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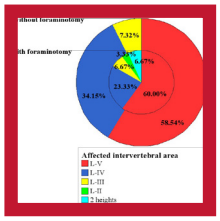
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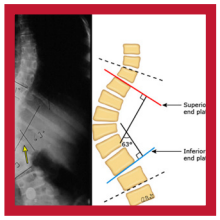
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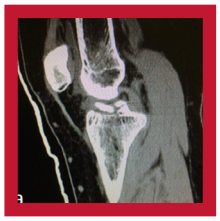
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Changes on the Soft Tissues of the Oral Cavity during the Orthodontic Treatment Depending on the Type of Orthodontic Appliance

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ABSTRACT

Introduction : Periodontal status and malocclusions are closely related. Retention places that enable for detention of food caused by various malocclusions, make self-cleaning and proper hygiene difficult and as such endanger the integrity of the soft tissues. Correctly applied orthodontic treatment has positive effects on periodontal tissues as it reduces the risk of damage and inflammations. One of the key factors for successful orthodontic therapy is adequate maintaining of the oral hygiene, which includes removal of dental plaque, the main cause of deterioration of the soft tissues of the oral cavity.

Aim of the study:

- Establish the connection between changes in the soft tissues of the oral cavity and the type of used orthodontic appliance.
- Establish the time interval for appearance of changes on the soft tissues of the oral cavity.

Patients and Methods: This research included 120 patients who were divided into three groups depending on the type of the orthodontic appliance used (mobile orthodontic appliance - active, mobile orthodontic appliances - functional and fixed orthodontic appliances). Examinations were performed three times: at the beginning of the treatment, after three months of therapy and after six months of therapy. In order to analyze the status of the soft tissues of the oral cavity and level of hygiene we used: Silness-Löe plaque index and Löe-Silness gingival index.

Results: In patients divided by the type of orthodontic therapy, a statistically significant difference in the value of indexes after three and six months of wearing orthodontic appliances was found in patients who wore fixed orthodontic appliances. There was a difference in increased index values among this group when compared to subjects treated with mobile orthodontic appliances.

Conclusion: During the orthodontic therapy, especially with fixed orthodontic appliances, patients must pay attention to adequate oral hygiene maintenance in order to avoid any unwanted changes on soft tissues of the oral cavity.

Key words: orthodontic malocclusions, oral hygiene, gingival index, plaque index.

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Introduction

Orthodontic treatment reflects on the whole state of the dentoalveolar structures, as well as on the complete health status of the patient. Correct positioning of the teeth significantly reduces the chances for the development of caries and parodontal ailments, while outward appearance that is achieved by the end of the treatment contributes to the improved mental health and restores patient's self-confidence. [1,2]

Establishing the habit of correct hygiene maintenance during the orthodontic therapy, regardless of the therapy type, whether it is fixed or mobile, is of paramount importance for preservation of hard and soft tissues of the oral cavity, success of the orthodontic treatment and retaining of the achieved results. The patients have to be informed about the importance of maintaining of the oral health in great detail.

Dental plaque is created on all surfaces of the teeth but it accumulates only on those areas that are not exposed to self-cleaning during eating. Those areas are: parts of the teeth next to free gingiva and gingival sulcus, approximal contact, i.e. interdental areas between the teeth, as well as other parts that are not reached by hard and sharp food. In order to remove the dental plaque it is necessary to use the correct toothbrush and to educate the patient on proper technique of teeth brushing.[3]

Efficient removal of dental plaque and following the instructions received from the therapist regarding the proper hygiene maintenance are key success factors for orthodontic treatment. [4-6]

More difficult maintaining of the oral hygiene necessitates additional instructions and explanations to the patients regarding how and what instruments to use to efficiently remove the dental plaque. It is also essential to provide constant motivation and support to the patients. During the orthodontic treatment, especially fixed one, it is significant to use preventive programs with the aim of improving the oral hygiene quality. [7-9]

Aim of the Study:

- Establish the connection between changes in the soft tissues of the oral cavity and the type of used orthodontic appliance.
- Establish the time interval for appearance of changes on the soft tissues of the oral cavity.

Patients and Methods

This research included 120 patients of both sexes, ages 12 to 20. All patients had permanent dentition. In accordance with regulations on protection of personal data, all data was anonymized. Patients were divided into three groups depending on the type of appliance used in the therapy:

- First group consisted of 40 patients wearing mobile appliances – active.
- Second group consisted of 40 patients wearing mobile removable – functional.
- Third group consisted of 40 patients wearing fixed orthodontic appliances.

The dental examinations were performed under day light using the flat mirror, dental probes and parodontal probe. Collected data was entered into custom made forms, separately for every patient. Examinations were performed three times: at the first examination and three and six months after the start of the therapy. The research was conducted at Dental office of "Dom zdravlja" Banja Luka and private dental practice "Astrodens" Banja Luka in 2012.

In order to assess the state of the soft tissues of the oral cavity as well as the level of the oral hygiene, the following indexes were used:

1. Silness-Löe plaque index.
2. Löe-Silness gingival index.

Silness-Löe plaque index is used to establish the thickness of the dental plaque and not how widespread it is. Examined surfaces include gingival thirds of vestibular, oral, distal and mesial surfaces of the tooth crown. It is possible to examine all or just the representative teeth.

Representative teeth and surfaces that are examined are:

1. vestibular surface of upper right first molar.
2. vestibular surface of upper right first incisor.
3. vestibular surface of upper left first molar.
4. lingual surface of lower left first molar.
5. vestibular surface of lower left first incisor.
6. lingual surface of lower right first molar.

Prior to determining of this index, the patient should rinse the teeth thoroughly and teeth to be examined are to be dried by air flow. Plaque index of a person is calculated by adding all the values, ranging from 0 to 3, for each of the examined teeth after which the sum is divided by the number of examined teeth.

Dental plaque index is determined by following criteria: index 0 means that there is no plaque on the gingival third of the tooth crown; index 1 denotes a thin film of plaque at the edge of gingiva and on the surface of the tooth adjoining it, it is not visible by the naked eye, it is exposed by using the probe on the aforementioned area; index 2 means that there is a moderate amount of plaque that is now visible by unaided eye, there are deposits on the edge of gingiva, on the surface of the tooth adjoining it, but also in gingival sulcus; index 3 denotes significant amount of dental plaque

that covers the edge of gingiva, surface of adjoined tooth and fills the gingival sulcus.

Löe-Silness gingival index is the index most widely used to establish the status of gingiva. By using this index we can assess the state of gingiva on the vestibular, oral, mesial and distal side of the tooth. The assessment is based on the changes in the color, swelling and bleeding of gingiva.

Index 0 denoted healthy gingiva, the gingiva is pale pink in color, firm and has fine-grained surface. Papilla are contained in the interdental area and do not protrude outside of it. The shape of the papilla depends on the position of the teeth. Index 1 denoted slight inflammation, the edge of gingiva is more reddish than normal. There is a slight edema and increased emitting of gingival exudate. Gingiva is not bleeding when gently provoked by blunt dental probe. Moderate inflammation is marked by index 2 and is represented by gingiva that is red. There is a significant edema and enlarged free gingiva. Bleeding occurs on gentle pressure by the probe. Strong inflammation is marked by index 3, the gingiva is very red and enlarged. There is a tendency for spontaneous bleeding. There are also ulcerations on the gingiva.

Total gingival index is obtained by adding together all values established for all four sides of present teeth and then divided by four. This value is further divided by the number of teeth. Patients with index values below 1 have slight inflammation of gingiva, while values between 1 and 2 indicate moderate gingival inflammation. Average values between 2 and 3 suggest severe inflammation of the gingiva.

For the statistical analysis of the data we used standard descriptive statistics such as: mean value and standard deviation, as needed. In order to compare differences between the groups of the patients we used ANOVA (Analysis of Variance). Statistically significant difference was accepted to exist when the p was less than 0.05 ($p<0.05$).

All the relevant results were presented in tabular and graphical form by using corresponding type of diagram. For statistical analysis, preparation and presentation of the data we used following software: R v2.12, OpenOffice and Microsoft Office.

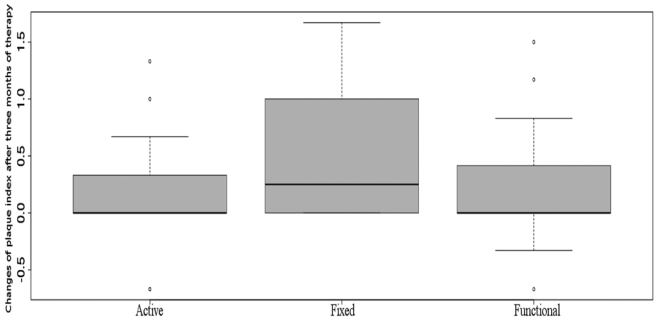
Results of the Research

Plaque index

After three months of wearing orthodontic appliances we have found statistically significant differences in values of plaque index, when compared to initial values, based on the type of the appliance used in the therapy. Mean values of plaque index after three month of the therapy were 0.16 for active appliances, 0.20 for functional appliances and 0.50 for fixed appliances. After performing ANOVA analysis we established values of $F=14.11$ and $Pr(>F) < 0.00001$ which suggests statistically significant difference. Mean values and standard deviations are presented on the image 1.

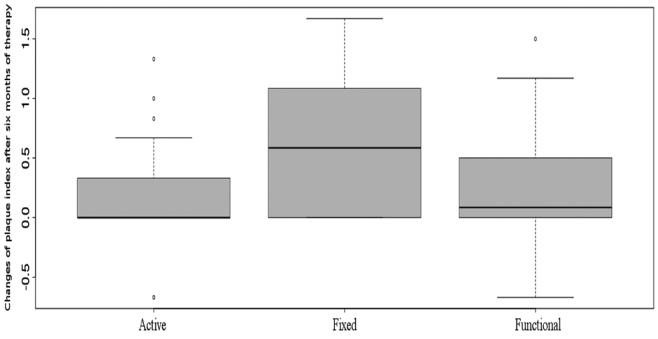
With patients grouped by the type of orthodontic therapy, after six months of the therapy, significantly higher mean values for plaque index were found with the patients wearing the fixed orthodontic appliances (0.60) when compared to patients wearing active (0.19) and functional (0.26) appliances. ANOVA analysis of plaque index values after six months of the therapy produced $F = 20.02$ and $Pr(>F)<0.00001$ which suggests statistically significant difference for three types of the therapy.

Image 1. **Mean values and standard deviations of plaque index change after three months of therapy**



With patients grouped by the type of orthodontic therapy after six months, statistically significant differences were found with patients wearing fixed orthodontic appliances with significantly higher mean values of dental plaque index when compared to patients wearing mobile appliances. Mean values and standard deviations are given in image 2.

Image 2. **Mean values and standard deviations of plaque index change after six months of therapy**

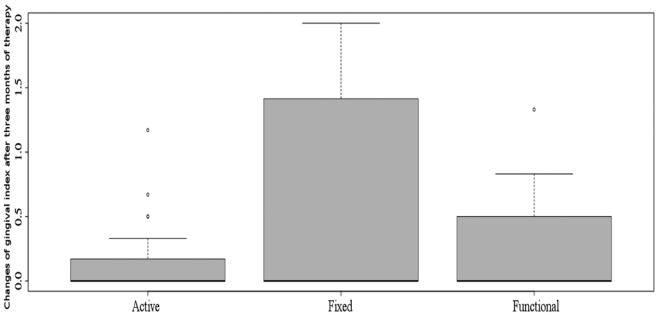


Gingival index

By examining the values of the gingival index after three months of the orthodontic therapy, with patients grouped

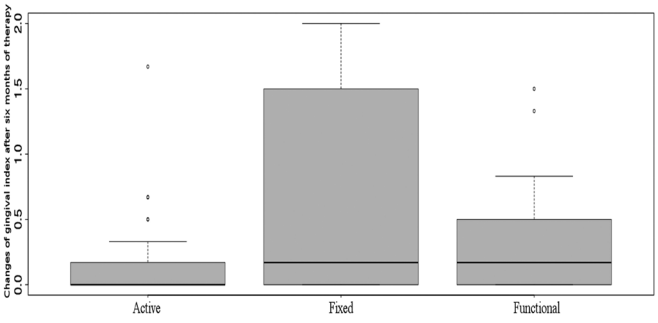
by the type of the appliance worn, higher mean values were found at patients wearing the fixed orthodontic appliances (0.52) when compared to patients wearing active (0.12) and functional (0.23) appliances. Obtained differences were statistically significant (ANOVA F = 16.36 and Pr(>F)<0.00001). Mean values and standard deviations are presented in image 3.

Image 3. **Mean values and standard deviations of gingival index change after three months of therapy**



Six months after the start of the therapy, we measured the gingival index values again. Mean value of the gingival index in group of the patients wearing the fixed orthodontic appliances was found to be 0.65, while patients wearing active appliances were found to have 0.16 and functional appliances 0.28 change in mean value. The differences were established to be statistically significant (ANOVA F = 23.74 and Pr(>F)<0.00001). Mean values and standard deviations are given in image 4

Image 4. **Mean values and standard deviations of gingival index change after six months of therapy**



By examining the obtained values of gingival index after six months of the orthodontic therapy with patients grouped by the type of orthodontic appliance used, there was a statistically significant difference and increased mean values of gingival index in the group of patients wearing the fixed orthodontic appliances when compared with patients wearing mobile orthodontic appliances.

Discussion

Orthodontic treatment enables for establishing of the proper function of occlusion, and through that improved oral health, but it also carries with it an increased risk of introducing damage to the soft tissues of the oral cavity if the patient does not rigorously follow the instructions of the orthodontist, especially regarding the oral hygiene. Establishing the habit of maintaining of the proper oral hygiene during the course of the orthodontic treatment, regardless of the type of the treatment, is of paramount importance for preservation of the soft tissues of the oral cavity as well as for success of the orthodontic treatment and retaining of the achieved results.[7]

By utilizing adequate oral hygiene, the patients can successfully prevent accumulation of the dental plaque. The therapist has to, above all, motivate the patients to properly maintain the oral hygiene, train them in choosing a correct dental brush and using it afterwards, i.e. to apply the correct technique of teeth brushing and control them to make sure they really do utilize it.[3]

By analyzing the results obtained in this research, we have noted the statistically significant difference between the groups of the patients grouped by the type of appliance used. Increased values of plaque and gingival index after three and six months of wearing of the orthodontic appliance were found in patients wearing the fixed orthodontic appliances when compared to patients wearing mobile appliances. Increased values are likely the consequence of inadequate level of oral hygiene as well as wearing the appliances that further complicate maintaining the oral hygiene. Obtained results are in accordance with a number of authors that covered this issue.[10-13]

A large number of studies have shown the lack of adequate hygiene during the orthodontic treatments, which in turn had as a consequence appearance of ailment of the soft tissues of the oral cavity during the therapy. [14-17]

Marić, Čupić and Vukić-Ćulafić found that plaque index was 78.94% in patients undergoing the orthodontic treatment. After the education on proper maintaining of the oral hygiene, after two months control period, plaque index was reduced to 41.83%. There is a need for a more frequent motivating of the patients for proper maintaining of the oral hygiene as well as longer term activities of all health workers with the aim of reducing of accumulation of dental plaque and reduction in new caries lesions and lower incidence of gingival inflammations.[15]

Matić, Ivanović and Nikolić have shown that establishing a habit of proper hygiene maintaining during the orthodontic therapy, regardless of the type of the therapy, is of great

importance for preservation of soft and hard tissues of the oral cavity and for the success of the orthodontic treatment, as well as for preserving the results of the therapy. [17]

Studies performed by Liu and associates have shown that fixed orthodontic therapy in large number of cases provides ample ground for increased deposits of dental plaque and gingivitis, as they observed significant increase in plaque and gingival index even after three months of orthodontic therapy. Same studies have shown that due to simpler maintaining of the oral hygiene and smaller number of retention places, the status of gingiva was much better in patients wearing mobile orthodontic appliances when compared with patients wearing fixed orthodontic appliances.[18]

Radlinska and associates, as well as Pietrzak and associates have concluded in their studies that the proper maintaining of the oral hygiene, with the right training and motivation during the mobile orthodontic therapy does not introduce deterioration of soft tissues of the oral cavity. [19,20]

Research performed by Gomes and associates has shown that there are no ill effects of orthodontic therapy, mobile or fixed, if the patients follow instructions received from orthodontists about proper maintaining of the oral hygiene. 10 Their results are in accordance with the results obtained by Skold Larsson and associates in 2003 as well as Perinetti and associates in 2004.[11,21]

In comparative study carried out by Bollen and associates, studies exploring the effect of orthodontic therapy on parodontal tissues published in six different journals in the period from 1980 to 2006 were examined. The studies have shown that in patients undergoing the orthodontic treatment, there was gingival recession of 0.03 mm, 0.13 mm loss of alveolar bone and 0.23 mm of increase of the depth parodontal pockets when compared to control group. The existing evidence suggests that orthodontic treatment has small ill effects on parodontal tissues if the patients adhere to instructions received from therapists. [12]

Conclusion

- Changes on gingiva during the orthodontic therapy are more frequent in therapy with fixed orthodontic appliances.
- Examining the presence and the amount of the dental plaque after three and six months of dental therapy shows increase in levels of dental plaque, especially in patients wearing fixed appliances.

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Promjene na mekim tkivima usne duplje u toku ortodontske terapije u zavisnosti od vrste ortodontskog aparata

SAŽETAK

Uvod: Parodontalna oboljenja su usko povezana sa malokluzijama. Retenciona mjesta za zadržavanje hrane, nastala kao posljedica pojedinih malokluzija, otežavaju samočišćenje i pravilno održavanje oralne higijene i tako ugrožavaju integritet mekih tkiva. Pravilno spovedena ortodontska terapija ima pozitivne učinke na parodontalna tkiva jer smanjuje mogućnost nastanka oštećenja i upala. Jedan od ključnih faktora za uspješnu ortodontsku terapiju je adekvatno održavanje oralne higijene, a samim tim i uklanjanje dentalnog plaka, glavnog uzročnika oštećenja mekih tkiva usne duplje.

Cilj rada:

- Utvrditi zavisnost pojedinih promjena na mekim tkivima usne duplje u odnosu na vrstu korištenog ortodontskog aparata.
- Utvrditi vremenski interval nastanka promjena na mekim tkivima usne duplje.

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Ispitanici i metode: U ovo istraživanje je bilo uključeno 120 pacijenata, podijeljenih u tri grupe, u zavisnosti od vrste korištenog ortodontskog aparata (mobilni ortodontski aparat-ploča, mobilni funkcionalni aparat-aktivator i fiksni ortodontski aparat). Pregledi su obavljeni tri puta: na početku terapije, te nakon tri i šest mjeseci nošenja ortodontskog aparata. Za analizu stanja mekih tkiva usne duplje i nivoa oralne higijene korišteni su: Plak indeks po Silness-Löe-u i Gingivalni indeks po Löe Silness-u.

Rezultati: Kod ispitanika podijeljenih prema vrsti ortodontske terapije, statistički značajna razlika u vrijednostima indeksa, nakon tri i šest mjeseci nošenja ortodontskog aparata, nađena je kod ispitanika koji su nosili fiksne ortodontske aparate. Razlika se manifestovala u povišenim vrijednostima indeksa kod ove grupe u odnosu na grupe pacijenata koji su nosili mobilne ortodontske aparate.

Zaključak: U toku ortodontske terapije, a naročito fiksne, pacijenti moraju posvetiti pažnju adekvatnom održavanju oralne higijene da bi se izbjegle neželjene promjene na mekim tkivima usne duplje.

Ključne riječi: ortodontske nepravilnosti, oralna higijena, gingivalni indeks, plak indeks

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The Public Health Significance of Controlling Contaminants in Samples of Milk and Dairy Products in the Republic of Srpska in the period 2010-2012

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ABSTRACT

Introduction: Controlling the presence of contaminants or harmful substances in milk and dairy products provides early detection of risks since their presence, even in legally permitted concentration, increases the risk of damaging human health, especially children's health, such as allergic manifestations, and they can have potentially toxic, carcinogenic and genotoxic effects.

Aim of the Study: The aim is to determine the frequency of the presence of contaminants in samples of milk and dairy products in the Republic of Srpska from 2010 to 2012 (metals, radionuclides, aflatoxins and residues of antibiotics and pesticides), and especially to point out their public health significance because of possible health risks. The aim of the paper is to emphasize the need for monitoring all the other contaminants in milk and dairy products specified in regulations.

