (asthma, pollinosis, atopic dermatitis, food allergy, chronic urticaria, etc.): ☐Y ☐N

**HISTORY OF DRUG ALLERGY:**
Do you have drug allergy to report? ☐ Y ☐N
Suspected drug(s): __________________________

*Clinical manifestation of reported reaction*

<table>
<thead>
<tr>
<th>Cutaneous</th>
<th>Gastrointestinal and respiratory:</th>
<th>Neurologic:</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐Maculopapular rash</td>
<td>☐Nose discharge and sneezing</td>
<td>☐Paresthesia</td>
<td>☐Tachycardia</td>
</tr>
<tr>
<td>☐Erythema</td>
<td>☐Throat tightness</td>
<td>☐Loss of consciousness</td>
<td>☐Hypotension</td>
</tr>
<tr>
<td>☐Urticaria</td>
<td>☐Itching or eye discharge</td>
<td>☐Tinnitus</td>
<td>☐Collapse</td>
</tr>
<tr>
<td>☐Angioedema</td>
<td>☐Dyspnea</td>
<td>☐Vertigo</td>
<td>☐Arrhythmia</td>
</tr>
<tr>
<td>☐Pruritus only</td>
<td>☐Cough</td>
<td>☐Other</td>
<td>☐Anaphylaxis</td>
</tr>
<tr>
<td>☐Other</td>
<td>☐Wheezing</td>
<td></td>
<td>☐Other</td>
</tr>
<tr>
<td></td>
<td>☐Nausea, vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐Diarrhea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management following drug reaction: ☐No therapy ☐Immediate treatment ☐I don’t remember

Where did drug allergy take place? ☐Health care institution ☐Home ☐Other

Route of administration of suspected drug ☐Oral ☐Muscular ☐Intravenous ☐Topical ☐I don’t know

When did the allergic reaction happen? ☐During the last 10 years ☐10-20 years ago ☐More than 20 years ago

Have you taken the suspected drug after the allergic reaction? ☐Y ☐N ☐I don’t know

Have you taken a similar drug (that could cross react) after the allergic reaction? ☐Y ☐N ☐I don’t know

Have you undergone any allergology testing after the reaction? ☐Y ☐N

Which? ☐Skin tests ☐Blood analysis ☐Provocation tests ☐Other ☐I don’t know

*Probability of allergic reaction based on history and documentation:* ☐Certain ☐Probable ☐Possible ☐Doubtful ☐Unrelated/Not assessable
In agreement with other studies, antibiotics accounted for the majority of putative allergies in the present study. It is noteworthy that antibiotic consumption in Serbia is among the highest in Europe, and until recently antibiotic purchase was not restricted by country policy, making these drugs easily available for self-medication. The average antibiotic consumption in Europe is around 20 DDD/1000 inhabitants per day, while in Serbia it was 33.1 DDD/1000 inhabitants per day in 200614. The high antibiotic utilization may in part explain the frequency of self-reported allergies to antibiotics. Beta-lactams and antibiotics with greater historical use had a higher ‘allergy prevalence’ in our survey. Previous studies have reported the suspected prevalence of allergy to penicillin to be between 0.7% and 8% of the general population15. Our data revealed an even higher prevalence, probably due to over-reporting since the majority of diagnoses were based solely on clinical history and patient judgment. The second most frequent allergy reported in our study was to NSAIDs, which is of concern to the anesthetists since these drugs are part of a common postoperative analgesic protocol. NSAIDs rarely cause true allergic reactions but are commonly involved in various type A adverse drug reactions, which are dose predictive such as nausea, gastrointestinal intolerance or pruritus16. Anyway, the use of aspirin and NSAIDs is rarely accompanied by idiosyncratic adverse reactions, some of which can be extremely serious, e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome or aseptic meningitis17. Since a specific IgE to NSAIDs has not been identified, these hypersensitivity reactions are called anaphylactoid and are clinically indistinguishable from anaphylactic reactions18. Due to the high benefit of aspirin use in primary and secondary prevention of coronary artery disease, several desensitization protocols for patients with hypersensitivity to aspirin and NSAIDs have been proposed19. Patients in our survey typically designated a particular agent to be responsible for allergy with reported previous safe use of other NSAIDs. Other drugs of importance during perioperative period where marked less frequently, with the exception of iodine radiocontrast media and latex. Allergies to anesthetic agents were mentioned extremely rarely and were always a subject of special attention.