Material and Methods: The frequency of the presence of contaminants in the samples of milk and dairy products (n= 407) was determined on the basis of legally prescribed methodology of sampling, chemical analyses and preparation of expert opinion on food safety in accordance with current food regulations. Descriptive statistical indicators were used (a number of the samples, minimum and maximum concentrations). Chi square test (χ^2) of contingency was used for testing the significance of differences in presence of contaminants and residues analyzed and recommended by regulations in samples of milk and dairy products.

Results: The results of public health research of contaminants in samples of milk and dairy products indicate that no health defective food samples were determined at tested parameters – metals, radionuclides, aflatoxins, and residues of antibiotics and pesticides. A statistically significant number of samples examined on heavy metal content (83.29% or 339 samples) was determined comparing to the number of samples examined on the other contaminants and residues recommended by regulations in milk and dairy products (χ^2=1000.776, p<0.001)

Conclusion: The data obtained can serve as a basis for further analysis in the context of milk and dairy product sample monitoring. Although samples of milk and dairy products are safe, a long-term exposure to residues of harmful substances results in cumulative effect and damage health, meaning that each early detection of food risk found through continuous controls has a public health significance for preservation and promotion of population health in the Republic of Srpska.

Key words: public health significance, contaminants in milk and dairy products, health risk

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Introduction

According to the current Ordinance on maximum permitted levels for certain contaminants in foodstuffs, the contaminant is a chemical, radiological, biological or physical substance harmful for human health, not intentionally added to food but its presence in food is a result of crop production, animal breeding and veterinary medicines administration during food processing, preparation, transport or storage, or the contaminant is a consequence of environmental pollution.[1] According to the Law on Food of the Republic of Srpska, food is considered harmful to human health if it contains contaminants, residues of pesticides, antibiotics, veterinary medicines and the other medical products exceeding values permitted.[2]

The human body consists of a large number of essential metals but certain metals represent a continuous danger to human health. Arsenic and lead have acute toxic and chronic cumulative effects to organ system. According to the International Agency for Research on Cancer, arsenic is classified in a Group-1 human carcinogens due to sufficient evidence of carcinogenic effects to humans, and lead is classified in a Group-2 possibly carcinogenic to humans due to sufficient evidence of lead carcinogenicity in experimental animals, whereby numerous evidences imply that mechanism of carcinogenesis is the same at animals and man.[3-5]

Due to the contaminated food6,7, the entire population is exposed to chronic pesticide poisoning. Public health problems of radioactive contamination of environment as well as food comprehend the incidents in nuclear power plants indicating the absence of barriers for chemical pollutions.[3,4,8]

Aflatoxins B1, G1 and M1 are of public health significance because of health risks, hepatotoxic, nefrotoxic, neurotoxic, carcinogenic and mutagenic activity. Aflatoxin B1 is one of the most powerful human mutagens and teratogens. Aflatoxin B1 is classified in group 1 or mycotoxins with proven carcinogenic effect.8 The uncontrolled use of antibiotics as biostimulants for animal feeding is important for public health since they can be found indirectly in milk and dairy products causing an increased frequency of antibiotic resistance in the human population.[9,10]

Aim of the Study

1. To determine frequency of presence of contaminants in samples of milk and dairy products (metals, radionuclides, aflatoxins and residues of antibiotics and pesticides) in the Republic of Srpska from 2010 to 2012;

2. To point out public health significance of the presence of contaminants in samples of milk and dairy products because of possible health risks;

3. To emphasize the need for monitoring all the other contaminants or hormones, dioxins and polychlorinated biphenyls (PBC) in milk and dairy products specified in regulations.

Material and Methods

Research on the frequency of presence of contaminants was conducted on a total number of 407 samples of milk and dairy products submitted from the foreign and domestic trade in the Republic of Srpska from June 2010 to March 2012. Research included samples of milk and dairy products grouped in subgroups (pasteurized and sterilized milk, raw milk, cheese, yogurt, sour cream and the other dairy products such as chocolate milk, dairy dessert and beverage, ice cream, milk powder and the other dairy products). The content of metals was determined using Atomic Absorption Spectrophotometry (AAS) on the device 'UNICAM' England, a flame technique for the analysis of lead and cadmium, a hydride technique for arsenic analysis, a cold vapor technique for mercury analysis. The content of radionuclides ^{134}Cs ^{137}Cs was determined by gamma spectrometric method of high resolution; ISO 18589-1, ISO 10703 on the device 'Gamma spectrometar-Canberra Packard 7500 SL'.

The sum of aflatoxins (B1, B2, G1, G2) was analysed using HPLC method (High Performance Liquid Chromatography). The content of aflatoxin M1 was determined by liquid chromatography after immunoaffinity chromatography purification. The content of pesticide residues (alpha HCH, beta HCH, lindane, delta HCH, aldrin, heptachlor epoxide, endosulfan, endosulfan sulfate, DDE, DDD, Endrin, the sum of PCB) was determined by Gas Chromatography/Mass Spectrometry (GC/MS), and the content of residues of Diazinon, Metalaxyl and Vinclozolin by Gas Chromatography/Mass Spectrometry (GC/MS).

Determination of sample safety was conducted in accordance with the applicable regulations on food safety.[1,2] SPSS 16.0 was used for statistical analysis. Chi-square test (χ^2) of contingency11 was used for comparing differences in a number of food group of 'milk and dairy products' for presence of contaminants and residues analyzed and recommended by regulations as well as for comparing differences in a number of different foodstuffs analyzed for presence of a particular contaminant.

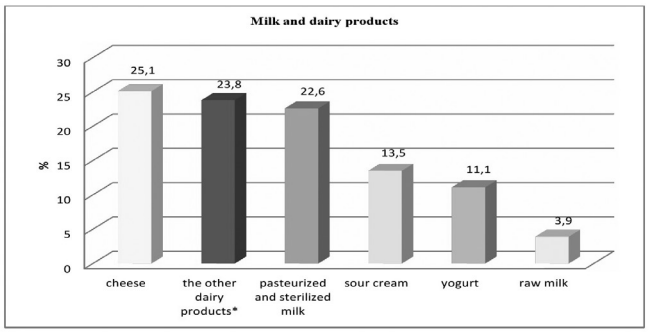
Results

Results on the presence of contaminants in samples of milk and dairy products are based on the laboratory analysis of 407 samples in the territory of the Republic of Srpska from 2010 to 2012.

Figure 1. shows percentage of foodstuffs within the

analyzed group of 'milk and dairy products'.

Figure 1. Percentage of foodstuffs within the analyzed group of 'milk and dairy products' from 2010 to 2012



**chocolate milk, dairy dessert, milk cream, milk pudding, dairy beverage, frozen desserts, ice cream, milk powder, condensed milk and the other dairy products*

Figure 2. shows percentage of contaminants and residues of antibiotics and pesticides analyzed within the group of 'milk and dairy products' in the Republic of Srpska from 2010 to 2012.

Figure 2. Percentage of contaminants and residues of antibiotics and pesticides analyzed within the group of 'milk and dairy products' from 2010 to 2012

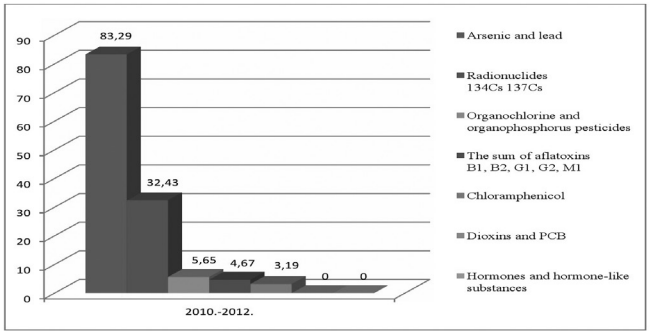


Table 1. shows the data of analyzed samples, and minimum and maximum concentrations of contaminants in samples of milk and dairy products from 2010 to 2012 including the analysis of the following contaminants - arsenic, lead, radionuclides 134Cs 137Cs, the sum of aflatoxins B1, B2, G1, G2, M1 and residues of chloramphenicols and pesticides (alpha HCH, beta HCH, lindane, delta HCH, aldrin, heptachlor epoxide, endosulfan, endosulfan sulfate, DDE, DDD, Endrin, the sum of PCB, Diazinon, Metalaxyl and Vinclozolin).

Table 1. A number of analyzed samples, and minimum and maximum concentrations of contaminants in samples of milk and dairy products from 2010 to 2012

Types of contaminants in milk and dairy products	N of analyzed samples			
		Unit of measurement	Minimum concentration	Maximum concentration
Arsenic	339	mg/kg	< 0.02	< 0.1
Lead	339	mg/kg	< 0.05	< 0.05
Radionuclides ^{134}Cs i ^{137}Cs	132	Bq/kg	< 0.2	< 0.2
Organochlorine and organophosphorus pesticides*	23	mg/kg	< 0.005	< 0.005
The sum of aflatoxins B_1, B_2, G_1, G_2, M_1	19	µg/kg	< 0.5	< 0.5
Chloramphenicol	13	mg/kg	0.00	< 0.1

**alpha HCH, beta HCH, lindane, delta HCH, aldrin, heptachlor epoxide, endosulfan, endosulfan sulfate, DDE, DDD, Endrin, the sum of PCB, Diazinon, Metalaxyl and Vinclozolin*

Table 2. shows testing of the significance of differences in presence of contaminants and residues analyzed and recommended by regulations in milk and dairy products from 2010 to 2012, and results are expectedly positive due to determination of a statistically significant number of samples analyzed on the content of heavy metals (83.29% or 339 samples) in relation to the number of samples analyzed on the other contaminants and residues recommended by regulations in milk and dairy products (χ^2=1000.776, p<0.001).

Table 2. **Testing the significance of differences in presence of contaminants and residues analyzed and recommended by regulations in milk and dairy products from 2010 to 2012**

Food group		Milk and dairy products	
REG/Sample	χ^2	*df*	*p*
	1000.776	4	<0.001

Discussion

90% of environmental pollutants reach humans through the food. In the entire food chain, food products can be 'enriched' with contaminants which can lead to adverse health consequences, especially important for children's health.[12-15]

Public health control of harmful substances in milk and dairy products is of crucial importance because of the frequency of milk consumption in all population groups, especially in infant, child and adolescent population groups. Health Survey of the adult population (>18 years of age) of the Republic of Srpska in 2010 showed that 41.3% of the population consumed at least one cup of aforementioned food group meaning that this research on the content of harmful substances is justified since it is the one of core groups of foodstuffs.[16]

In all samples of milk and dairy products, determined arsenic concentrations range from <0.02 to <0.1mg/kg, and determined lead concentrations <0.02mg/kg. Determined concentrations of aflatoxins B1, B2, G1, G2, M1 are < 0.5μg/kg, radionuclides ^{134}Cs and ^{137}Cs <0.2Bq/kg. Determined concentrations of residues of chloramphenicol are <0.1mg/kg, and organophosphorus and organochlorine pesticides <0.005mg/kg (table 1).

In the Republic of Srpska, in the research of the harmful substances in the samples of milk and dairy products, no samples posing threat to human health were determined. Consistent results, as in the research shown, were confirmed by the Food Safety Agency of Bosnia and Herzegovina in food monitoring since there were no milk and dairy product samples posing threat to human health examined for presence of residues of organochlorine and organophosphorus pesticides in 2009, mycotoxins in 2010, metals in 2011 and antibiotics in 2014.[17]

Public health research on milk and dairy product samples in Iran from 2006 to 2007 identifies 4.4% of unsafe samples of raw and pasteurized milk because of aflatoxin M1 18 contamination.

During food monitoring in Bosnia and Herzegovina in 2009, 500 food samples were analyzed and unsatisfactory samples of milk and products were determined due to the increased concentratio of lead and arsenic. In a risk assessment, during 2013, in Bosnia and Herzegovina, aflatoxin M1 was determined at 3.3% samples of raw milk, pasteurized milk and milk intended for milk-based products.[17]

In the research of contaminants and residues in milk and dairy product samples, 83.29% of milk and dairy product samples were analyzed for the presence of arsenic and lead, and 32.43% for the presence of radionuclides 134Cs i 137Cs. The residues of organochlorine and organophosphorus pesticides were analyzed in 5.65% of milk and dairy product samples. Aflatoxins B1, B2, G1, G2, M1 and the chloramphenicol residues were analyzed in less than 5% of milk and dairy product samples (figure 2).

During the monitoring of food in Bosnia and Hezegovina in 2009, out of a total of 150 analyzed milk and dairy product samples, 48.67% was positive on the presence of the residues of antibiotics. The Food Safety Agency of Bosnia and Herzegovina carried out a risk assessment in 2010 on 2124 food samples examined for presence of the residues of chloramphenicol and sulfonamides indicating 0.09% of unsafe samples because one milk sample was positive for chloramphenicol residue. In Bosnia and Herzegovina, in 2011, there were 0.16% of unsafe samples out of 1882 food samples tested for chloramphenicol and sulfonamides, because three milk and dairy product samples were positive for sulfonamide residues. During the monitoring of food in 2015, the Food Safety Agency of Bosnia and Herzegovina reported 0.17% of unsatisfactory samples belonging to the group of milk and dairy products for the presence of the residues of antibiotics.[17]

Determination of the residues of antibiotics in food is of huge public health importance because of the possibility of reducing the health risks due to the increased frequency of antibiotic resistance in the human population19 and occurrence of antibacterial drug residues in food.[9,10]

A statistically significant number of milk and dairy product samples tested for the content of heavy metals (83.29%) was determined comparing to the number of samples tested for the other contaminants and residues recommended by regulations. The other contaminants such as dioxins, polychlorinated biphenyls, hormones and hormone-like substances, being mandatory in food regulations, were not analyzed in any sample of milk and dairy product (χ^2=1000.776, p<0.001) (figure 2, table 2).

The public health importance of the purposes of determining the presence of dioxins, polychlorinated biphenyls and hormones in the food monitoring including milk and dairy products is indicated by their potentially toxic and carcinogenic effects.[20]

Conclusion

Ist No milk and dairy product samples posing threat to human health were determined in the research of contaminants and residues of antibiotics and pesticides in the Republic of Srpska from 2010 to 2012. During that period, there was a statistically significant number of milk and dairy product samples tested for the content of heavy metals (83.29%) comparing to the number of samples tested for the other contaminants and residues recommended by regulations in milk and dairy products.

Dioxins, polychlorinated biphenyls and hormones and hormone-like substances, being mandatory in food regulations, were not required by official inspection controls in any sample of milk and dairy products, and the results are expectedly positive and statistically significant (χ^2=1000.776, p<0.001).

The data obtained can serve as a basis for further analysis in the context of milk and dairy product sample monitoring. Although samples of milk and dairy products are safe, a long-term exposure to residues of harmful substances results in cumulative effect and damage health, meaning that each early detection of food risk found through continuous controls has a public health significance for preservation and promotion of population health in the Republic of Srpska.

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Javnozdravstveni značaj kontrole kontaminanata u uzorcima mlijeka i proizvoda u Republici Srpskoj u periodu 2010-2012. godine

SAŽETAK

Uvod: Kontrola prisustva kontaminanata, odnosno štetnih materija u mlijeku i mliječnim proizvodima, omogućuje rano prepoznavanje rizika, jer njihovo prisustvo, i u zakonski dozvoljenim koncentracijama, povećava rizik za oštećenje zdravlja ljudi, posebno djece, kao što su alergijske manifestacije, a mogu imati potencijalno toksično, kancerogeno i genotoksično djelovanje.

Cilj rada: Utvrditi učestalost prisustva kontaminanata u uzorcima mlijeka i proizvoda u Republici Srpskoj u toku perioda 2010. do 2012. godine (metali, radionuklidi, aflatoksini i ostaci antibiotika i pesticida), a posebno ukazati na njihov javnozdravstveni značaj zbog mogućih zdravstvenih rizika. Cilj rada je ukazati na potrebu praćenja i svih drugih kontaminanata predviđenih propisima u mlijeku i mliječnim proizvodima.

Materijal i metode: Utvrđivanje učestalosti prisustva kontaminanata u uzorcima mlijeka i proizvoda (n= 407) sprovedeno je na osnovu zakonski propisane metodologije uzorkovanja, hemijskih analiza i izradom stručnog mišljenja o zdravstvenoj ispravnosti hrane u skladu sa važećim propisima o hrani. Korišteni su pokazatelji deskriptivne statistike (broj uzoraka, minimalne i maksimalne koncentracije). Za testiranje značajnosti razlike prisustva analiziranih kontaminanata i rezidua u uzorcima mlijeka i mliječnih proizvoda i preporučenih propisima korišten je χ^2 test kontigencije.

Rezultati: The Rezultati javnozdravstvenog istraživanja kontaminanata u uzorcima mlijeka i proizvoda ukazuju da nisu utvrđeni zdravstveno neispravni uzorci hrane za ispitivana obilježja - metali, radionuklidi, aflatoksini i ostaci antibiotika i pesticida. Utvrđen je statistički značajno veći broj uzoraka ispitanih na sadržaj teških metala (83,29% ili 339 uzoraka) u odnosu na broj uzoraka ispitanih na druge kontaminante i rezidue preporučene propisima u mlijeku i mliječnim proizvodima (χ^2=1000.776, p<0.001).

Zaključak: Dobijeni podaci mogu poslužiti kao osnov za dodatne analize u okviru monitoringa uzoraka mlijeka i proizvoda. Iako su uzorci mlijeka i proizvoda zdravstveno ispravni, dugotrajna izloženost ostacima štetnih materija ima za posljedicu kumulativni efekat i oštećenje zdravlja, pa svako rano prepoznavanje rizika iz hrane kroz kontinuiranu kontrolu ima javnozdravstveni značaj za očuvanje i unapređenje zdravlja stanovništva u Republici Srpskoj.

Ključne riječi: javnozdravstveni značaj, kontaminanti u mlijeku i proizvodima, zdravstveni rizici

ORIGINAL ARTICLE

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The Significance of Foraminotomy in Lumbar Herniated Disc Surgery

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ABSTRACT

Introduction: Spinal column represents a strong and flexible body axis. It is consisted of vertebrae which are connected by the intervertebral disk and solid fibrous joints.

Aim of the Study: To ascertain whether or not and to what extent foraminotomy affects the final outcome of lumbar herniated disc surgery.

Patients and Methods: This retrospective study analyzed 71 patients who were operated at the Clinic of Neurosurgery in Banja Luka, in the period from 2009 to 2016. Extirpation of disc was performed in 41 respondents, while in 30 patients, a nerve root was further alleviated, along with the extirpation of disc. All patients were operated under the same conditions.

Results: There was no statistically significant difference in the age of women and men who underwent classical discectomy and foraminotomy. There was a statistically significant difference in the disc protrusion and extrusion in patients who underwent conventional discectomy and those who underwent foraminotomy, along with conventional discectomy. There was no statistically significant difference in diagnosis in respondents who underwent conventional discectomy and those who underwent foraminotomy, along with conventional discectomy. There was statistically significant difference in the severity of pain in patients who underwent conventional discectomy and those who underwent foraminotomy, along with conventional discectomy. There was a statistically significant difference in clinical recovery, where the findings were in favor of the respondents who underwent foraminotomy, compared to the respondents who did not.

Discussion: The treatment of this syndrome is complex, multidisciplinary and with problematic success, and in cases when the operation is performed, the results are not as good as in the primary operation.

Conclusion: The results of this study show that the patients who underwent foraminotomy during the operation of prolapsed lumbar disc have a clinically better result.

Keywords: foraminotomy, discectomy, protrusion, extrusion

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Introduction

Spinal column represents a strong and flexible body axis. It is consisted of vertebrae which are connected by the intervertebral disk and solid fibrous joints.

The spine is constantly under the force of gravity pressure and the transfer of body weight which is increasing from top to bottom. Hence, vertebrae are more massive.[1]Dynamic segment is consisted of two vertebrae connected with the following: discus, ligaments, facet joints, paravertebral muscles and fascia.

The disc functions as a joint and absorber that is able to withstand a load of 500-600 kg. It is a fibrous-cartilage plate with a protruding upper and lower surface which is firmly attached to the vertebral end plate. Two parts are distinguished at a disc, that is, external and internal. The external one, annulus fibrosus, strongly abuts vertebrae and is built around diagonally placed fibers.[2] The internal one, nucleus pulposus, doesn't have its own vascularization.[2-4] Discs are additionally connected with ligaments anterior longitudinal et posterior that prevent excessive bending backward and forward. By discus lowering, ligg.flava leads to hypertrophy of the discus whose "harvesting" additionally narrows the canal at the posterior side.[5] Disc herniation, in a form of protrusion, extrusion and subligamentous extrusion leads to pain in the back and / or leg, sensory and motor disorders, and in the most unfavorable variant, it causes sphincter and erectile dysfunction. The problems are clinically manifested via positive Lazarevic's sign.

Diameters of the spinal canal that are, so to speak, considered physiological are as follows: the central is 14 mm and more, bipedicular distance is 18 mm, the width of the lateral recess is 4 mm.[6.7]

Lumbar radiculography had been the method of choice in the diagnosis of discopathy until the 80's when it lost its primacy over magnetic resonance imaging (MRI) and computed tomography (CT) which provided a three-dimensional image of discuse.[7]

In 90% of patients with the disc prolapse, the treatment is conservative, whereas other l0% require surgical treatment7-10 Surgical treatment is indicated in cases when the effects of conservative treatment are absent and radicular pain episodes become more frequent and accompanied with the development of sudden neurological deficit such as urinary incontinence or progressive motor weakness.[8,9]

The fact that in 5-40% of treated patients, pain or leg pain continued after the surgery (FBSS) (Failed Back Surgery Syndrome) emphasises the importance of rigorous selection of the patients requiring surgery.[7-10]

The most common surgical causes of FBSS (Failed Back Surgery Syndrome):

- Recurrent herniation
- Fragment of disc still pinching a nerve
- Lateral stenosis
- Facet joint trauma with or without synovial cysts
- Central stenosis

In the US, 12% of excused absence is due to this problem with the financial implications that are measured in billions of dollars.[10]

Aim of the Study

To ascertain whether or not and to what extent foraminotomy affects the final outcome of lumbar herniated disc surgery.

Patients and Methods

This retrospective study analyzed 71 patients who were operated at the Clinic of Neurosurgery in Banja Luka, in the period from 2009 to 2016. Extirpation of disc was performed in 41 respondents, while in 30 patients, a nerve root was further alleviated, along with the extirpation of disc. All patients were operated under the same conditions and all indications were set based on the anamnesis, clinical imaging and diagnostic procedures: MRI, CT scan, lumbar radiculography or a combination of some of these methods. Postoperative treatment was the same: a stationary balneotherapy began four weeks after the surgery and lasted four weeks. Parameters that were monitored in the respondents were as follows: the length and intensity of pain before the surgery, the pain after surgery, neurological deficit before and after surgery, as well as the time that was required to return to work. The patients were analyzed by sex, age and profession.

Results

This retrospective study was consisted of 71 patients and divided into two groups .The first group was consisted of 41 (57.7%) respondents who underwent conventional discectomy, while the other group was consisted of 30 (42.3%) respondents who underwent foraminotomy, along with conventional discectomy. There were 37 (52.1%) women and 34 (47.9%) men. Average age of all the respondents was 44.34 years, that is, in the group that underwent foraminotomy, it was 44.67, while in the group that did not undergo foraminotomy, it was 44.10. There was no statistically significant difference in the age of women and men treated with the use of conventional

discectomy and foraminotomy (p = 0.1194).

Dyscopathies were the most frequent in the respondents whose job implied poor body posture, long sitting and standing (43.7%). Furthermore, dyscopathies were present in the respondents who were conducting vigorous physical labor (23.9%), intellectual professions (22.5%) and moderately vigorous physical labor (9.9%).

In 40.8% of patients problems lasted less than 3 months, in 2l. l% they lasted 3 to 6 months, and in 38% the problems lasted more than 6 months. High intensity pain before the surgical treatment was present in 33.8% of respondents, the pain of medium intensity in 42.3% and the pain of light intensity in 23.9% of respondents. The pain of high intensity was present in l3 patients who underwent foraminotomy and in 20 patients with the same intensity of pain who did not undergo foraminotomy.

Neurological deficit was present in 53.5% of respondents. The severe deficit which was manifested through minimum contractions that were felt only under the fingers was present in l. 4% of respondents. 9.9% of respondents moved in the direction of gravity, 28.2% moved against the gravity but did not overcome the resistance, while 7% of respondents moved against gravity and overcame the resistance. Before the surgery, three patients had sphincter dysfunctions that were clinically manifested in urinary disorders and defecation. In two subjects, foraminotomy was not performed, while in one it was.

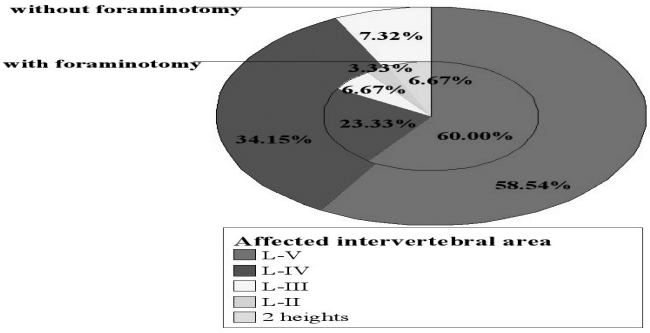
Before the operation, 50 (70.4%) respondents were able to walk 100 meters, 6 (8.5%) respondents between l00 and 300 meters, while l5 (2l.l%) respondents were able to walk over 300 meters.

Disc protrusion was present in 34 (47.9%) respondents and disc extrusion in 30 (42.3%), sequestering in l.4%, migration in 5.6%, and degenerative changes in 2.8% of respondents. In the group where foraminotomy was performed, the protrusion was verified in 52.9%, extrusion in 30% and migration in 25% of respondents. In the group where foraminotomy was not performed, the extrusion was present in 70%, protrusion in 24% and migration in 6% of respondents. There was a statistically significant difference in the disc protrusion and extrusion in patients who underwent conventional discectomy and those who underwent foraminotomy, along with conventional discectomy (p = 0.0116).

MRI was used for diagnosing in 28 respondents (39.4%), CT in 12 (16.9%) and lumbar myelography in 8 (11.3%) respondents. The combination of CT and myelography was used in 13 (18.3%) respondents. All diagnostic procedures were conducted in 3 (4.2%) respondents.

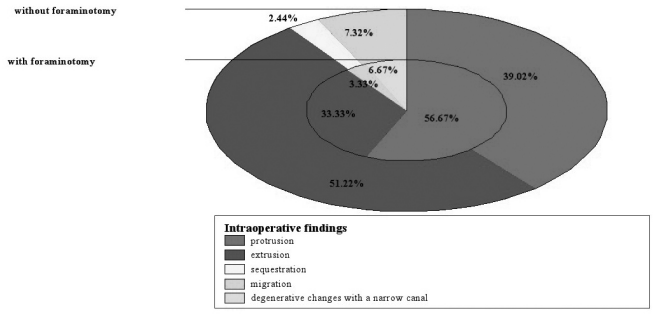
The most commonly affected intervertebral area was the L-V. (Figure 1.) There was no statistically significant difference in diagnosis in patients who underwent conventional discectomy and those who underwent foraminotomy, along with conventional discectomy (p = 0.0771).

Figure 1. The affected intervertebral area according to groups



The most common operational approach, conducted on 73.2% of respondents, was interlaminectomy. Hemilaminectomy was performed in 23.9% of respondents and flavectomy in 2.8%. Intraoperative findings confirmed the protrusion of intervertebral discs in 46.5% of respondents, extrusion in 43.7%, sequestration in 2.24% and migration in 7, 32% of respondents. (Figure 2.)

Figure 2. Intraoperative findings according to groups

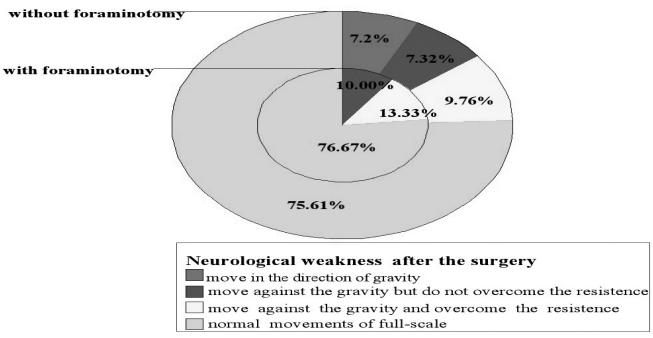


After the operation, 26.8% of respondents did not feel pain, intermittent pain of medium intensity was present in 43.7%, and the pain of medium intensity was present in 29.6% of respondents. Postoperatively, 3/4 of patients had normal movements of full-scale and none of the patients suffered from sphincter dysfunctions. There was a statistically significant difference in the severity of pain in patients who underwent conventional discectomy and those who underwent foraminotomy, along with conventional discectomy (p = 0.0116).

95.8% of respondents were able to walk over 300 meters after the surgery. Furthermore, after the surgery, 64.8% of respondents returned to their full-time employment, 4% of

respondents returned to the part-time employment, 21.1% changed their job, while 12.7% of respondents retired. More patients (71.8%) who had undergone foraminotomy returned to their previous workplace.

Figure 3. Neurological weakness after the surgery according to groups



After the surgery, none of the respondents had pain of high intensity. Postoperatively, neurological findings in patients who did not undergo foraminotomy were as follows: 22 patients had regular neurological findings before and after the surgery, l2 patients exhibited neurological improvement, while in 7 patients, pre-existing neurological deficit remained after the surgery. (Figure 3.)

In terms of neurological deficit, in the group of patients who underwent foraminotomy, the results were as follows: l6 respondents had normal neurological findings preoperatively and postoperatively, the improvement of neurological deficit occurred in 11 patients postoperatively, while in 3 patients, pre-existing neurological deficit remained after the surgery.

The analysis of walking functions before and after the surgery in the group of patients who did not undergo foraminotomy showed the following: 3l patient improved, while 10 patients remained at the preoperative level. The respondents presented satisfying length of walk after the surgery.

There was a significant statistical difference in clinical recovery - finding in favor of the patients who underwent foraminotomy compared to those who underwent only conventional discectomy (p = 0.0249). In the group who underwent foraminotomy, 22 patients showed the improvement in terms of the length of walk, while 8 respondents remained at preoperative level. The respondents presented satisfying length of walk.

Discussion

Verbiest i sar. In their study, Verbiest et al. examined 86 patients operated due to lumbar herniated disc. The disc extirpation was performed in 41 respondents, whereas in the remaining 45 respondents, the additional release of roots in the intervertebral foramen –foraminotomy was done. Out of the total number of treated patients, 84.8% of respondents who had undergone foraminotomy and 64.3% who had not, completely returned to their profession.[7]

In the examined series, MRI was used preoperatively in 40% of patients and it was a sufficient tool for diagnosis. The most common combination used in diagnosis was: CT and myelography in 18% of cases. In 30% of cases it was necessary to conduct two or more diagnostic procedures.

In his study, Davis stated that intraoperatively, in 90% of respondents it was the case of disc extrusion or protrusion which correlated with intraoperative one in 85%.8 In the examined series, sphincter dysfunctions occurred in 3 patients who had not had them postoperatively.

In his study, Lewis stated that, before the surgical treatment, 52% of patients had normal neurological findings, while 48% had a motor deficit which was more or less pronounced. [9]

In his series, S. Shapiro examined 64 patients who had motor deficit preoperatively and the following results were obtained: motor deficit remained in 8 respondents, it improved in 22 respondents , while the complete neurological recovery occurred in 34 respondents.10 If there is a neurological deficit in the clinical picture, (qaudae equinae syndrome) a relatively good result can be expected in terms of recovery of function of the sphincter, but solely in cases when the operation is done in the first 48 hours.[10]

In the examined study, six months or more was necessary for 54.9% of operated respondents to return to work.

DeOrio JK states that the intervertebral area is affected by herniated disks, LV and LIV in 90% of cases. In 60% of cases it is LV herniation and in about 30%, it is LIV.[11] In the examined series, the localization of herniation of intervertebral discs was identical.

In the study conducted by Law JD, out of total number of respondents who had undergone foraminotomy, 54.9% returned to work within 3 months.[12] Operation of lumbar disc in adolescents and children shows similar results as with adults, with more frequent occurrence of trauma.[12]

During the follow-up of these patients in the postoperative period, the need for reoperation occurred in about 80% of cases.12 Perennial monitoring of patients with herniated lumbar disc, without neurological deficit and who were treated conservatively, showed a solid recovery in 90% of cases.[12]

By group analysis in the examined series, we can notice that, in the group of respondents, more of them returned to

their profession completely, while in the control group, the percentage of those with an easier job was slightly higher than in the group of respondents, while the percentage of retired respondents was similar in both groups.

Foraminotomy is frequently performed within reoperation, suggesting that the performance of the same during the disk operation would have its justification.[8]

Conclusion

The results of this study show that the patients who underwent foraminotomy during the operation of prolapsed lumbar disc have a clinically better result. Proper selection of patients for surgery is crucial in order to accomplish good results: clinical picture, correct diagnosis, absence of a favorable response to conservative treatment within 4 months. The treatment of this syndrome is complex, multidisciplinary and with problematic success, and in cases when the operation is performed, the results are not as good as in the primary operation.

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Značaj foraminotomije kod operacije lumbalne discus hernije

SAŽETAK

Uvod: Kičmeni stub predstavlja snažnu i elastičnu osovinu tijela. Sastoji se od pršljenova koji su međusobno povezani intervertebralnim pločama i čvrstim fibroznim vezama.

Cilj rada: Doći do saznanja da li i u kojoj mjeri foraminotomija utiče na konačni ishod operacije hernije lumbalnog diska.

Ispitanici i metode: U retrospektivnoj studiji analiziran je 71 ispitanik operisan na Klinici za neurohirurgiju u Banjoj Luci, u periodu od 2009. do 2016. godine. Kod 41 ispitanika urađena je ekstirpacija diska, dok je kod 30 ispitanika uz ekstripaciju diska dodatno oslobođen i korijen nerva. Svi pacijenti su operisani pod istim uslovima.

Rezultati: Ne postoji statistički značajna razlika u životnoj dobi žena i muškaraca liječenih klasičnom discektomijom i foraminotomijom. Postoji statistički značajna razlika u protruziji i ekstruziji diskusa kod pacijenata kod kojih je rađena klasična discektomija i pacijenata kod kojih je, uz klasičnu disektomiju, rađena i foraminotomija. Ne postoji statistički značajna razlika u dijagnostici kod ispitanika kod kojih je urađena klasična discektomija i onih kod kojih je, uz klasičnu disektomiju, rađena i foraminotomija. Postoji statistički značajna razlika u jačini bola kod pacijenata kod kojih je urađena klasična discektomija i pacijenata kod kojih je, uz klasičnu disektomiju, rađena i foraminotomija. Značajna je statistička razlika u kliničkom oporavku - nalaz u korist ispitanika kod kojih je rađena foraminotomija u odnosu na ispitanike kod kojih je urađena klasična discektomija.

Diskusija: Liječenje ovog sindroma je kompleksno i multidisciplinirano sa problematičnim uspjehom, a ukoliko se radi operacija, rezultati nisu tako dobri kao kod primarne operacije.

Zaključak: Rezultati ove studije pokazuju da pacijenti kojima je u sklopu operacije prolapsa lumbalnog diska urađena i foraminotomija imaju klinički bolji rezultat.

Key words: Foraminotomija, discektomija, protruzija, ekstruzija

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Assessment of the Level of Oral Health Education and Awareness among Members of Public Opinion in the territory of Banja Luka

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ABSTRACT

Introduction: The level of dental care development can be a good indicator of prosperity in society. Prevention of dental diseases and the provision of appropriate care require well planned and coordinated programs integrated into the overall health care system.

Aim of the Study: The aim is to determine the level of oral health knowledge and contemporary possibilities of prevention in population groups of public opinion in charge of decision-making and funding of prevention programs in potential executors in the prevention program, as well as parents of preschool children in Banja Luka.

Patients and Methods: The study was conducted on a sample of 310 respondents randomly selected in urban and rural areas in the municipality of Banja Luka. The testing was conducted by means of anonymous questionnaire about the level of oral health education of the respondents, attitudes about the prevention of oral diseases and health education in dentistry. Respondents consisted of 60 representatives of legislative and executive authorities, 60 people from the media, 80 teachers in kindergartens, 60 parents of children up to six years and 50 dentists from the state sector.

Resultsi: The majority of respondents (65%) believed that it is possible to determine the risk before the onset of tooth decay, which was statistically significant ($p < 0.001$). Only 6% of respondents know epidemiologically proven fact that there are people without dental caries (caries-free). The government representatives were 100%, while parents were 75% convinced that there is enough knowledge about dental health. All groups significantly highlighted the mass media and educational institutions as holders of health education.

Conclusion: There is a diversity of opinion between the groups questioned, which significantly affects on making the image of the complete sample being not true reflection of public opinion. The respondents are not familiar enough with modern knowledge, possiblities and accomplishments in preventive dentistry.

Keywords: oral health, prevention, public opinion, caries risk, health education

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Introduction

Ideal The purpose of medicine is to prevent an impairment of health and the purpose of each society is to provide such economic, social and political conditions in which most of the population could be in a state of complete physical, mental and social balance, which represents the base of definition of the health by World Health Organization (WHO), found in its Consitution.[1]

The development of dental care can be a good indicator of development of society. Prevention of dental diseases and the provision of adequate care for dealing existing pathology, require planned and coordinated programs, integrated into the overall health care system in accordance with the socio-economic base in community.[2]

The recent trends in the development of preventive dentistry are the introduction of oral health in system of monitoring and maintaining the balance of the entire organism. Since oral diseases are classified as mass chronic, non-communicable diseases and therefore have common risk factors, preventive approach is directed toward their detection and control.[3-6] In that regard, new aims for improving oral health by 2020 have been set. [7,8]

The level of awareness of legislative and executive authorities on importance of oral health and its vulnerability in the country and city community will influence the actions that profession needs to undertake to get it introduced to the procedure of legal regulation and prevention programs funding.

The health system in dentistry should be primarily oriented toward primary health care and prevention. WHO global targets are to mobilize health promotion and health education at the local, regional, national and global level.[8-10]

In addition to basic epidemiological indicators, it is necessary to determine the level of knowledge and attitude of all those in the chain responsible for program implementation. Only on the basis of the data obtained in the studies of educational diagnosis it is possible to plan the most important (and in our condition perhaps the only cost-effective) method of prevention and that is health education.

Aim of the Study

Determining the oral health knowledge level and contemporary possibilities of oral prevention in population groups in charge of decision-making about implementation and funding of prevention programs in potential executors in the prevention program as well as parents of younger population.

Patients and Methods

This study was the part of a larger study conducted within the framework of the scientific-research activities of the Department of Pediatric and Preventive Dentistry, Faculty of Medicine, Banja Luka. Prior to beginning of the study, necessary approval was obtained from the Director of the Centre for pre-school education Banja Luka where the survey was conducted among parents whose children were beneficiaries of the Centre. The Ethical committee and the Director of the Public Health centre Banja Luka also approved the study protocol for the part of the research conducted in this health institution.

The cross-sectional analytical study was conducted from January to March of 2008 in Banja Luka among members of local authorities-responsible for the adoption and implementation of legal regulations, workers in the media as potential promoters of a healthy lifestyle, teachers of the Centre for pre-school education Banja Luka-responsible for education in general and health education of children, parents of pre-school children-educators and teachers of their children and dentists - responsible for promotion and maintenance of oral health.

The survey was conducted by means of anonymous questionnaire in written form. For the purpose of this study, the questionnaire was made by two researchers. After the respondents signed an informed consent interview was conducted “face to face” with each participant by a single researcher. The questions referred to the general information about the subject, socio-demographic information, level of oral health knowledge, attitudes toward prevention in dentistry and oral health education. The assessment of the level of oral health knowledge was performed by using a group of four questions, where each question had the possibility of only one answer. The attitudes about prevention in dentistry were presented with three questions, which also had the possibility of only one answer. The assessment of oral health education level was carried out using four questions. Three questions had the possibility of one answer, but one question, “Where should it be important to health educate parents of pre-school children?” had the possibility of multiple answers. The total sample consisted of 310 respondents, randomly chosen from urban and rural areas of Banja Luka.

The sample included respondents from the following target groups:

- Respondents from local legislative and executive authorities - 60 subjects among the members and delegates in the Assembly of Banja Luka, responsible for the adoption and implementation of legal regulations.

- Workers in the media – 60 subjects from electronic

and print media in Banja Luka (journalists, editors) as potential promoters of a healthy lifestyle.

- Educators - 80 subjects, teachers in kindergartens of the Centre for pre-school education Banja Luka, responsible for education and health education of children.

- Parents of children up to six years (whose children attended kindergartens of the Centre) - a sample of 60 subjects.

- Health workers in the Dental department of the Public Health Centre Banja Luka - sample of 50 dentists.

After completing the interviews, data were grouped and processed by other researcher in order to obtain the greatest possible accuracy of the interpretation of the results.