In accordance with other studies, female preponderance in allergy reporting was observed in our survey as well19,20. Although data from human studies are lacking, sex hormones might play a role since the effect of estrogens on mast cell activation and allergic sensitization has been confirmed in animal studies21. Patients from urban areas were more likely to claim a drug allergy in our population. Although it is obvious that air pollution in urban areas is responsible for a higher incidence of asthma in modern cities, we could not find valuable explanation for our finding. It also remains unclear why the self-reported allergies were three times more common among users of herbal medications. It is gender unrelated since we found no difference in the rate of herbal medication consumption between men and women. We made an assumption that some of them might cross-react with drugs and also that their concomitant use disabled distinction of causal relation to putative allergy.

During questioning of our participants, we paid special attention to description of clinical features of the self-reported allergic reactions. As in the majority of reports, cutaneous reactions were the most common presentation of stated allergy22,23. Other symptoms involving different sites were in the vast majority of cases mild and self-limited reactions. Meticulous analysis after completion of questionnaires revealed that in many cases the reported symptoms were well known adverse reactions to a drug believed to have caused an allergy. For example, reporting cough or angioedema was common in patients claiming an allergy to ACE inhibitors, or nausea and abdominal discomfort in those with self-reported allergy to macrolides and tetracyclines. There was even a case of reporting a wanted and expected drug effect as an allergy, as in case of a patient reporting heavy sleepiness after diazepam consumption.

Diagnostic work-up in patients with hypersensitivity drug reactions consists of detailed history taking, physical examination and laboratory testing immediately after reaction (total IgE, mastocyte tryptase, methylhistamine). Retrospective diagnosis after hypersensitivity reaction is based on in vivo testing (skin tests), organ challenge tests, and in vitro testing (detection of allergen-specific IgE antibody and molecular-based allergy diagnosis)24,25. Skin tests represent the cornerstone of identification of causative allergens and are regarded as the gold standard for detection of
IgE antibodies with demonstration of wheal and flare reaction. In practice, the rate of allergology tested subjects is far less than those with allergy claim.

A study conducted in the general population in Portugal demonstrated that about one half of participants with stated allergy had undergone any diagnostic procedure; 22.7% of them were submitted to skin tests and 26% to blood analysis\textsuperscript{13}. Analyzing surgical population, Tamayo \textit{et al.} report that two-thirds of patients were subjected to some allergy investigation and that in 66.7% the only diagnostic test was a skin prick test\textsuperscript{26}. Our findings differ substantially, as only 38 (8.7%) patients had previous allergology testing with diagnosis confirmed in 12 of them. Bavbek \textit{et al.} showed that just 3.2% of medical students in Turkey with self-reported hypersensitivity were referred to an allergologist\textsuperscript{27}. We can assume that the results in our survey could be explained by the low availability of allergology services in our country and the lack of guidelines for general practitioners covering this topic. Another reason might be the fact that clinical symptoms in the majority of patients were mild, not causing much worry and need for additional diagnosis.

The problem of an insufficient clinical characterization of allergies in Serbia is reinforced by the fact that reporting adverse drug reactions is at a very low level. The official national institution for pharmacovigilance, the Agency for Medicine and Medical Devices of Serbia (ALIMS) announced that only 910 reports of adverse drug reactions were submitted in 2011 and only 102 in 2005\textsuperscript{28}. This fact probably contributes to the over-reporting of drug allergies since all kinds of adverse reactions are labeled as allergies by patients and their health care practitioners.

Current guidelines of the European Society of Anaesthesiology on preoperative evaluation of the adult non-cardiac surgery patient suggest allergology testing only in patients with a positive clinical history and those at risk of anaphylactic/anaphylactoid reaction during anesthesia\textsuperscript{29}. In the absence of diagnostic work-up, facing with a patient claiming drug allergy, anesthesiologist must act as if the patient is really allergic, which means at least avoiding the claimed agent. Retrospective analysis of our practice revealed that 6% of our patients were administered the drug they marked as the causative agent for allergy. In most cases, the drug was antibiotic or analgesic and the most probable reasons for this malpractice were inadequately labeled allergy note in medical chart, or rejection of diagnosis of allergy by unconvincing patient history. Poor allergy documentation has been reported previously by other authors\textsuperscript{30}. It is interesting to note that none of the medical records examined in our survey contained a single description of a self-reported allergic reaction.