For statistical analysis and presentation of results SPSS 16.0 for Windows, MS Office Word and Excel MS Office was used. Data were analyzed by standard procedures of descriptive and comparative statistics. The results are presented numerically and tabulated. Qualitative characteristics are shown in the frequency and percentage representation. The statistical significance of the obtained distribution was analyzed by X_2 – test. The question with multiple possibility answers was not analyzed by X_2 - test, but solely the percentage analysis was done.

Results

After processing the data, the results were grouped and analyzed based on the level of oral health education of respondents (Table 1), the attitudes on oral health education (Table 2) and attitudes of respondents toward prevention in dentistry (Table 3).

The majority of respondents (65%) believed that it is possible to determine the risk before the onset of tooth decay, which was statistically significant (p <0.001) (Table 1). After analyzing groups individually that relationship was even higher, but assessed level of knowledge of educators and governments reduced it. The subjects did not show a clear and significant commitment of public opinion regarding the proven scientific fact that tooth decay can be prevented. Even more surprising was the answer of 72% of examined dentists who though that tooth decay could not be prevented and depended mostly on genetics.

Table 1. The level of oral health knowledge of the respondents

		Media	Authority	Educators	Parents	Dentists	∑	P
Is it possible to determine the risk before the apparence of tooth decay?	Yes	48 (80%)	24 (40%)	51 (64%)	42 (70%)	36 (72%)	201 (65%)	<0,001
	No	12 (20%)	36 (60%)	29 (36%)	18 (30%)	14 (28%)	109 (35%)	
Can dental caries be prevented?	Partly and depends mostly on genetics	24 (40%)	24 (40%)	36 (45%)	42 (70%)	34 (72%)	160 (52%)	<0.001
	Yes, completely	36 (60%)	36 (60%)	44 (55%)	18 (30%)	14 (28%)	148 (48%)	
Is it possible that there are children with all healthy teeth?	Impossible	0	0	37 (46%)	18 (30%)	4 (8%)	59 (19%)	<0,001
	Rarely	30 (50%)	0	27 (34%)	27 (45%)	36 (72%)	120 (39%)	
	A few %	24 (40%)	46 (77%)	16 (20%)	15 (25%)	10 (20%)	111 (36%)	
	Over 30%	6 (10%)	14 (23%)	0	0	0	20 (6%)	
Is dental health important for general health?	Yes	60 (100%)	60 (100%)	48 (85%)	40 (67%)	50 (100%)	258 (83%)	<0,001
	No	0	0	32 (15%)	20 (33%)	0	52 (17%)	
∑		60	60	80	60	50	310	

The participants were not very familiar with epidemiologically proven fact that over 30% of children in developed countries are caries free-only 6% of them gave correct answer, which also contributed to the statistical significance (p <0.001).

A statistically significant difference (p <0.001) was also present in the attitude of the subjects that children have sufficient knowledge about dental health. The situation varied within each group of subjects. In the group of media and educators there was complete division on this issue. All the respondents representing authorities and large number of parents were confident in the fact that there is sufficient knowledge about dental health. Only the majority of dentists though that there is not enough knowledge (Table 2).

Table 2. **Attitudes of respondents toward oral health education**

		Media	Authority	Educators	Parents	Dentists	∑	P
In your opinion, do parents and children of preschool age have enough knowledge about dental health?	Yes	30 (50%)	60 (100%)	40 (50%)	45 (75%)	20 (40%)	195 (63%)	<0,001
	No	30 (50%)	0	40 (50%)	35 (25%)	30 (60%)	135 (44%)	
Where should it be important to health educate the parents of pre-school children?	There is no need for that	0	12 (20%)	8 (10%)	0	0	20 (6%)	
	Gynecologists and paediatricians	0	0	0	0	0	0	
	In kindergartens and schools	24 (40%)	12 (20%)	56 (70%)	45 (75%)	45 (75%)	182 59%	
	The mass media	48 (80%)	48 (80%)	28 (35%)	15 (25%)	15 (25%)	155 (50%)	
Is dental health education given sufficient attention in preschools?	Yes	6 (10%)	12 (20%)	48 (60%)	23 (38%)	10 (20%)	99 (32%)	<0,001
	No	54 (90%)	48 (80%)	32 (40%)	37 (62%)	40 (80%)	211 (68%)	
Is dental health education given sufficient attention in mass media?	Yes	6 (10%)	12 (20%)	48 (60%)	37 (62%)	7 (14%)	110 (35%)	<0,001
	No	54 (90%)	48 (80%)	32 (40%)	23 (38%)	43 (86%)	200 (65%)	
∑		60	60	80	60	50	310	

All the groups emphasized the mass media (50%) and educational institutions (59%) as the ones that should be the most responsible for health education. Slight advantage, but not statistically significant, was given to educational institutions. The difference within the groups of subjects was very heterogeneous. The media and the government were absolutely convinced that the media (80%) have the most important role on that issue, only then schools and kindergartens (40%, 20%). The parents, teachers and dentists preferred the educational institutions (70%, 75%). None of the groups mentioned gynecologists and pediatricians as possible health education performers of parents.

There was a statistical significance (p <0.001) within the total sample related to all three groups of questions about attitudes toward prevention in dentistry (Table 3).

Table 3. **Atitudes of respondents about prevention in dentistry**

		Media	Authority	Educators	Parents	Dentists	∑	P
Are the programs of prevention of oral diseases:	Too expensive	30 (50%)	0	12 (15%)	9 (15%)	13 (26%)	64 (21%)	<0,001
	Acceptable	18 (30%)	36 (60%)	52 (65%)	23 (38%)	19 (38%)	148 (48%)	
	There are levels that can be fit	12 (20%)	24 (40%)	16 (20%)	28 (47%)	18 (36%)	98 (31%)	
What part of dentistry should be better developed?	Sector for the treatment of existing diseases	12 (20%)	0	36 (45%)	38 (63%)	23 (46%)	109 (35%)	<0,001
	Programs to prevent diseases - prevention	48 (80%)	60 (100%)	44 (55%)	22 (37%)	47 (54%)	201 (65%)	
Are you wiling to support a special preventive program to improve dental health?	Definitely	54 (90%)	60 (100%)	80 (100%)	60 (100%)	0	254 (82%)	<0,001
	There are major problems	6 (10%)	0	0	0	0	6 (2%)	
	Eligible costs	0	0	0	0	0	0	
	Only if the dentists agree	0	0	0	0	50 (100%)	50 (16%)	
∑		60	60	80	60	50	310	

Discussion

The organization of health system and dental services requires a precise analysis of starting points, human and financial capacities, knowledge and willingness of each participant in the triangle (financiers-executors-citizens).[11,12] A number of studies have indicated that the level of knowledge of all participants in the chain of prevention program implementation is directly related to the health status of the population. [13-20]

According to WHO standards, high-quality preventive program in dentistry should have a precise elaborate of preparatory phase, which should fully provide consent and active involvement of all stakeholders (citizens, financiers and executors).[13]

In our study, the level of "knowledge" of the media, government and educators about the existence of caries-free children suggests that a significant number of respondents were not familiar with the achievements of modern dentistry. In response to this question the parents showed more knowledge, while dentists did not meet the expected professional level of knowledge, despite majority of correct answers.

Since the respondents did not notice that there was not sufficient knowledge of parents and children about dental health, the lack of implementation of preventive measures in practice is understandable. The worldwide studies have shown that the level of knowledge about the necessity of taking certain preventive measures did not correlate with their implementation, and in countries with a high prevalence of dental caries, low level of health culture attached to regular preventive dental visits was recorded. [13,21-24]

A modern approach to the oral diseases means connecting them into a group of mass chronic non-communicable diseases.[3-6,13] There is a number of indisputable scientific but also practical facts for this primarily related to common risk factors, such as diet (frequency, quality, sugars, fast food, minerals, trace elements), lack of physical activity

(in this case chewing), unhealthy habits and similarly. WHO and most of experts agree that a multidisciplinary approach to health promotion is the most acceptable. It is especially important that direct transmitters of health messages should be those parts of the health system naturally responsible for specific population.[25-27] The gynecologists, pediatricians and their supporting services such as patronage and various counseling are the most responsible when we talk about health education of parents.[13] The integrated scientific and professional way of thinking is far from ours, and therefore of the public, which is best demonstrated by the fact that respondents did not know that parents are the possible performers of health education. The dentists are excluded as a possible answer consciously, in order to make it easier to outline differences within the groups.

The representatives of the media and the authorities fully rely on the media as an effective means of health education, while other groups attached greater importance to educational institutions and educational staff. On the base of the entire sample in terms of under-representation of dental health education in preschool institutions and in the media, there was a statistically significant agreement that the situation is not satisfactory. For now, there is no explanation of what made parents and educators to believe that dental health is sufficiently represented in the media. Literature differently interprets importance of the media in improving oral health and generally it is given less importance in relation to the fluoride toothpaste and diet changes.[28-30]

There was statistically significant difference between groups of parents and educators about satisfactory presence of dental health programs. The subjects of these groups should be the most reliable as direct executors and beneficiaries of these programs, but there is an obvious disagreement with the current situation, knowledge and application of basic principles of oral health.[11] Attitudes of other three groups is important because introduction of modernized health education programs depends on their impact.

The majority of respondents (79%) believe that prevention programs in dentistry can fit into the current state of the country. It was stronger shown that programs are completely acceptable apart from the premise that they should be applied partly. The biggest skeptics were the media and the dentists, ones that have the greatest responsibility in promoting the program. In the groups representing government and educators (teachers) there was no doubt in opinion about possibility of implementing the program. This is one of the clear indicators of a halt in the transfer of information.

Total sample showed a statistically significant preponderance toward support of a preventive approach (65%), but analysis within groups pointed to the traps of such a global observation. It is almost unanimous attitude of the authorities and the media that prevention should have absolute priority and this have significantly raised results in the total sample.

The groups that should have a preventive mindset (educators and dentists) were undecided and there was no statistical significance for the obtained differences ($p>0.05$). In turn the parents showed a greater commitment to improvement of caries treatment ($p <0.05$) as they directly face the growing pathology, complications of dental caries, increased costs of treatment and loss of time due to dental appointments. In fact no one of respondents has provided an organized and continuous dissemination of information as indicative of the possibilities and achievements in preventive dentistry.

World Health Organization and other professional associations hold an attitude that raising the level of awareness and taking personal responsibility for oral health should be encouraged through a more complex approach marked as promotion of health.[5,10,27,31-33]

Conclusion

There is diversity in attitudes between the groups which significantly affects in creating the image of the complete sample being not true reflection of public opinion. Respondents are not familiar with modern knowledge, abilities and accomplishments of preventive dentistry. The majority of the population and the profession itself are primarily concerned with therapeutic access. It is necessary to reorganize current dental care with the guidance to primary and preventive approach, focusing on implementation of continuous oral-health education in the territory of Banja Luka, as well as the entire Republic of Srpska.

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Procjena nivoa oralno-zdravstvenog obrazovanja i svijesti među pripadnicima javnog mnjenja na teritoriji Banjaluke

SAŽETAK

Uvod: Razvijenost stomatološke zaštite može da bude dobar pokazatelj razvijenosti samog društva. Prevencija stomatoloških oboljenja i pružanje odgovarajuće njege zahtijeva planirane i koordinirane programe integrisane u cjelokupni sistem zdravstvene zaštite.

Cilj rada: Utvrđivanje nivoa znanja o oralnom zdravlju i savremenim mogućnostima prevencije u populacionim grupama javnog mnjenja zaduženim za donošenje odluka i finansiranje preventivnih programa kod potencijalnih izvršioca u preventivnom programu, kao i kod roditelja djece predškolskog uzrasta u Banjoj Luci.

Ispitanici i metode: Istraživanje je sprovedeno na uzorku od 310 ispitanika izabranih metodom slučajnog izbora u urbanoj i ruralnoj sredini na teritoriji opštine Banja Luka. Ispitivanje je obavljeno u vidu anonimne ankete o nivou oralno-zdravstvenog obrazovanja ispitanika, stavova o prevenciji oralnih oboljenja i zdravstvenom vaspitanju u stomatologiji. Ispitanike su činili: 60 predstavnika zakonodavne i izvršne vlasti, 60 radnika iz medija, 80 vaspitača u vrtićima, 60 roditelja djece do šest godina, te 50 stomatologa iz državnog sektora.

Rezultati: Većina ispitanika (65%) smatra da je moguće odrediti rizik prije pojave karijesa, što je bilo statistički značajno ($p<0,001$). Svega 6% ispitanika poznaju epidemiološki dokazanu činjenicu da postoje osobe bez karijesa (caries-free). Predstavnici vlasti su bili 100%, a roditelji 75% ubjeđeni da postoji dovoljno znanja o zdravlju zuba. Sve grupe značajno ističu masovne medije i obrazovne ustanove kao nosioce zdravstvenog vaspitanja.

Zaključak: Postoji raznolikost u stavovima između ispitivanih grupa koja značajno utiče da slika kompletnog uzorka nije pravi odraz javnog mnjenja. Ispitanici nisu dovoljno upoznati sa savremenim znanjima, mogućnostima i dostignućima u preventivnoj stomatologiji.

Ključne riječi: oralno zdravlje, prevencija, javno mnjenje, karijes rizik, zdravstveno vaspitanje

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Varicose Veins and Uterine Prolapse in Female Patients Treated for Idiopathic Scoliosis

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ABSTRACT

Introduction: In the available literature there are sporadic data about the relationship between the impaired collagen synthesis and poor posture on one side, and the occurrence of varicose veins and uterine prolapse on the other side. However, there are no studies which specifically target this issue.

Aim of the Study: To determine the prevalence of varicose veins and/or uterine prolapse occurrence in women previously treated for idiopathic scoliosis in comparison to the control group - women who have never been treated for idiopathic scoliosis.

Patients and Methods: The study was designed as a cross-sectional study. The frequency of occurrence of varicose veins and/or uterine prolapse in a group of women previously treated for scoliosis was compared with a control group. The results were obtained through descriptive analysis and through conclusive results of statistical tests, where $p < 0.05$ was set as a statistically significant value.

Results: In comparison to the control group, the frequency of varicose veins occurrence was higher, with a statistically significant difference in the group of women treated for idiopathic scoliosis. There was not a single case of uterine prolapse.

Conclusion: Modern approach to scoliosis treatment requires the involvement of multidisciplinary teams for scoliosis in specialized health care facilities which have developed the expertise in this field. These teams should work on prevention, early detection and diagnosis, promoting the adequate treatment approaches anchored in evidence based medicine, but also get involved in the continuous research striving to improve the quality of life of their patients.

Key words: idiopathic scoliosis, varicose veins, uterine prolapse, collagen

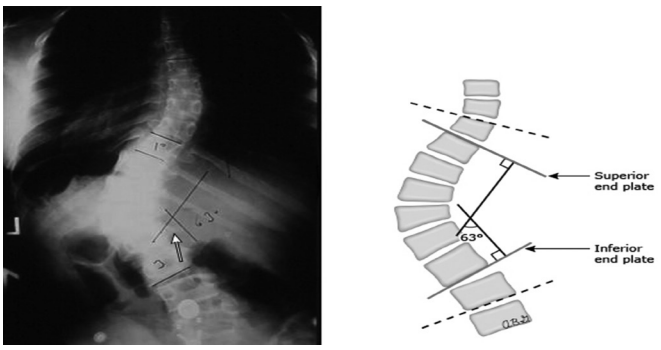
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Introduction

Spine deformities represent 27.5% of all deformities of locomotor apparatus. Spine deformities include functional or structural changes of spine, esthetic problems, back pain and functional impairments of cardiovascular and respiratory systems. According to the Scoliosis Research Society, scoliosis is every lateral deviation of the spine in frontal plane with an angle greater than ten degrees per Cobb. (Figure1.).[1]

Figure 1. Measuring the scoliosis angle per Cobb



(Kane WJ. Scoliosis prevalence: a call for a statement of terms. Clin Orthop Relat Res 1977;126:43-6)

Scoliosis is a complex, three-dimensional spine deformity with a curve in frontal plane, with rotation in a horizontal plane and a change of profile in a sagittal plane. According to the definition, (up to date), idiopathic scoliosis represents a pathological entity of unknown and probably not a single cause. [2-4] Based on data from year 2007, the prevalence of scoliosis among school children in Serbia was 10.2% which, in comparison with data from year 1997 is an increase of 1.4%. Progression of scoliotic curves which require treatment is significantly more frequent, even up to the eight times higher among girls. The proportion of affected girls increases with the increase of the curve degrees. [5] The worst prognosis is linked with thoracic idiopathic scoliosis which develops in first five years of life. The reason is the interference with lung development and its secondary impact on restirictive respiratory disorders, hypoxemia, pulmonary hypertension, chronic pulmonary hearth, cardiac decompensation and respiratory insufficiency. Some authors state that idiopathic scoliosis over 700 leads to the irreversible pulmonary damage. As a rule, adolescent idiopathic scoliosis over 1000 causes the damage to lungs.[6-8]

Chronic venous diseases encompass a group of pathological conditions which are developed due to increased venous pressure leading to progressive stasis and consequent inflammatory and trophic changes of subfascial structures, subcutaneous tissue and skin. Risk factors for development of chronic venous diseases include age, family history of venous diseases, loosening of ligaments, prolonged standing, the BMI increase, smoking, sedentary life style, trauma of lower extremities, previous venous thrombosis, the presence of an arteriovenous shunt, some hereditary factors, high estrogen and pregnancy.[9-14] Diagnosis of varicose veins is established following the assessment done by the angiologist. The assessment includes the clinical examination of superficial veins and ultrasound assessment of deep veins of lower extremities. The findings can be as it follows:

1. Normal condition of venous system – no clinical signs and no ultrasound signs of changes.
2. Moderate diseases of venous system – clinically visible varicose veins without trophic changes with the ultrasound verification of obstruction in superficial veins or in perforate veins (stage C2-3 according to CEAP Classification).
3. Severe venous disease – clinically visible trophic changes with the ultrasound verification of obstruction in deep veins system (stage C4-6 according to CEAP Classification).[14]

Theories which link the uterine descent with idiopathic scoliosis are theories discussing the role of connective tissue in building the key structures responsible for stability of perineum but also the stability of the entire locomotor apparatus.[14-16] Diagnosis of uterine prolapse is based on gynecological examination which can verify three degrees of uterine descent:

1. First degree (descensus uteri) – the cervix is below the interspinal line but above the introitus of vagina.
2. Second degree (prolapsus uteri) – is the higher degree of descent whereby the cervix and part of vagina descent to the level of introitus, and sometimes the cervix is outside of introitus.
3. Third degree (prolapsus uteri totalis) – the highest degree of the static disorder whereby the entire uterus and vagina are outside of introitus.[16-18]

In the context of this study, the starting theory is that bone instabilities are associated with changes in collagen strength and its metabolism. Further on, the assumption is that factor of connective tissue (its quality) is one of the important factors in multifactorial etiopathogenesis. Some studies have showed that, in certain hereditary pathological conditions, the loss of matrix protein in skin has an impact on blood vessels and that varicose veins are more frequently present in those disorders. One of such disorders is idiopathic scoliosis.[18-20] The change in collagen synthesis is described in findings of varicose veins as such. Smoot muscle cells extracted from varicose veins were synthetizing more type I collagen, less type III collagen and similar quantities of collagen V. This disbalance is a possible reason for mechanic traits of the tissue which, under such conditions, has a lower quality.[21] Also, more findings indicate the relationship between connective tissue disorders, also some other hereditary disorders and onset of the pelvic organ descent.[21-23] Hence, there is an assumption that these two conditions are parts of the same entity as the idiopathic scoliosis.

Aims of the Study

The main aim of this study is to determine the presence of varicose veins and/or uterine prolapse in women

previously treated for idiopathic scoliosis and in women who have never been treated for idiopathic scoliosis, then to compare these two groups.

Patients and Methods

The study was designed as a cross-sectional study which followed the presence of varicose veins and/or uterine prolapse in group of women who were previously assessed and treated by Team for scoliosis at the Institute for physical medicine and rehabilitation „Dr Miroslav Zotović"in Banja Luka. All participants have undergone the study procedures during the period 08/01/2015 - 12/30/2015. Inclusion criteria were: female sex, reproductive age, medical records about the type of treatment, signed informed consent for participation in the study; exclusion criteria were: scoliosis which developed as part of some other, diagnosed condition or trauma and pregnancy. At the time of the study, a control group with women of approapriate age was established. They were recruited among female patients who happened to be in-patients in rehabilitation programs at the Institute for physical medicine and rehabilitation „Dr Miroslav Zotović" in Banja Luka, for other pathological processes on locomotor apparatus and who had never been treated for idiopathic scoliosis. All participants in the control group were exposed to the same examinations and the same questions.

Based on medical records from the Team for scoliosis, all participants were grouped according to the type of treatment, which at the same time determined the severity / degree of scoliosis:

1. Group 1 (Participants treated with physiotherapy only),
2. Group 2 (Participants treated with combination of physiotherapy and application of orthosis / corset)
3. Group 3 (Participants treated with surgery)

Assessment of the venous system was done by a specialist of physical medicine and rehabilitation - subspecialist angiologist. Clinical examination of superficial veins of lower extremities was complemented with the ultrasound examination done with LOGIQ P6 PRO apparatus. Based on obtained data, the condition of venous system was classified as normal condition, moderate venous disease and severe venous disease, as previously described.

The gynecological examination was performed in all participants who were previously treated for idiopathic scoliosis and in all participants in the control group. The examination included clinical gynecological examination and grading of the uterus descent, which was then classified in three different degrees, as previously described.

Data collected in this study were recorded in MS Excel 2007 database, while the statistical program SPSS 17 was used for all statistical analyses. Data were processed using the standard statistical methods, both from domain of descriptive statistics and domain of statistical deduction (nonparametric X^2 test). The value of $P < 0.05$ was taken as a cut off for statistically significant values. For assessment of the sample size, the study used formula and nomogram tables according to Cohen. The conclusion was that valid statistical assessment requires minimum of 86 participants. This study was approved by the respective Ethical Committee.

Results

Results are presented through two modalities: descriptive data and data obtained with tests of statistical deduction. Tables and graphs were used to display results.

Descriptive presentation of the obtained data

We have shown descriptive statostocalfeatures for age at which the treatment started, current age, body mass and body height, for both groups, the experimental and the control one (Table 1).

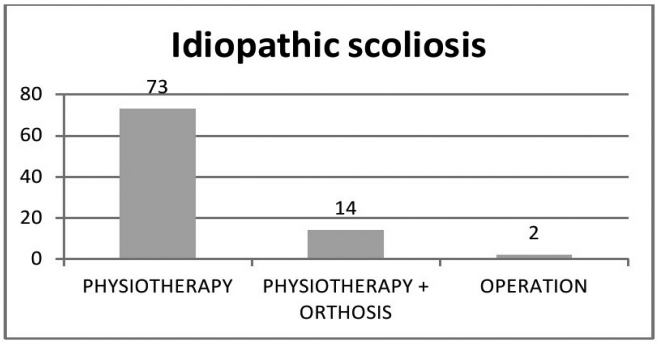
Table 1. Descriptive display of the observed parameters

Idiopathic scoliosis	The average value	Mode	Median	SD	Min.	Max.
Age when treatment started*	11.7	12	12	2.9	6	17
Current age*	30.9	20	34	7.9	20	43
Body mass**	63.6	60	62	9.6	45	86
Body height***	168.6	164	167	6.5	157	186
Control group	The average value	Mode	Median	SD	Min.	Max.
Current age*	29.9	27	29	6.7	17	42
Body mass**	67	66	66	12.7	43.5	119
Body height***	169	169	169	6.2	144	188

**age; **body mass in kilograms; ***body height in centimeters*

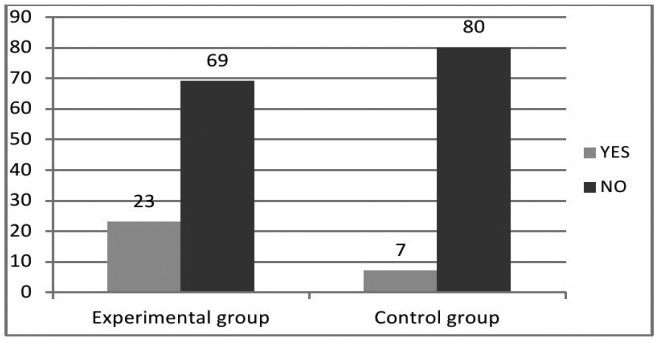
Graph 1. indicates the representation of certain treatment modalities for idiopathic scoliosis in the experimental group.

Graph 1. Distribution of the type of treatment for idiopathic scoliosis in the experimental group



Graph 2. indicates the presence of varicose veins in experimental in comparison with the control group.

Grph 2. Presence of the varicose veins in experimental and control group



Considering the fact that there was not a single case of uterine prolapse, we did not present those data in graph.

The use of tests of statistical deduction

Table 2. Varicose veins and uterine prolapse in experimental and control group

	Experimental group (n=89)	Control group (n=87)	Asym. Sig (2tailed)
Varicose veins	23	7	0.002*
Uterine prolapse	0	0	**

**X2 = 9.854; df 1; (p<0.01)*

***no statistical test was done*

Discussion

Experimental group (women treated for the idiopathic scoliosis) included 89 women, while the control group (women who had never been treated for idiopathic scoliosis) included 87 women. Based on data presented in Table 1, the average value for the current age in experimental group was 30.9, and in the control group 29.9; as for the body height, the average value in experimental group was 168.6 cm, and in the control group 169 cm; body weight – in experimental group the average value was 63.6 cm, while in the in the control group was 67 kg. Values of these parameters are close and we can state that, by these parameters, the control group is very similar to the experimental group.

In our context, the age at which diagnosis of idiopathic scoliosis was established and treatment started varies between 6 and 17 years (the middle value was 11.7). This corresponds with a period of the most intense growth, when visual and functional deficit becomes most pronounced but also at age when the self-inspection is most present and most critical.

Graph 1. shows the distribution according to the treatment type (stage of disorder) for the idiopathic scoliosis. Majority of participants were treated with physiotherapy only (PT) - 73 participants (82%), with the combined treatment (PT) + corset in 14 participants (15.7%), and following the surgical treatment in 2 participants (2.3 %). Such results are in line with scientific facts as the highest percentage of mild degree deformities can be corrected pretty quickly with an adequate treatment and only a small percentage requires more serious approach. The first recommendation is the early detection and referral for conservative treatment which prevents the progression of the curve and complications linked to the advanced scoliosis, while the use of orthosis should be combined with physical treatment whenever necessary. The latter can be seen as assistance during the intense growth, with an aim to prevent the severe deformity which in turn requires more serious correction. In the sample of this study, there were only two cases of surgical treatment. One participant had surgery at the age of 9, the other at the age of 15, both with satisfactory effect.

Graph 2. displays the distribution of varicose veins in experimental group and in the control group. It is visible that varicose veins were more common in the experimental (23/89; 25.8%) then in the control group (7/87; 8.1%).

Table 2. shows the distribution of varicose veins in population of women who were treated for the idiopathic scoliosis in comparison with the control group. Using the nonparametric X^2 test we obtained value $X^2=9.854$; for df1, Asymp.Sig (2 tailed) = 0.002 < 0.01, which rejects the hypothesis about the variables independence and accepts the hypothesis that the difference is statistically significant ($p<0.01$). Hence, women who were treated for idiopathic scoliosis had the statistically significant frequency of the varicose veins presence.

In the context of this study, the starting theory is that bone instabilities are associated with changes in the collagen strength and its metabolism. Further on, it is assumed that in multifactorial etiopathogenesis, one of the important factors is connective tissue (quality). As the results of this study revealed that presence of varicose veins is more common in women who used to be treated for idiopathic scoliosis, we can state that the theory about the impact of connective tissue may have the bigger influence than it is assumed.

As there was not a single case of the uterine prolapse in our sample, we analyzed data from previous similar studies. One study from year 2000 was following the prevalence of the urinary incontinence and pelvic organs prolapse in women with Marphan's syndrome and Ehlers Danlos syndrome. All findings were indicative for the possible etiological relations between the connective tissue disorders and pelvic organs prolapse. In 2000, Mattox and associates presented the correlation study for abnormal curve of the vertebral column and prolapse of the pelvic organs. This study was the continuation of the study done by Lind et al., who followed the relationship between the thoracic spine kyphosis and uterine prolapse. Mettox and associates concluded that the abnormal change in spine curve, particularly loss of lumbar lordosis may be a significant risk factor for development of the prolapse of the organs in minor pelvis.[24,25] Based on data and findings from the literature, we believe that age structure of our participants was the key factor which explains why we did not find a single uterine prolapse in the entire sample.

Conclusion

The presence of varicose veins in women treated for idiopathic scoliosis shows a statistically significant difference when compared with the women in the control group. The study did not find a single case of the uterine prolapse in either experimental or control group and possible reason is the age of participants.

Based on the results of the study, we can conclude that beside the treatment for idiopathic scoliosis we need to look for other conditions or disorders which can worsen the condition or make the treatment more complicated.

Modern approach to treatment of idiopathic scoliosis requires specialized multidisciplinary teams for scoliosis in facilities which developed expertise. Teams should engage in prevention, early diagnostics and adequate treatment.

Idiopathic scoliosis should be seen as a disorder of multifactorial ethiopathogenesis and be treated accordingly, especially considering its potential to cause the damage to vital organic systems (circulatory system and lungs).

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Proširene vene i prolaps materice kod pacijentkinja liječenih od idiopatske skolioze

SAŽETAK

Uvod: U dostupnim literaturnim izvorima postoje izolovani podaci o vezi poremećene sinteze kolagena i loše posture sa pojavom proširenih vena i prolapsa materice, ali ciljanih studija nema.

Cilj rada: Utvrditi učestalost proširenih vena i/ili prolapsa materice kod žena liječenih od idiopatske skolioze u odnosu na kontrolnu grupu – žene koje nikada nisu liječene zbog idiopatske sklolioze.

Ispitanici i metode: Studija je kreirana kao studija presjeka. Učestalost proširenih vena i prolapsa materice kod žena liječenih od idiopatske skolioze je posmatrana u odnosu na kontrolnu grupu. Rezultati su obrađeni deskriptivno i upotrebom testova statističkog zaključivanja, a vrijednosti gdje je $p < 0.05$ uzete su kao statistički značajne.

Diskusija: Učestalost proširenih vena je statistički značajno veća u grupi žena koje su liječene zbog idiopatske skolioze u odnosu na kontrolnu grupu, dok nije zabilježen niti jedan slučaj prolapsa materice.

Zaključak: Savremeni pristup liječenju idiopatske skolioze podrazumijeva postojanje multidisciplinarnih timova za skoliozu u ustanovama koje se bave ovom problematikom. Njihov zadatak je rad na prevenciji, ranoj dijagnostici, adekvatnom terapijskom pristupu zasnovanom na medicinskim dokazima, ali i kontinuirana istraživačka aktivnost koja za cilj ima poboljšanje kvaliteta života.

Key words: idiopathic scoliosis, varicose veins, uterine prolapse, collagen

ORIGINAL ARTICLE

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Surgical Treatment of Traumatic Flail Chest - Twenty Years of Experience

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ABSTRACT

Introduction: Traumatic flail chest is segment of the chest wall, which is caused by multiple fractures or by separation of bone structures (at least three sequential broken ribs or separated into two fracture lines). These injuries are mainly seen in polytrauma patients.

Aim of the Study: Our aim is to show the therapeutic benefits of surgical treatment (operative stabilization) of the flail chest.

Patients and Methods: We retrospectively analyzed patients who underwent surgery at the Clinic of Thoracic Surgery, University Clinical Centre of the Republic of Srpska, Banja Luka, in the period from 01. 12. 1997 - 04. 06. 2016.

Results: 50 patients with traumatic flail chest with average age of 47.42 years were surgically treated in the twenty-year period at the Clinic of Thoracic Surgery, University Clinical Centre of the Republic of Srpska, Banja Luka. The average length of a hospital stay was 15 days. Survival rate in the operated group was 91.43%.

Conclusion: If conservative measures such as internal stabilization, the use of analgesics, antibiotics, oxygen therapy and airway toilet does not lead to stabilization of respiratory function, surgical chest wall stabilization is necessary.

Ključne riječi: movable flail chest, surgical stabilization

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Introduction

Pokretni Flail chest is post-traumatic thoracic segment of the wall that does not have continuity with the remaining bony skeleton of the chest. It occurs with lost support of at least three ribs in two lines with the trauma.[1]

Pathophysiological disorder occurs due to the paradoxical movement: during inspiration flail chest moves toward the inside of the chest, while it moves outward in the expirium. This reduces the efficiency of breathing and the volume of inhaled air. This condition is followed by typical clinical triad: intrabronchial hemorrhage, ineffective cough and anoxia.[1,2]

Post-traumatic flail chest is a cause of high mortality, especially in polytrauma patients. Early work on the moving flail chest recorded a mortality of up to 80%.2 Standard treatment is focused on the treatment of lung parenchymal injury and pain control, often with the use of mechanical ventilation with positive pressure. Several previous studies have shown that there are multiple benefits of operative, surgical, stabilization of the flail chest.[3]

Aim of the study

The aim of the work consists in the presentation of therapeutic benefits of surgical treatment (operative stabilization) of flail chest.

Patients and Methods

Hospital records were processed by using the retrospective analysis of data on patients treated at the Clinic of Thoracic Surgery, Clinical Centre of Banja Luka with traumatic flail chest in the period from 01. 12. 1997 - 04. 06. 2016. Both methods described so far: osteosynthesis systems and intramedullary stabilization (Kirschner's wires and wire stitches) were used for stabilization of the flail chest. CT scanning was performed preoperatively to assess the volume of the thoracic trauma. All surgical treatments were performed under general endotracheal anesthesia, used by double-lumen tube by Karlens. Posterolateral thoracotomy with exploration of the pleural cavity was used as an operational method for the treatment of parenchymal lung lesions, intrathoracic hemorrhage and intrapleural clot removal. In the case of laceration of the parenchyma and lesions intrathoracic structures, two intrathoracic drainage were placed in the front and back line, in the fifth and seventh intercostals space.

Results

Our study covers a twenty-year period, from 01. 12. 1997 - 04. 06. 2016 during which the Clinic of Thoracic Surgery, University Clinical Centre of the Republic of Srpska, Banja Luka, surgically treated 50 patients with traumatic created flail chest. Surgery was performed on 43 men (86%) and seven women (14%). Patients' average age was 47.42 years. In 48% (24 patients), the mechanism of injury was traffic traumatism. Postoperative mortality rate is 8.57%. Causes of mortality are associated comorbidity in the elderly and associated polytrauma (abdominal injury, locomotor system, craniocerebral injury). Survival in the operated group was 91.43%. The average length of hospitalization was 15 days. On 24 patients (48%), a suture lung parenchyma was performed with the thoracotomy and stabilization of flail chest due to its laceration. Four patients (8%) underwent an extensive resective surgery of lung parenchyma (lobectomy or bilobectomy type). Six patients (12%) underwent suture hemidiaphragm due to its laceration. Only six patients (12%) underwent a fenestration of pericardium. Three patients (6%) were registered with a chronic postoperative pain.

Discusion

Prolonged artificial ventilation is still the most commonly used method for the treatment of the unstable segment of the chest wall.[2]

The goal of surgical stabilization of the unstable chest wall is to shorten the time of application of respirators and avoid complications due to its prolonged applications.[4] Most studies have shown that surgical stabilization leads to a reduction in mortality in thoracic trauma, shortens time in the intensive care unit, and reduces the length of application of mechanical ventilation. [2-5]

Indications for use of this surgical procedure are not yet standardized, but the following are generally accepted by the thoracic surgeons:

- unstable chest wall if there is an indication for thoracotomy due to intrathoracic injury,
- unstable chest wall without contusion of the lung parenchyma,
- paradoxical movements of the unstable segment of the chest wall in patients on a ventilator (PEEP insufficient stabilization),
- extensive deformity of the chest wall.[4,5]

Some authors suggest the following indications:

- the existence of strong pain despite the slight paradoxical movements, which could lead to respiratory insufficiency,
- associated abdominal injuries after splenectomy and disposal rifts diaphragm,
- exploratory thoracotomy due to penetrating wounds.[5]

Advantages of this surgical procedure are:

- pain reduction,
- reduction of the time that a patient spends on a ventilator,
- early extubation of the patient,
- complete reduction of the fracture with perfect anatomical consolidation.[2-5]

Most of thoracic surgeons believe that the extensive posterolateral thoracotomy is the optimal approach, without the need for additional thoractic incisions.[6]

Poor coalesced fractures of ribs in flail chest treated with artificial ventilation, as well as the consequent pain are additional arguments in favor of the rib fixation.[6]

The average age of treated patients in our series was 47.42 years, slightly lower than in the literature, which states the average age of 52 years.

The average length of hospital stay which is mentioned in the literature is fifteen days; our results are consistent with the allegations in the professional literature.

Authors state that the average survival after operative treatment of patients with traumatic flail chest above 78%. Survival in our series of surgically treated patients with traumatic flail chest is slightly larger than the specified percentage of the scientific literature and is 91.43%. A possible explanation is, partially, in lower average age of treated patients.

Most authors consider that the operational stabilization flail chest of the chest wall can be done in the first seven days after injury. In mentioned series of patients, operative stabilization of the flail chest of the chest wall is made within four days of injury, in most patients the first or second day of the injury.

Conclusion

Flail chest is a serious therapeutic problem which, if not treated appropriately, leads to disturbances in ventilation and gas exchange and ultimately to respiratory failure.

If conservative measures such as the inside stabilization, the use of analgesics, antibiotics, oxygen therapy and airway toilet does not lead to a stabilization of respiratory function, surgical stabilization of the chest wall is necessary.

Such a relatively simple surgical procedure is far less risky compared to all the complications that can arise without it, increases the survival rate and significantly reduces hospitalization.

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Hirurški tretman pokretnog kapka - dvadesetogodišnje iskustvo

SAŽETAK

Uvod: Traumatski pokretni kapak je segment grudnog zida, koji nastaje višestrukim prelomom ili separacijom koštanih struktura (najmanje tri rebra serijski prelomljena ili odvojena u dvije frakturne linije). Ovakva povreda se najčešće sreće u sklopu politraume.

Cilj rada: Prikazati terapijske prednosti hirurškog tretmana (operativna stabilizacija) pokretnog kapka.

Ispitanici i metode: Retrospektivnom analizom obrađeni su pacijenti operisani na Klinici za torakalnu hirurgiju UKC RS Banja Luka u periodu od 01. 12. 1997. do 04. 06. 2016. godine.

Rezultati: U navedenom dvadesetogodišnjem periodu, na Klinici za torakalnu hirurgiju UKC RS Banja Luka, operativno je tretirano 50 pacijenata sa traumatskim pokretnim kapkom, srednje životne dobi od 47,42 godine. Prosječno trajanje hospitalizacije je 15 dana. Preživljavanje u grupi operisanih je 91,43 %.

Zaključak: Ukoliko konzervativne mjere kao što su unutrašnja stabilizacija, primjena analgetika, antibiotika, oksigenoterapija i toaleta disajnih puteva ne dovedu do stabilizacije disajne funkcije, operativna stabilizacija zida grudnog koša je neophodna.

Ključne riječi: pokretni kapak, operativna stabilizacija

PROFESSIONAL PAPER

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Air Pollution Effect on Morbidity of the Population of the Republic Of Srpska

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ABSTRACT

Introduction: Air pollution is caused by the emission of harmful gaseous and particulate matter, resulting mainly from human activity, but also by emission from natural sources.

Aim of the Study: The aim of this study was to investigate the most common air pollutants in the Republic of Srpska region (one of the entities in Bosnia and Herzegovina) and their effect on population health, as well as to compare the obtained results with the European and world data.

Patients and Methods: We used a descriptive study approach to analyze the health of the population in the Republic of Srpska, through data obtained by the Public Health Institute of the Republic of Srpska, for the five-year period.

Results: The population of the Republic of Srpska is mostly affected by circulatory system diseases, followed by neoplasms.

Conclusion: Bearing in mind the pathophysiological mechanisms by which air pollution is involved in the onset and exacerbation of cardiovascular, respiratory, cancer and other diseases, as well as their representation in our population, one can draw a parallel between the air quality in the Republic of Srpska and the trend of the morbidity of its population.

Ključne riječi: air pollution, morbidity, particulate matter.