It is estimated that 40% of patients who are allergic to penicillin cross react with cephalosporins, influencing the choice of antibiotic for antibacterial prophylaxis\textsuperscript{31}. The fact that there was a high rate of positive history of allergy to penicillin in our survey did not influence the perioperative antibiotic prescription with no adverse effects. Antibiotic prophylaxis was administered to all patients and the choice of antibiotic was guided by hospital protocol. In patients with self-reported allergies to antibiotics, the antibiotic was chosen on discretion of the attending anesthesiologist. Many patients with claimed allergy to penicillin had received cephalosporins after the reported reaction and it was sufficient to exclude the allergy to cephalosporins. In cases where no similar drug was taken after the allergic reaction, the choice was made based on the estimated probability of a true allergy and was mainly influenced by the severity of previous reaction and documented history of allergic diseases. The assignment of self-reported allergy to a group with a certain level of probability was not made for diagnostic purposes and it did not influence fur-
ther actions as part of the protocol. The intention of this survey was not to assess the frequency of drug allergies by confirming it with subsequent allergology testing. Our goal was rather to determine the magnitude of drug allergy self-reporting and to highlight the problem of mislabeling the predictable adverse drug reactions as allergies.

The results of our study show that self-reported drug allergies are prevalent in adult surgical population in Serbia, which obliges all health care workers dealing with the patient during perioperative period to avoid the drug claimed to have caused an allergy. On the other hand, the majority of these reactions are poorly documented and the information obtained from patients is unreliable. It creates a significant problem of denying an effective treatment and faces clinicians with the lack of an appropriate substitute in a limited resource setting. More detailed preoperative history taking can help anesthesiologist assess the validity of a stated reaction and decide on the probability of a true allergy. General practitioners are encouraged to report adverse drug reactions to pharmacovigilance agencies and to refer patients with suspected allergies to allergology testing for accurate diagnosis of drug allergy.

References

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**Sažetak**

SAMOPRIJAVLJENE ALERGIJE NA LIJEKOVE KOD KIRURŠKIH BOLESNIKA U SRBIJI

**J. Veličković, I. Palibrk, B. Miljković, D. Veličković, B. Jovanović, V. Bumbasirević, M. Djukanović i V. Šljukić**

Podatak o alergiji na lijekove je od velikog značenja u perioperacijskom razdoblju, a medicinska dokumentacija obično ne sadrži dokumente koji potvrđuju prijavljenu alergiju. Cilj ovoga istraživanja bio je ispitati učestalost i značajke samoprijavljenih alergija na lijekove od strane odraslih kirurških bolesnika u Srbiji i analizirati utjecaj takvog anamnestičkog podatka na propisivanje lijekova u perioperacijskom razdoblju. Studija je obuhvatali bolesnike podvrgnute elektivnim kirurškim intervencijama iz područja opće kirurgije tijekom jednogodišnjeg razdoblja u tercijarnoj zdravstvenoj ustanovi. Oni su ispitivani primjenom strukturiranog upitnika o postojanju alergija i njihovoj naravi. Medicinska dokumentacija je pregledana nakon otpusta iz bolnice kako bi se ispitalo propisivanje lijekova tijekom hospitalizacije. Od 1126 bolesnika evaluiranih tijekom studije, 434 (38,5%) ih je prijavilo ukupno 635 reakcija na lijekove. Najčešće samoprijavljene alergijske reakcije su bile na antibiotike (68%), nesteroidne protuupalne lijekove (16,4%) i jodni kontrast (3,9%). Samoprijavljivanje alergija je bilo češće kod žena, stanovnika urbanih područja i korisnika biljnih lijekova. Većinu prijavljenih reakcija su činile kožne (72%) i respiracijske (34%), dok je anafilaksu prijavilo 3,2% bolesnika. Samoprijavljivanje alergija je bilo češće kod žena, stanovnika urbanih područja i korisnika biljnih lijekova. Većinu prijavljenih reakcija su činile kožne (72%) i respiracijske (34%), dok je anafilaksu prijavilo 3,2% bolesnika. Samo 38 (8,7%) bolesnika je nakon reakcije podvrognuto nekom alergološkom testiranju. Pregled povijesti bolesti je pokazao da je 26 (6%) bolesnika tijekom hospitalizacije primilo lijek na koji su prijavili alergijsku reakciju u prošlosti, što nije bilo praćeno neželjenim učincima. Samoprijavljivanje alergija na lijekove je veoma često kod kirurških bolesnika u Srbiji, što je u suprotnosti s niskom stopom ispitanih i dokumentiranih alergija. Kako se bolesnicima ne bi uskratila učinkovita terapija ili odlagala operacija, zdravstveni radnici bi trebali više pozornosti posvetiti preciznoj klasifikaciji neželjenih reakcija na lijekove.

**Ključne riječi:** Alergija na lijekove; Alergija; Lijekovi, popratni učinci i štetna djelovanja; Ankete i upitnici; Kirurški odjel, bolnički; Srbija