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Introduction

The emission of harmful gaseous and particulate matter causes an air pollution, which occurs mainly as a result of human activity, but also by the emission from natural sources. Air pollution occurs when the concentrations of certain pollutants reaches the levels of potentially toxicity, i.e. for human health as well as for plants and animals. Air pollutants may be categorized as: "primary air pollutants" i.e. those pollutants directly emitted to the atmosphere by some pollution source (e.g. from vehicle exhaust or chimneys), and the "secondary air pollutants" i.e. those formed in the atmosphere as a result of reactions (oxidation and transformation) between the primary pollutants, e.g. the secondary particulate matter and ozone.[1] Particulate matter (PM) is a widespread air pollutant that consists of a mixture of solid and liquid particles suspended in the air.[2]

Primary particles, originating from combustion sources, usually are consisted of a carbonaceous core with

chemicals (such as sulfates, metals and polycyclic aromatic hydrocarbons) absorbed to their surfaces. Secondary particles are formed by chemical reactions in the atmosphere of primary particles with gases (such as nitric oxides, ozone and sulfur oxides, which are strong oxidants), leading to the formation of nitrates and ammonia. According to the size of the particles, the PMs are classified as 1) PM10, i.e. those with particles aerodynamic diameter less than 10 micrometres; 2) PM2.5, i.e. those with particles diameter less than 2.5 micrometres (also known as fine particulates) and 3) PM0.1, i.e. those particles with diameter less than 0.1 micrometres - also known as ultrafine particulates.2 The PMs are known to be harmful to human health.[3]

Exposure to air pollution can have acute and chronic effects. Acute exposure can cause: mortality, increased respiratory symptoms, decreased lung function, effects on plasma viscosity, heart rate variability, pulmonary inflammation and hospitalization or other health care visits. Effects of chronic exposure to air pollution are increased mortality rates, reduced survival times, chronic cardiopulmonary disease and reduced lung function. The most susceptible are elderly, infants, persons with chronic cardiopulmonary disease, pneumonia, influenza and asthma.[4]

It is known that air pollution can cause worsening of the respiratory diseases. Moreover, other diseases can be caused and/or worsened by air pollution, primarily neoplasms and circulatory diseases. Therefore, the aim of this study was to investigate the most common air pollutants in the Republic of Srpska and their effect on population health, as well as the comparison the obtained results with the European and world data.

Patients and Methods

We used a descriptive study approach to analyze the health of the population of the Republic of Srpska, through data obtained by the Public Health Institute of the Republic of Srpska, for the period 2009-2013. The study involved around 1.4 million people (inhabitants of the Republic of Srpska). These data were compared with guidelines thresholds suggest by World Health Organisation as well as with data (Eurpean and world level) published by other authors.

Results

The main air pollutants in the Republic of Srpska were: PM10 and PM2.5, nitrogen oxides, ozone (O3), sulphur dioxide (SO2), polycyclic aromatic hydrocarbons (PAH), benzene, 1,3-butadiene, carbon monoxide (CO) and lead (Pb).

According to the Gazette of the Republic of Srpska, air quality categories shall be determined according to the level of pollution, starting with the prescribed limit and tolerance values defined in Regulation on the values of air quality (Fig. Gazette of RS, no. 124/12), as well as on the basis of the measurement results. If there is no prescribed tolerance limit for a pollutant, its value is taken as the tolerance value. Categories of air quality are determined once a year for the previous calendar year. The following table presents air quality in relation to the averaging period. In order to protect human health, limit values as well as tolerance limits has been established.

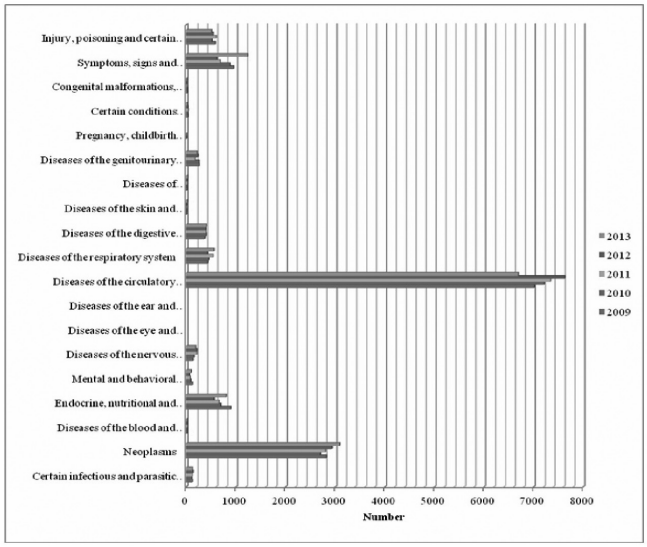
Table 1. Air quality in relation to the averaging period

Pollutants	The average period	Limit	Tolerance limit	Margin of tolerance
SO_2	1 hour	350 μg/m³ (1)	150 μg/m³	500 μg/m³
	24 hours	125 μg/m³ (2)		125 μg/m³
	calendar year	50 μg/m³		50 μg/m³
NO_2	1 hour	150 μg/m³ (3)	75 μg/m³	225 μg/m³
	24 hours	85 μg/m³	40 μg/m³	125 μg/m³
	calendar year	40 μg/m³	20 μg/m³	60 μg/m³
PM10	24 hours	50 μg/m³ (4)	25 μg/m³	75 μg/m³
	calendar year	40 μg/m³	8 μg/m³	48 μg/m³
CO	8 hours	10 mg/m³	6 mg/m³	16 mg/m³
	24 hours	5 mg/m³	5 mg/m³	10 mg/m³
	calendar year	3 mg/m³		3 mg/m³

Source: Regulation on the values of air quality (Gazette of RS, no. 124/12)
Legend:
(1): not to be exceeded more than 24 times in a calendar year.
(2): not to be exceeded more than 3 times in one calendar year.
(3): not to be exceeded more than 18 times in a calendar year.
(4): not to be exceeded more than 35 times in a calendar year.

Graph 1. presents the population health structure and the most common causes of death among population in the Republic of Srpska.

Graph 1. Deaths by causes of death[5]



It can be seen that population of the Republic of Srpska is mostly affected by circulatory system diseases, followed by neoplasms. The overall mortality rate was 1042.98 per 100.000 for men and 921.32 per 100.000 for women. The most common causes of death were: diseases of the circulatory system (6687), neoplasms (3090), endocrine, nutritional and metabolic disease (800) and diseases of the respiratory system (556).5 The percentage of deaths caused by diseases of the respiratory system is on the rise, and it is about 4% in the total death.

Discussion

Even short-term exposure to low levels of pollutants can damage lungs at the cellular level. For instance: sulfuric acid compounds and ozone may hinder the immune system's ability to defend against infection.[6] Ozone is a highly reactive gas that triggers oxidative stress when it enters the airways. Air quality and air pollution affect not only human respiratory system, but also the whole organism. Air pollution is now becoming an independent risk factor for cardiovascular morbidity and mortality with molecular mechanisms for PM-caused cardiovascular disease that include direct toxicity to cardiovascular system or indirect injury by inducing systemic inflammation and oxidative stress in peripheral circulation.[7] Due to the size and chemical composition of PM0.10, it is much easier to cross the pulmonary epithelium and the lung-blood barrier and accumulate in blood.[7] After deposit on vascular endothelium, PM0.10 can aggravate the local oxidative stress and inflamation, resulting the atherosclerotic plaque instability, and finally may lead to thrombus formation.[8]

Increased oxidative stress and activated inflammatory pathway in pulmonary due to exposure to PM particulate play a substantial role in the indirect pathway.[7]

Considerable evidence has proved that particulate air pollutants can trigger an inflammation related cascade when they deposit in the lung,[9,10] resulting in increased circulating level of pro-inflammatory cytokines such as CRP, IL-6, IL-8 and IL-1β.[11] Systemic inflammatory is a well-known risk factor for atherosclerosis progression, and this pro-inflammatory mediators are close related to increased blood coagulability and endothelial dysfunction and which finally can exacerbate myocardial ischemia.[7]

Numerous findings indicate that even a few hours to weeks of short-term exposure to PM particulates can trigger cardiovascular disease-related mortality and events, especially among the susceptible individuals at great risk including the elderly or the patients with preexisting coronary artery disease.[7] The results of study performed by Raza et al. suggest that short-term elevations of O3 urban background levels are associated with an increased risk of out-of-hospital cardiac arrest with no indication of a threshold level, in a region with ~50 mg/m3 annual O3 levels.[12]

Two-hour exposure to particles was associated with an increased risk of ventricular arrhythmias in patients with implantable cardioverter devices, pointing to the possible importance of shorter exposure periods.[13]

Li and colleagues found an increase of 10μg/m3 in two-day moving average concentrations of particulate matter ≤ 10μm in aerodynamic diameter (PM10), sulfur dioxide (SO2) and nitrogen dioxide (NO2) was significantly associated with increases of 0.36%, 0.86% and 1.30% in daily coronary heart disease mortality in 8 Chinese cities, respectively, with pooled exposure-response curves that were almost linear and no apparent thresholds were identified.[14]

Air pollution is associated with markers of inflammation, coagulation and endothelial activation. Hajat et al. showed that 5 μg/m increase in long-term ambient PM2.5 was associated with 6% higher interleukin-6 and increase in long-term NO was associated with 7% higher level of D-dimer, making these data consistent with the hypothesis that long-term exposure to air pollution is related to some markers of inflammation and fibrinolysis.[15] Multicenter study of 11 European cohorts pointed to an association between long-term exposure to PM constituents and coronary events.[16]

Ozone is thought to increase cardiovascular death rates in high-risk groups by inducing damage in pulmonary mast cells.[17] The impacts of ozone on nonaccidental, cardiovascular and possibly cerebrovascular mortality

increases during summer, and is amplified during the warmest days.[18] According to European environmental agency, 95% of the total EU urban population is exposed to ozone levels exceeding the World Health Organization (WHO) Air Quality Guidelines (AQG).[19]

Air pollution guidelines and legal limits have generally not been based on cardiovascular outcomes. For example, WHO recommends that average levels of PM10 (24 h average), ozone (8 h average), sulphur dioxide (SO2) (24 h average) and nitrogen dioxide (NO2) (1 h average) should not exceed 50, 100, 20 and 200 mg/m3, respectively, but these limits were derived principally from data on mortality (for PM10 and ozone) and respiratory outcomes among vulnerable individuals (for SO2 and NO2).

Research on mortality rates in heavily polluted areas reveals statistically significant links between high levels of air pollutants and increased numbers of deaths, primarily among the elderly.[20]

Results from 23 European cities/areas of the APHEA 2 project (Air Pollution and Health: A European Approach) show that, in warm season, a 10 mg/m3 increase in the 1-hour and in 8-hour ozone concentration was associated with a 0.5% significant increase in the daily number of cardiovascular deaths, with the larger effects observed in the southern cities.[21]

Some data suggest that exposure to particulate matter may be associated with decreased birth weights.[22,23] An ecological study of infant mortality and air pollution was conducted in the Czech Republic in the period 1986-1988, where Bobak et al. found a weak positive associations between neonatal mortality and total suspended particulates (TSP-10) and SO2 .[24]

Hwang and Chan (2002) reported that, in Taiwan, the rates of daily clinic visits for lower respiratory tract illness were associated with current-day concentrations of nitrogen dioxide, carbon monoxide, sulfur dioxide and particulate matter less than or equal to 10 μm.[25] A study in Boston population, performed by Mostofsky et al. (2012), showed that the association between higher concentration of PM2.5 particles and higher risk of ischemic stroke.[26] Pac et al. (2013) found that mean daily PM10 level higher than 50 μg/m3 increased asthma-related hospital morbidity in Poland, with sulfur dioxide shown to be the most important predictor.[27] A study in the United Kingdom performed by Sofianopoulou et al. (2013) indicated that an increse of 10 μg/m3 in ambient PM10 was associated with an increse of 1% in salbutamol prescribing, showing that monthly respiratory prescribing in primary care is a useful indicator of the extent to which air pollution exacerbates asthma and chronic obstructive pulmonary disease (COPD) symptoms.[28-32]

WHO air quality annual guidelines suggest the limit for PM10 to be less than 20 μg/m^3 for European Member States. However, in the year 2010 this limit had been accomplished only by 9 of the 34 Member States. Bosnia and Herzegovina had set a limit slightly less than 50 μg/m^3.[2] When we talk about PM2.5, Bosnia and Herzegovina had set a concentration of PM2.5 in the range 10-15 μg/m3 for the year 2005,[29] while WHO air quality annual guidelines suggest the limit to be 10 μg/m^3.[2]

Emissions of primary PM2.5 have reduced by about a third for both the European Environment Agency member countries 2013 (EEA-33) and the European Union member countries (EU-28) compared to their levels in 1990. More importantly, the timeline of emissions reductions shows that the EEA-33, as a whole, is on track towards achieving the total reduction target implied by the Gothenburg Protocol. However, country-specific PM2.5 timelines suggest that not all countries are on track to meet their individual commitments by 2020. These countries may therefore need to implement emissions reduction measures beyond those currently applied.[30-32]

Conclusion

It is estimated that approximately 3% of cardiopulmonary and 5% of lung cancer deaths are attributable to PM globally. In the European Region, this proportion is 1–3% and 2–5%, respectively, in various subregions.[31] Our research showed that the most common air pollutants in Republic of Srpska are secondary particles. Also, in the Republic of Srpska most patients were suffering from cardiovascular diseases and neoplasms. Therefore, the impact of air pollution and the occurrence of these diseases can lead to interconnection.

Results emerging from a recent study indicate that the burden of disease related to ambient air pollution may be even higher. This study estimates that in 2010, ambient air pollution, as annual PM2.5, accounted for 3.1 million deaths and around 3.1% of global disability-adjusted life years (DALY).[32]

Exposure to PM2.5 reduces the life expectancy of the population for about 8.6 months on average. Results from the scientific project "Improving Knowledge and Communication for Decision-making on Air Pollution and Health in Europe" (Aphekom), which uses traditional health impact assessment methods, indicate that average life expectancy in the most polluted cities could be increased by approximately 20 months if the long-term PM2.5 concentration was reduced to the WHO (AQG) annual level.[2]

When it comes to air quality, Bosnia and Herzegovina, and therefore the Republic of Srpska did not reach the quality of air recommended according to the WHO guidelines.

Bearing in mind the pathophysiological mechanisms by which air pollution is involved in the onset and exacerbation of cardiovascular, respiratory, cancer and other diseases, as well as their representation in our population, one can draw a parallel between the air quality in the Republic of Srpska and the trend of the morbidity of its population. However, there are limitations in this study, in terms of precise data, due to the lack of accurate data because of absence of the recent census in the Republic of Srpska and Bosnia and Herzegovina.

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Uticaj zagađenja vazduha na obolijevanje stanovnika Republike Srpske

SAŽETAK

Uvod: Zagađenje vazduha nastaje zbog emisije štetnih gasova i čestica koji su rezultat uglavnom ljudskih aktivnosti, ali i emisije iz prirodnih izvora.

Cilj rada: Cilj ovog istraživanja je bio da se ispitaju najčešći zagađivači vazduha u Republici Srpskoj i njihov uticaj na zdravlje stanovništva, kao i poređenje dobijenih rezultata sa evropskim i svjetskim podacima.

Ispitanici i metode: Koristili smo deskriptivni studijski pristup za analizu zdravlja stanovništva u Republici Srpskoj. Podaci su dobijeni iz izvještaja Instituta za javno zdravstvo Republike Srpske za period od pet godina.

Rezultati: Stanovništvo Republike Srpske najčešće obolijeva od kardiovaskularnih bolesti, a zatim od neoplazmi. Najčešći zagađivači vazduha u Republici Srpskoj su: sekundarne čestice, azotni oksidi, ozon, sumpor dioksid, policiklični aromatični ugljovodonici, benzen, 1,3-butadien, ugljen-monoksid i olovo.

Zaključak: Imajući u vidu patofiziološke mehanizme kojima zagađen vazduh učestvuje u nastanku i pogoršanju kardiovaskularnih, respiratornih, malignih i drugih oboljenja, kao i njihovu zastupljenost u našoj populaciji, može se povući paralela između kvaliteta vazduha u Republici Srpskoj i trenda obolijevanja njenog stanovništva.

Ključne riječi: zagađenje vazduha, obolijevanje, čestice

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Frequency of Risk Factors in Patients with Acute Myocardial Infarction

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ABSTRACT

Introduction: Various risk factors contribute to the occurrence of acute myocardial infarction as the most serious type of ischemic heart disease and the leading cause of sudden death worldwide.

Aim of the Study: The aim of this study was to assess the frequency of changeable and unchangeable risk factors in patients with acute myocardial infarction in the Republic of Srpska.

Patients and Methods: This cross-sectional study included patients treated for acute myocardial infarction at the University Clinical Center of Banja Luka, in the period from January 1st to December 31st, 2011. The patients were from the municipalities of Banja Luka and Laktaši. We analyzed the following risk factors: hypertension, total cholesterol values, diabetes, increased body weight and obesity, smoking, family history and physical inactivity.

Results: Out of 273 patients, the majority were male (64%), and there was a statistically significant difference between age and sex ($p < 0.01$) of the respondents. The most common risk factor for both genders was hypertension (70.1%), while the least frequent risk factor was diabetes mellitus (25.6%). Smokers and ex-smokers accounted for 58.1%, with a statistical significance between men and women ($p < 0.01$). The average BMI in both genders was in the overweight category (27.69 kg / m2). A positive family history was found in almost half of the respondents (49.4%), with a statistically significant difference between age groups and family history ($p = 0.036$).

Conclusion: Acute myocardial infarction mainly affects men in their sixties, while women are averagely affected nine years later than men. The number one risk factor for both genders is hypertension. Given the large impact of risk factors on the occurrence of acute myocardial infarction, priority must be given to the prevention and control of the aforementioned, especially in the primary health care.

Key words: acute myocardial infarction, risk factors, patient

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Introduction

Risk factors, as predictors of risk for morbidity and mortality in cardiovascular disease (CVD), have been in use since the late 19th century.[1,2]

The first large international study focused on the correlation between risk factors and CVD was the Framingham Heart Study in which, during the period between 1948 and 1951, approximately 5,208 healthy respondents between the ages 30 and 60 were enrolled. A working hypothesis of this study was that heart and blood vessel diseases do not have one risk factor, such as in the case of infectious diseases; it is rather caused by multiple factors that steadily make changes on the subject. Four years after the beginning of the study, with 34 cases of heart attack, investigators identified high cholesterol, arterial hypertension (AH), obesity and ECG abnormalities as the most important factors in the development of CVD. After 1961, Kannel introduced the term "risk factors".[3]

The risk factors can be changeable and unchangeable. Unchangeable risk factors are age and gender (men age>55; women after menopause and age>65 years), while changeable risk factors can be modified (hypercholesterolemia, arterial hypertension, tobacco smoking, diabetes mellitus, overweight and obesity, stress and physical inactivity).

According to the study from west Sweden, acute myocardial infarction (AMI) among women is commonly affected by multiple risk factors. Hence, women more commonly have diabetes and arterial hypertension, while cigarette smoking is the only factor of lower frequency.[4] On the other side, men have 3-6 times higher risk of developing disease compared to women, since women develop disease approximately ten years later. The risk of developing diseases is increased with aging.

Smoking 1-5 cigarettes daily increases the risk for developing AMI by 38.4%,[6] contributing to the fact that the risk for CVD is proportional to the number of cigarettes consumed. Both men and women are equally affected by the harmful effect of smoking (either active or passive); although the effect is probably stronger in women since it affects their natural hormonal protection at a younger age.[7]

Smoking has a synergistic effect with other risk factors and it also impacts an increase in CVD when combined with hypertension and diabetes. Studies have shown that, among randomly chosen patients with ACS, smokers, when compared to non-smokers, are twice as likely to have STEMI, indicating a protombotic effect of smoking.[8]

Hypertension is an equally important risk factor in both genders and its frequency increases with age. The likelihood of developing changes on the CV system depends on the blood pressure values and the length of hypertension. The blood pressure values greater then 110/75 mmHg increase the risk for development of CVD in any age group.[9] The threshold for lower blood pressure level that does not increase the risk for CVD development has not been determined yet.[10-13] According to the CINDI research study, conducted in Republic of Srpska in 2002, hypertension prevalence was 47%.[14,15]

In contrast to hypertension and diabetes, hypercholesterolemia is asymptomatic and is discovered accidentally during routine laboratory analysis. Cardiovascular risk is accompanied with hyperlipidemia and smoking, especially among young people (<55 years in men and <65 years in women), when compared to older generations.[6] A 10% reduction in total cholesterol decreases the frequency of coronary artery disease approximately by 25% five years after, while lowering LDL by 1 mmol/l reduces the frequency of ACS by 20%.[16]

Diabetes mellitus and CVD are distinctly connected and are studied together. In the EURODIAB IDDM Complication study, which included 3250 respondents with diabetes mellitus type 1 from 16 European countries, the CVD prevalence was 9% in men and 10% in women; it also increased with age and the length of diabetes (6% in age group 15-29; up to 25% in age group 45-59).[10] Coronary disease risk is increased 2-3 times in men and 3-5 times in women with diabetes.[10,11]

Epidemics of increased body weight and obesity have strong negative influence on quality of life and is one of the most important current health problems. During the last two decades, the prevalence of overweight people in european countries have tripled. Weight that is higher than what is considered as healthy is present in almost 50% of adults, and one third of the European population is obese.16 According to our studies in 2002, the prevalance of overweight was 39.8% and obesity 17.7% (greater in women) among people.[14,15]

Physical activity is used to estimate the quality of health, while physical inactivity is considered to be an important risk factor for the development of disease. Studies have shown that weight greater than what is considered as healthy (BMI≥25) and physical inactivty (<3,5 h of excercise per week) in combination, could be responsible for 59% of premature deaths due to CVD.[17]According to the European guide for CVD prevention, healthy people should have 2,5-5 hours per week of physical activity or moderate intensity aerobic training.[18]

Some studies, such as the PROKAM study, confirmed the importance of positive family history as an independant risk factor in first generation relatives among men younger than 55 years of age and women younger than 65.[19,20] However, it is not yet determined to which extent a positive

family history is an independant risk factor and to which is dependent on other risk factors, such as hypertension, diabetes and hyperlipidemia.[21,22]

Aim of the Study

The aim of this study was to investigate the frequency of preventable and nonpreventable risk factors in patients with AMI in the Republic of Srpska.

Patients and Methods

A cross-sectional study included patients treated for acute myocardial infarction at the University Clinical Centre in Banja Luka, in the period from January 1st to December 31st, 2011. The first inclusion criterion was that the patients were residents of Banja Luka and Laktaši; the second was the written consent for participation in the research, which was obtained from patients.

Patients who had had positive laboratory markers for myocardial necrosis (e.g., troponin I), along with supportive evidence in the form of typical symptoms, suggestive electrocardiographic (ECG) changes, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, were diagnosed as having AMI at the University Clinical Centre of Banja Luka. The list of patients with AMI was obtained from the administrative office of the University Clinical Centre of Banja Luka.

Research instruments

Data were extracted from the patients' medical history and discharge letters, as well as from their electronic and paper records. The protocols at the Primary Care Centres were analysed, followed by telephone interviews carried out by the researchers. Furthermore, a special form that was related to each respondent was filled in.

The data on arterial hypertension, the value of total cholesterol, diabetes, increased body weight and obesity, smoking, positive family history, and physical inactivity were included in the retrospective analysis of the cardiovascular risk factors.

Arterial hypertension is high blood pressure with diastolic blood pressure measurements ≥ 90 mmHg and systolic ≥ 140 mmHg. Blood pressure values and therapy was recorded for each patient individually.

Cholesterol values, recorded during check-ups in the family medicine office before AMI had been developed, were obtained from patients' medical records. Cholesterol greater than 5 mmol/l was considered as an increased value.

Patients' medical records and discharge letters were used as a source of information on type of diabetes mellitus (I or II) and hyperglycemia. Two types of glucose values in blood were recorded: first, obtained during check-up if the patient did not have diabetes, or an average glucose value if the patient had diabetes; second, the glucose value when patient got accepted in coronary unit.

Patients' medical records (when information was available), discharge letters and direct interviews with the patient were used to obtain information about body mass index (BMI), smoking, and family history. Normal BMI was 18-24,9 kg/ m2; overweight was 25-29,9 kg/m2; and obesity was determined at BMI 30 kg/m2(obesity I, II, and III grade).

During conversation with the patients, the smoking history was obtained, whether or not the patient was a current, ex-smoker, or non-smoker. Positive family history included the presence of CVD in parents (father before 55 years of age and/or mother before 65 years of age).

Physically active patients were considered to have had moderate physical activity of 30 min on most days in a week (i.e. walking, gardening, house work) before hospitalisation.

Statical analysis

Data extracted from the secondary sources were entered in patient's study record and afterwards, in electronic form using Microsoft Excel 2010.

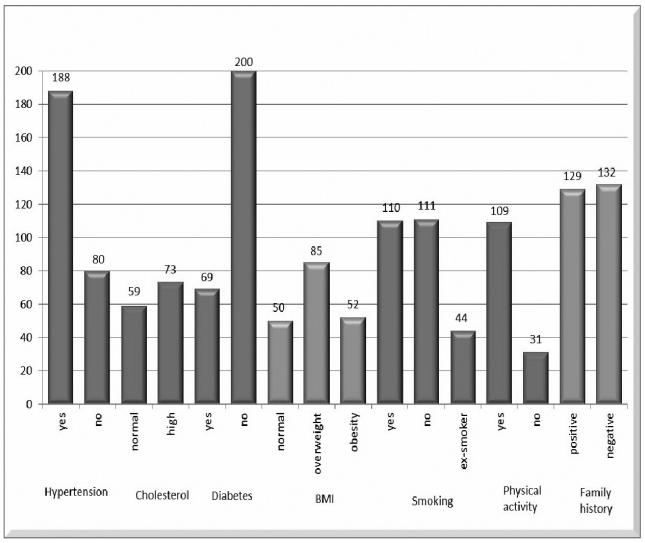
The data were analysed and presented using descriptive statistics (absolute and relative numbers, measures of central tendency, standard deviation) and appropriate statistical tests ($\chi 2$/test, Mann-Whitney U test, Fisher test) using SPSS analytical software. A probability level or p value less than 0.05 ($P<0.05$) was considered statistically significant.

Results

The study included 273 patients with AMI. The average age of the participants was 65,43±11,677 years. Using the Mann-Whitney U test (U = 5841,500; p = 0,000), the statistically significant difference was found between female (Md = 72,00; n = 97) and male gender (Md = 63,00; n = 176). Women with AMI in the study were approximately older than men.

The frequency of cardiovascular risk factors in patients with AMI is presented in Figure 1. Hypertension was the most common risk factor (70,1%). Diabetes mellitus, mainly type 2 (23%) was the least presented risk factor (25,6%). 58.1% of the respondents were current and ex-smokers. Positive family history was found in approximately 50% of the respondents.

FIGURE 1. Representation of risk factors among patients with AMI



The risk factors were evaluated according to sex and age. Using χ2 test, the statistically significant difference was found between the genders in smoking status (χ2=31.442;p=0,000) and the level of arterial blood pressure (χ2 = 7,151; p = 0,007) (Table 1). Compared to females, more frequently, men were smokers and had hypertension.

Systolic and diastolic blood pressure values were recorded during the first medical contact; the mean value was 146/90 mmHg.

Increased cholesterol levels were found in 73 examinees. There was no statistically significant difference between men and women in cholesterol level (χ2= 0.020; p = 0,887), as well as in BMI (U = 3846.000; z=-0. 083; p = 0.934; r = 0.006; p=0,131) (Table 1).

Men had diabetes more frequently (χ2=4.340;p=0,037) and were also more physically active than women (χ2=20.060; p=0,000). A statistically significant difference, regarding the positive family history between genders, was not found (Table 1).

Table 1. Distribu Distribution of risk factors according to gender

Risk factors		Gender			
		M	F	Total	p
Smoking, n (%)	Yes	84 (31,7)	26 (10)	110 (41,5)	**0,000**
	No	51 (19,2)	60 (22,7)	111 (41,9)	
	Ex-smoker	37 (14)	7 (2,6)	44 (16,6)	
Hypertension, n (%)	Yes	112 (41,8)	76 (28,4)	188 (70,1)	**0,007**
	No	62 (23,1)	18 (6,7)	80 (29,9)	
Total cholesterol, n (%)	Nomal	38 (28,8)	21 (16)	59 (44,7)	0,887
	Increased	49 (37,1)	24 (18,2)	73 (55,3)	
Body weight, n (%)	Nomal	29 (15,5)	21 (11,2)	50 (26,7)	0,131
	Overweight	63 (33,7)	22 (11,8)	85 (45,5)	
	Obesity	33 (17,6)	19 (10,2)	52 (27,9)	
BMI (mean, SD)		27,52(5,2)	27,93(3,9)	27,69(4,3)	0,934
Diabetes, n (%)	Yes	37 (13,8)	32 (11,9)	69 (25,7)	**0,037**
	No	137 (51)	63 (23,4)	200 (74,3)	
Physical activity, n (%)	Yes	89(63,6)	20(14,3)	109(77,9)	**0,000**
	No	12(8,6)	19(13,6)	31(22,1)	
Family history, n (%)	Yes	84(32,2)	45(17,2)	129(49,4)	1,000
	No	86(33)	46(17,6)	132(50,6)	

p<0,01 is significant and bolded

The mean value of glucose in blood before AMI was 6,45±2,15 mmol/l, while during the first medical contact, it was 12,68±6,87 mmol/l.

The respondents were classified into 4 age groups. The greatest number of the respondents (28,6%) was in the age group 65-74 years.

A statistically significant difference was found in presence of hypertension between different age groups (χ2= 31,721; p = 0,000). Increased blood pressure was most frequently found in the age group 65-74 years. Positive family history was most frequently found in the age group <64 years (χ2= 8.570, p = 0.036) (Table 2).

Table 2. Distribution of risk factors according to age

Risk factors		Age group				P
		<= 54	55 - 64	65 - 74	>= 75	
Smoking, n(%)	Yes	40(15,1)	36(13,6)	23(8,7)	11(4,2)	-
	No	7(2,6)	22(8,3)	38(14,3)	44(16,6)	
	Ex-smoker	3(1,1)	14(5,3)	15(5,7)	12(4,5)	
Hypertension, n(%)	Yes	20(7,5)	49(18,3)	61(22,8)	58(21,6)	**0,000**
	No	30(11,2)	23(8,6)	17(6,3)	80(29,9)	
Total cholesterol, n(%)	Nomal	13(9,8)	18(13,6)	16(12,1)	12(9,1)	0,546
	Icreased	15(11,4)	15(11,4)	25(18,9)	18(13,6)	
Diabetes, n(%)	Yes	3(1,1)	19(7,1)	22(8,2)	25(9,3)	-
	No	48(17,8)	53(19,7)	56(20,8)	43(16)	
Physical activity, n(%)	Yes	30(27,5)	36(33)	22(20,2)	21(19,3)	-
	No	4(3,7)	5(4,6)	9(8,3)	13(11,9)	
Family history, n(%)	Yes	33 (12,6)	38(14,6)	31(11,9)	27(10,3)	0,036
	No	18(6,9)	33(12,6)	42(16,1)	39(14,9)	

**p was not calculated for risk factors where n<5*

Discussion

In this study, it has been shown that the most frequent risk factors among patients with AMI are hypertension and smoking.

According to the WHO, Bosnia and Herzegovina, along with Serbia, belonged to the group of countries with the highest prevalence of tobacco smoking in Europe. Presently, Bosnia and Herzegovina is on the bottom of that ladder (below 20%), in contrast to Serbia where there has not been changes.[23] The highest prevalence of smoking among men in Europe is in Ukraine (62%) and among women in Serbia (27%).[24] In this study, we found that 58.1% of patients with AMI consumed or is still consuming tobacco. It was also found that smoking has a tendency to decline with age.

According to Braunwald[24], the four major changeable risk factors for CVD - smoking, obesity, increased blood pressure and high cholesterol, are more commonly found in Europe and Central Asia compared to other parts of the world. The above mentioned risk factors are also recognized in our country as important factors that greatly influence the development of CVD either individually or together. Besides these risk factors, family history, diabetes and physical inactivity are also important. In our study, the majority of respondents were male. It was found that women with AMI were, on average, nine years older than men, which was in agreement with other studies that showed that AMI was more frequently found among men than women, with the ratio 7:1 in the fourth and fifth decade; in the sixth one 1,5:1; in the seventh 1,5:1; while in the eighth decade, it was equally present among both sexes.[25] The CVD has been perceived as a man's disease and this stance dates from 2600 years B.C. in Eber's papyrus where is written: „If you found a man with cardiac discomfort, with pain in his arms, at the side of his heart, death is near."[26] With further advance in medicine, the perception about CVD has been changing toward a more favorable outcome. Presently, women are more likely to develop disease and die from not well known causes that are in connection with poor life standard, chronic stress and unchangeable hereditary factors. However, the studies have shown that women averagely develop their first AMI nine years later then men, which indicates high levels of risk factors in men at a younger age.[27]

Khot et all. showed that the prevalence of conventional risk factors, except for smoking, was higher among women than men (it has also been confirmed in the recent studies),[28] which is in contrast with our results.

The results of our study showed that men had hypertension more often as an individual risk factor; they were also smokers more frequently than women (three times more frequently smokers and five times more frequently ex-smokers), which is in accordance with the previously

mentioned study.

According to the recent data, hypertension is most frequently found among men in Croatia (50%), while among women in Bosnia and Herzegovina (45%).[24] In this study, it was determined that hypertension, as the most common risk factor, was present among 70.1% of patients with AMI, with the statistically significant difference between genders and different age groups.

In the studies ROSCOPS I, II and III, where patients with CHD were followed, the frequency of hypertension in Republic of Srpska was 74 %,81 % and 77 %.12,29 However, CHD was the major cause of death in patients with hypertension. According to the INTERHART study results, hyperlipidemia represents a 49% of attributable risk for development of the first stroke, while diabetes represents a 10% of attributable risk.[6]

In this study, the mean value of cholesterol, recorded earlier in patients, was 5,5 mmol/l. The mean age of the patients with normal cholesterol levels was 64 years, while in patients with increased cholesterol, it was 65 years. Compared to men, women were twice less likely to had had increased cholesterol levels.

One Belgian study in the public health institution showed that the prevalence of obesity was higher among women, while cigarette smoking was twice less frequent among obese and overweight patients with CHD, compared to patients with diabetes and CHD.[30]

Although obesity is a disease itself, and may, same as hypertension, influence the development and progression of many diseases, including CHD. According to some authors, the risk for CHD increases with an increase in BMI; respectively, high BMI is a strong predictor of fatal CHD.[31]

According to the body weight groups (WHO, 1997), patients in this study, either male or female, were mainly overweight. The median BMI value for women was 27.09 kg/m2, while for men, it was 26,85 kg/m2. Based on the fact that more than 50% of the respondents were overweight, it could be concluded that the increased body weight, together with obesity, was and still is an important risk factor for the development of CHD.

Almost 20% of patients with MI have diabetes, and it is expected that this number will continue to increase.[32] Diabetes mellitus in this study was found among 25.6% of patients with AMI, while 23% were patients with type 2 diabetes, which was equalised with CHD. While analysing this risk factor, it was found that almost the same number of men and women had diabetes (men insignificantly more); while twice more women and three and a half times more men did not have this risk factor. Two large clinical studies, Framingham and MRIFT, have showed that men with diabetes are twice more likely to develop CHD, while in women diabetes increases the risk for development of CHD three times more.[33,34]

In our study, data on physical activity showed that the respondents were physically active. Physical activity might be useful for secondary prevention of coronary disease, since continuous physical activity decreases mortality after MI.[35] The majority of patients had a positive family history and were younger than 65 years of age, while the patients older than 65 usually had a negative family history (it was taken with caution since older patients were not always aware of their family history).

Since risk factor control is very important for the prevention of CVD, the importance of prevention as the main concept of family medicine has to be emphasized among family medicine doctors in our country.

Conclusion

In this study, we have found that the majority of people developing AMI are older men across all institutions where the first medical help was first administered. Women with AMI are on average nine years older than men. The most frequent risk factors in the development of AMI in men are hypertension and smoking, while in women, it s only hypertension. Another important risk factor for the development of AMI is the increased body weight, regardless of sex. Out of four conventional risk factors for the development of AMI, diabetes is present least commonly. Since risk factors have great influence on the development of AMI, prevention must be emphasized, especially on the primary health care level.

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Učestalost faktora rizika kod bolesnika sa akutnim infarktom miokarda

SAŽETAK

Uvod: Djelovanjem različitih faktora rizika dolazi do nastanka akutnog infarkta miokarda kao najozbiljnijeg oblika ishemijske bolesti srca i glavnog uzroka iznenadne smrti širom svijeta.

Cilj rada: Cilj ove studije je bio procjena učestalosti promjenjivih i nepromjenjivih faktora rizika kod pacijenata sa akutnim infarktom miokarda u Republici Srpskoj.

Ispitanici i metode: Studija presjeka je uključivala pacijente sa područja opština Banja Luka i Laktaši, oboljele od akutnog infarkta miokarda, koji su liječeni na Klinici za kardivaskularne bolesti Univerzitetskog Kliničkog Centra Banja Luka u periodu od 1.1.2011. do 31.12.2011.godine. Analizirani su sljedeći faktori rizika: arterijska hipertenzija, vrijednost ukupnog holesterola, dijabetes melitus, prekomjerna tjelesna težina i gojaznost, pušenje, pozitivna porodična anamneza i fizička neaktivnost.

Rezultati: Od ukupno 273 pacijenta, većinu su činili muškarci(64%), a utvrđena je statistički značajna razlika između dobi ispitanika muškog i ženskog pola($p<0,01$). Najzastupljeniji faktor rizika kod oba pola je hipertenzija(70,1%), a najmanje prisutan faktor rizika je dijabetes melitus (25,6%). Pušači i bivši pušači su činili 58,1%, sa statističkom značajnošću između muškaraca i žena ($p<0,01$). Prosječan BMI kod oba pola je bio u kategoriji prekomjerne tjelesne težine (27,69 kg/m2). Pozitivna porodična anamneza je utvrđena kod gotovo polovine ispitanika (49,4%), sa statistički značajnom razlikom između starosnih grupa i porodične anamneze ($p = 0,036$).

Zaključak: Od akutnog infarkta miokarda uglavnom oboljevaju muškarci u 60-im godinama života, dok žene oboljevaju u prosjeku 9 godina kasnije nego muškarci. Broj jedan faktor rizika kod oba pola je hipertenzija. S obzirom na veliki uticaj faktora rizika na nastanak akutnog infarkta miokarda, prednost se mora dati prevenciji i kontroli istih, posebno na primarnom nivou zdravstvene zaštite.

Key words: akutni infarkt miokarda, faktor rizika, pacijent

SPECIAL ARTICLE

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Drug Induced Liver Injury: Pathogenesis, Clinical Features and Monitoring

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ABSTRACT

Introduction: Drug-induced liver injury (DILI) is a rare but potentially life threatening adverse drug reactions. DILI may mimic pathophysiology or histopathologic features of an acute or chronic liver disease, and they may be indistinguishable from those of other causes of liver injuries. Liver can be affected directly, in a dose-dependent manner, or idiosyncratically, independently of the dose, and therefore unpredictably developed.

Methods: In this special article we provided results given in the articles published in PubMed in the period 2006-2016. The search was made based on the most frequent reported drugs inducing liver injuries, diagnostic assessment, monitoring and outcomes of DILI.

Results: The true incidence of DILI still remains unknown but the incidence of up to 14 cases per 100,000 inhabitants/year has been most frequently reported. Antimicrobial agents, analgesics, hipolipemics and antiepileptics are the most common drugs causing DILI.

Conclusion: Although several biomarkers have been found through analytical tests, none of them have been able to display enough specificity and sensitivity in DILI diagnosis. Therefore, diagnostic assessment of DILI is still based on clinical examination, pharmacological treatment history, current RUCAM criteria, and liver function laboratory test.

Key words: drugs, hepatotoxicity, idiosyncrasies, pharmacogenetics, RUCAM criteria

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Introduction

Drug-induced liver injury (DILI) is defined as the damage caused by drug or herbal medications, leading to liver dysfunction, with or without the histopathological changes.1 According to the recently published prospective epidemiological study, the annual incidence of DILI was 13.9 cases/100,000 inhabitants in the period from 1997 to 2000 in France, 12/100 000 inhabitants in 2005-2007. in Korea, 19.1/100,000 inhabitants in 2010-2011 in Iceland, and 2.4 cases / 100,000 inhabitants in the one-year follow-up in the United Kingdom. Today, in Asian countries, herbal medicines used in traditional medicine represent a major cause of DILI (over 90 cases / 100,000 inhabitants/year).[1,2] Although DILI incidence is difficult to clearly determine due to many confusing (confounding) factors and under-reporting of adverse reactions to drugs (ADR), World Health Organization reports an increase in the incidence since 1990.[3]

Clinical forms of DILI

According to clinical, biochemical and histological characteristics, DILI can manifest in all forms of acute and chronic liver damage. Consequently, DILI may develop acute liver failure (ALF), acute hepatitis with and without jaundice, chronic hepatitis (rarely results in cirrhosis of the liver), or only as asymptomatic increase of liver enzymes. In a significant number of patients (25-30%), DILI is manifested in the form of immunoallergic drug reactions with the development of fever, rash and eosinophilia.[1-4] The aim of this review is to present the results of epidemiological, clinical and pre-clinical research, published in scientific publications cited in the database PubMed, in the period from 2006 to 2015. Publications are selected according to the following criteria: drugs that frequently cause DILIs, diagnostic criteria for causal assessment of DILI, monitoring the clinical status and laboratory parameters and outcomes of DILI. This review did not consider research related to DILI in children and those caused by herbal medicines and toxins.

Classification of DILI

Na Based on histopathological and pathophysiological outcomes of liver damage, DILIs are classified as hepatocellular, cholestatic and mixed.[5-7] This classification is of great importance as it contributes to prognosis and outcome of DILI. The classification based on patterns of laboratory changes in liver enzymes found in DILI was first proposed by the Council for International Organization of Medical Sciences, and modified by the Food Drug Administration (FDA)- Drug Hepatotoxicity Steering Committee.[5] Assessment of liver function is usually based on the activity of the enzyme alanine aminotransferase (ALT) and alkaline phosphatase (AP) that consist proposed biochemical DILI classification (Table 1).[5]

Tablr 1. Drug induced liver injuries based on liver enzymes laboratory findings [5]

Liver injury type	Laboratory calculation
Hepatocellular	ALT ≥ 3 x ULN i R = "(ALT/ULN)" /"(AP/ULN)" " ≥ 5"
	ALT ≤ 3 x ULN – non significant liver dysfunction.
Cholestatic	AP ≥ 2 x ULN i R = "ALT/ULN" /"AP/ULN" ≤ 2
	AP < 2 x ULN – non significant liver dysfunction.
Mixed	ALT ≥3 x ULN i AP ≥ 2 x ULN
	R = = "(ALT/ULN)" /"(AP/ULN)" >2 "i < 5" .

ULN-Upper limit of normal; R ration of liver enzymes values

Hepatocellular damage is associated with an increase in transaminases, which is usually normalize weeks after discontinuation of the drug. However, asymptomatic deterioration in liver function sometimes normalizes despite continued administration of the drug, and this phenomenon is called adaptation.[4-6] The phenomenon of adaptation was first observed in studies with isoniazid, when in 20-30% of treated patients, a moderate increase in transaminases occurred, which was later followed by decrease of these values to the reference levels, despite continued administration of the drug. It is assumed that the mechanism of adaptation includes "up and down" regulation of transport molecules and enzymes involved in drug metabolism, development of tolerance and finally, liver regeneration.[5,6] Clinically cholestatic liver damage caused by medications can manifest as fever, pain similar to acute biliary obstruction or chronic jaundice associated with itching. Regeneration of cholangiocytes is slower compared to hepatocytes, and recovery of cholestatic markers tends to decrease over the next 6-9 months.[6,8] One of the main indicators of prognosis of acute DILI is the presence of jaundice. Tests have shown that DILI associated with the increase of bilirubin levels greater than 3 times the upper reference value, in the absence of biliary obstruction and Gilbert's syndrome, is associated with an average mortality rate of about 10% (range 5-50% mortality).[4,5,9] This clinical and biochemical pattern is known as Hy's law, named after the Swiss scientist Hyman Zimmerman, who first determined this relation.[6,8] Additionally, the criteria according to Hy's law is accepted by the FDA as an indicator of serious toxicity and is used to assess drug safety in clinical trials.[6] However, more sensitive and specific indicators of liver damage are ALT> 8-10 x ULN (Upper Limit of Normal) or ALT> 3 x ULN associated with the level of bilirubin> 2 x ULN (modified Hy's Law).[5-8] In the combined DILI, there is a combination of acute hepatitis and cholestasis. It has been shown that drugs that cause cholestatic, can cause combined DILI and

vice versa.

The mechanism of drug hepatotoxicity

U Directly (intrinsic) and liver damage caused by idiosyncrasies are involved in the mechanism of drug hepatotoxicity involved.[10,11] Drugs that cause intrinsic DILI exhibit direct hepatotoxic effect as the active substance, or indirectly as a metabolite, and it is the most commonly dose-dependent e.g. paracetamol. Since the liver is the main organ for metabolism and detoxification of drugs, those that have significant hepatic metabolism usually cause DILIs. Reactions of idiosyncrasies can be immunological and non-immunological pathogenesis, often independent of the dose of administered drug. The immune-mediated (hypersensitivity) reactions idiosyncrasies are often associated with fever, skin rash, and eosinophilia, as well as presence of specific antibodies.[2,3] Additional sign-mediated immune response is rapid occurrence and more difficult recurrent clinic state, if the drug is re-administered.[5,11] Non-immunologically mediated idiosyncratic reactions are not usually associated with the above mentioned signs. Both, immunologically or non-immunologically mediated DILI are manifested in the form of hepatocellular or cholestatic/combined type.[6,7] The majority of clinically visible cholestatic hepatitis and combined/cholestatic reactions are associated with damage and inflammation of the bile ducts. It is assumed that a metabolite of the drug is subject to canalicular excretion, which expose epithelial cells of the bile ducts to direct toxic effects or immunologic sensitization of the metabolite.[7] Idiosyncrasies are associated with inflammation of liver tissue, while intrinsic DILI is characterized by fields of necrosis, and hepatocytes apoptosis of with minimal inflammation.[10]

Latency period to clinical manifested DILI

According to predictability, DILI can be classified as predictable and unpredictable. Predictable reactions caused by drugs appear relatively quickly after a short latency period (within a few days), dose-dependently (e.g. paracetamol), and as a result of direct action of the drug or indirectly of metabolites. Unpredictable reactions (idiosyncrasy to drugs) occur rarely, with various occurrences, sometimes with prolonged latent period (from one week to one year) and are not probably dose-dependent.[1, 2, 5, 11] However, cases of DILI several weeks (amoxicillin / clavulanate or trovafloxacin) or months after exposure to nitrofurantoin or ximelagatran have been described.[10]

The DILI outcome after discontinuation of TR causative hepatotoxic drug

Asymptomatic and mild degree DILI is usually fully recovered after discontinuation of the causative drug. After the suspension of hepatotoxic drugs, indicators of liver damage can persist for weeks or even up to one year in case of cholestatic DILI. However, it is known that decrease in transaminase levels may be indicative of the ALF, before the recovery of its functions, due to massive necrosis of hepatocytes. Poor prognostic indicators of DILI are presence of coagulopathy and encephalopathy.[4,11] Although patients with cholestatic DILI have a worse prognosis than patients with jaundice, which is not caused by the drug, most of them recover completely. Thus, it was shown that of 784 patients with cholestatic DILI associated with jaundice, 90.8% of them fully recovered, while 72 (9.2%) patients died or had undergone liver transplantation.[5,11] In addition, the results of several studies have shown that eosinophilic infiltration of the liver and eosinophils in peripheral blood were positive prognostic parameters that indicate a full recovery DILI.[11]

Risk factors for DILI

To date, factors that are responsible for the mechanism of hepatotoxicity, as well as the consequences of the complex interaction of the drug and the individual patient are recognized only for a few drugs or pharmacotherapeutic groups.[2] Sensitivity to the development of DILI is the result of the interaction of various factors such as age, sex, drug interactions with hepatotoxic potential, environmental factors (alcohol, low protein diet, toxins, environment and food), chronic liver disease, comorbidities, obesity and genetic predisposition. In general, the elderly and women showed greater sensitivity to the drug which causes liver damage, while children are more sensitive to valproic acid and erythromycin.[2,7-11] One research included cases with ALF, and showed that paracetamol often causes ALF particularly in women (74% of all cases of paracetamol-ALF), and the idiosyncracies (67%).[5] Risk factors such as malnutrition and alcohol consumption threaten liver function and promote the consumption of glutathione and potentiate the toxicity caused by paracetamol.[5-7] Pharmacogenetics development has shown that genetic polymorphisms of drug metabolic pathways are the most important determinant for the development of DILI.[12-14] Genetic polymorphism of N-acetyltransferase 2 and CYP (cytochrome) 2E1 are linked to predisposition for the development of hepatotoxicity of antituberculosis drugs, especially isoniazid.[12] Antiepileptic, valproate acid often causes DILI in children, probably because of the immaturity of CYP2C9, interactions with other antiepileptic drugs and the genetic polymorphism of mitochondrial DNA, which leads to the formation of reactive metabolites and mitochondrial damage in hepatocytes.[12] Hepatotoxicity of lipophilic statins in the elderly occurs as a result of a functional polymorphism of CYP3A4, decreased clearance and drug interactions with other inductors or CYP inhibitors.13 Diclofenac is the most common cause of DILI of all NSAIDs, which are associated with the genetic polymorphism of metabolizing enzymes CYP2C8, UDPGT 2B7, GST) and hepato-canalicular transporters (BSEP,

MRP2, MRP4) polymorphism of antioxidant enzymes and interactions at the level of cytochrome, creating a reactive metabolite, damaged antioxidant mechanism and reduced clearance of the drug.[12-14]

DILI caused by a combination of amoxicillin and clavulanic acid has been associated with certain human leukocyte antigen halotype (HLA), which contributes to the changed immune response to drug, then genetic polymorphism of canalicular transport molecules (ABCB4), which contributes to exposure of biliary tract to metabolites and development of cholestatic or combined liver damage.[5,12,14] SCL transporter polymorphism (OAT1PB1), which is responsible for the drug influx to enterocytes and hepatocytes, is associated with hepatotoxicity induced by methotrexate, statins, bosentan, rifampicin and troglitazone.

It is also known that structurally similar drugs can cause DILI, and that there is cross-reactivity and toxicity confirmed in DILI cases induced by different aromatic anticonvulsants (phenytoin, phenobarbital and carbamazepine), ACE inhibitors (captopril and enalapril), NSAIDs, and drugs of phenothiazine tricyclic antidepressants.[12-14]

Diagnostic assessment of the occurrence of DILI

The lack of objective diagnostic tests, or specific / sensitive biomarker for DILI, and various clinical manifestations are often the reason for late diagnosis of DILI.[9] In 2013, National Institute of Diabetes, kidney and digestive tract proposed the establishment of Drug-Induced Liver Injury Network (DILIN) as a system for registration, evaluation and diagnosis of drug hepatotoxicity, drugs in the daily practice and those in clinical trials. [9]

The key diagnostic elements for DILI, in addition to laboratory findings, belongs to the pharmacological anamnesis and evaluation of the following factors: start of DILI, clinical features, course of disease and recovery, risk factors, the exclusion of other diagnoses, as well as knowledge of the hepatotoxic potential of the drug. In addition, the most accurate diagnosis of DILI would be an exposure to a suspected drug, so called re-challenge and/or liver biopsy, although these are not always ethically justified procedures for patient safety nor DILI express typical histopathological findings.[9] In general, diagnosis of DILI is based on the evaluation of liver biochemical tests, including ALT and AP, additionally aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and bilirubin, and on that basis determine the biochemical classification of DILI.[9] The difference in ALT and AP expresses ratio (R), taking into account their ULN. R = ratio of ALT / AP ≥ 5 denotes hepatocellular injury, and the ratio R 2 denotes ≤ cholestatic injury, while R 2 and 5 are classified as DILI combined (Table 1).[5-8]

Preview of the drugs that commonly cause DILI

One of the earliest comprehensive studies of drugs that cause liver injury, causation and assessment of illness severity, was conducted in the international study (DILI Network Study), which analyzed the reported cases of DILI, in the three registers in Spain, Sweden and the United States, from 2004 to 2007.[15] The study included all patients (n = 1734) diagnosed with DILI based on clinical, biochemical findings and CIOMS/RUCAM criteria. There were 319 identified drugs with the highest probability for DILI, such as amoxicillin-clavulanic acid, flucloxacillin, erythromycin, diclofenac, sulfamethoxazole / trimethoprim, nitrofurantoin, isoniazid, combinations of antituberculotic drugs, and other drugs (Table 2).

Table 2. Comparison of 20 most frequent drugs causing DILI among three DILI registries (2004-2007) [15]

Drug	Total number of DILI reports	Spanish registry (n=650)	Swedish registry (n=784)	USA registry (n=300)
Amoxicillin / clavulanate	136	105	5	26
Flucloxacillin	129	-	129	-
Erythromycin	48	6	42	-
Diclophenac	38	16	19	3
Co-trimixazole	34	2	22	10
Isoniasid	31	11	7	13
Disulfiram	31	1	27	3
Ibuprofen	28	21	6	1
Carbamazepine	26	7	16	3
Nitrofurantoin	24	2	4	18
Paracetamol	24	12	2	10
Ticlopidine	20	13	7	-
Antituberculotics	19	19	-	-

Drug	Total number of DILI reports	Spanish registry (n=650)	Swedish registry (n=784)	USA registry (n=300)
Valporate	18	9	2	7
Ciprofloxacine	18	4	7	7
Halotan	17	2	15	-
Levofloxacine	15	5	-	10
Naproxen	14	2	12	-
Statins	11	10	-	1
Chlorpromazine	11	3	8	-

A significant percentage of identified hepatotoxic drugs (n = 265, 83.1%) was associated with at least one case of ALF. A prospective study of the same design was carried out in nine countries in Latin America, where the registers of DILI were established, in the period from 2011 to 2014.[16] Out of 250 diagnosed cases of DILI, the most frequent pharmacotherapeutic group identified as ethiological factors were antimicrobial agents, non-steroidal anti-inflammatory drugs (NSAIDs -diclophenac, ibuprofen and nimesulide) and sex hormones. However, somewhat different results were obtained in the analysis of DILI in Asia. In India, the antituberculotics were identified as the most common hepatotxins (58% of all DILI), then antiepileptics (11%), olanzapine (5%) and dapsone (5%).[17] In the retrospective study in Chinese hospitals of tertiary level in the four-year period, there were confirmed diagnosis of DILI in 361 hospitalized patients, with an overall mortality rate of 8:59% and the incidence of DILI 92.95/100,000 inhabitants. The most common type of DILI were hepatocellular (63.16%), cholestatic (13.85%) and the rest combined. Drugs and preparations that caused DILI were herbal preparations of traditional Chinese medicine (35.01% of patients with DILI), antithyreoid (14.4%, propylthiouracil, metamizole), antituberculosis drugs (14.13%, respectively, and combined), then antibiotics (quinolones, cephalosporins, vancomycin), cytostatics (cisplatin, gemcitabine, etoposide), immunosuppressants (methotrexate, leflunomide), and statins.

In the recent period, in hepatology are raised questions related to hepatotoxicity of many drugs, as there were given the different type and quality of published scientific data (case reports vs. series of cases), differences in data on hepatotoxicity in the instructions for use of the drug between Europe and the United States, and other reasons. Recently, a web portal LiverTox® has been set up, through which it is possible to access most recent, reliable data on the diagnosis, prevalence and disturbances of liver function, for all drugs registered in the United States.[18] The number of reported cases of drugs that cause DILI are divided into four categories: category A> 50 the total of known cases reported to the establishment of the web portal, B> 12 but <50 cases, C4> or <12, and D 1-3 confirmed cases of DILI, with additional fifth category T that refers to DILI caused by doses greater than therapeutic. According to the guidelines in LiverTox®, drugs categories A and B, especially drugs for which there is>100 reported cases of DILI, are undoubtedly hepatotoxicity drugs (antimicrobial drugs, NSAIDs, valproic acid, carbamazepine, phenytoin, statins, antispsyhotics-phenothiazines, oral contraceptives, amiodarone, interferon and anti-cancer drugs (methotrexate). [18]

Preview of drugs that cause a variety of clinical and biochemical forms of DILI

In the pathogenesis of DILI, the largest number of drugs hepatotoxicity is caused by non-immunological type, dose-dependent form of hepatocellular damage (Table 3).[5,6]

Table 3. Drug induced hepatocellular hepatitis, cholestatic and/or mixed DILI form[5]

Liver injury	Tip	Hepatotoxic drugs examples
Hepatocellular Hepatitis	Immunology mediated mechanism[a]	Alopurinol, diclophenac[b], dihydralazine, halotan, methyildopa, minocyclin, nevirapine, nitrofurantoin, phenitoine, propylthiouracil, trovafloxacin
	Non-immunology mediated mechanism[c]	Acarbosis, amiodarone, bosentan, dantrolen, diclophenac[b], disulfiram, phelbamate, flutamid, HAART treatment, statins, isoniasid, ketoconasole, labetalol, lephlunomide, methotrexate, nefazodon, nevirapine, nicotinic acid, paracetamol, pyrazinamide, rifampicin, tolcapone, troglitazone, valproate, ximelagatran, zafirlukast, zileutin
Cholestatic/ Mixed	Immunology mediated mechanism	ACE inhibitors, amytriptiline, amoxicilline/clavulanate, carbamazepin, chlorpromazine, co-trimoxasole, erythromycine, phenobarbital, sulphonamide, sulindak, other tricyclic antidepressants
	Non-immunology mediated mechanism	Anabolic steroids, azathioprine, cyclosporine, estrogen, oral contraceptives.

a) Characterized by fever, rash, eosinophilia or antibodies appearance; Rapid, positive response in different cases;

b) Diclophenac related reactions can be mediated by immune or non-immune mechanism;

c) Non-immune mediated reaction is related to fever, rash, eosinophilia or antibodies appearance; HAART= activated antiretroviral therapy.

DILI assessment criteria/ RUCAM scoring system

The formal criteria for assessment of causality and probability of DILI was ordered by CIOMS, designed in 1990 by a hepatologists from Europe and the United States.

Today, assessment of drug hepatotoxicity is based on so-called Roussel-Uclaf assessment method causes (Roussel-Uclaf causality assessment method - RUCAM), which is the scoring system with questions related to DILI. The system consists of seven criteria shown in Table 4.[15]

Table 4. CIOMS/RUCAM criteria in DILI assessment [15,19]

Liver injury type	Hepatocellular		Cholestatic/Mixed		Score
Time to onset	Initial challenge	Subsequnet challenge	Initial challenge	Subseq. challenge	/
Time from the beginning of the drug intake	5-90 days	1-15 days	5-90 days	1-90 days	2
	<5 ili >90 days	>15 days	<5 ili >90 days	>90 days	1
Time from the drug cessation	≤15 days	≤15 days	≤30 days	≤30 days	1
Risk factors	Alcohol		alcohol or pregnancy		1
	Age of patients ≥ 55 years		Age of patients ≥ 55 godina		1
Course of reaction	>50% improvement in 8 days		/		3
	>50% improvement in 30 days		>50% improvement in 180 days		2
	/		<50% improvement in 180 days		1
	No information or without improvement		No information or without improvement		0
	Worsening or improvement <50% in 30 days		/		1

Based on the collected points, causality and probability of DILI is categorized as highly probable (> 8), probable (6-8), possible (3-5), is unlikely (1- 2) or excluded (≤0). RUCAM system is verified using the re-challenge and DILI cases proved more sensitive (86%) and with higher specificity (89%) compared to other earlier criteria.[15,19]

Monitoring and preventive measures for the development of DILI

Almost all drugs that cause liver damage lead to an increase in ALT levels. The increase of ALT≤ 3xULN is associated with mild hepatic impairment, and it is also registered in placebo-controlled clinical trials (0.2-1%). Although ALT> 3xULN is considered to be a sensitive marker for liver damage, this value is not specific only for DILI. Significantly more sensitive predictors of liver failure are considered as ALT ≥10xULN, or elevated ALT and serum bilirubin of modified Hy's law. This finding suggests that the increase in serum bilirubin (except for Gilbert syndrome) indicates greater "attack" on liver or liver damage intense. FDA has proposed guidelines for the assessment of severe / serious degree of DILI as follows: ALT≥8 ULN, ALT ≥5 ULN for 2 weeks, ALT ≥3 ULN and serum bilirubin ≥2 ULN with prothrombin time-INR> 1:53 or symptoms of liver failure.[8,14] However, monitoring of ALT and serum bilirubin on a monthly basis, in the prevention of life-threatening DILI, has its limitations. Monthly monitoring of liver function would be the choice, in cases when doctors and patients will adhere to regular controls. As an example, it is interesting to cite the case of manufacturer's warnings about hepatotoxicity of troglitazone and necessity of ALT monitoring, after which it was found that only 33% of patients in the first month and 13% in the fifth month of treatment had done this test. Secondly, strict monitoring of liver function can lead to interruption of application of necessary and effective medication. It is important to note that severe DILI occur early and despite monitoring of liver function (eg. troglitazone). Therefore, "waiting for" increase in ALT> 3xULN sometimes causes too late reaction to prevent DILI.[8,14]

Recent approach in understanding the variability in response to treatment uses a combination of multivariate statistics (i.e. chemometrics) and metabolic profiling to predict metabolism and toxicity of a drug. It is also called metabolomics or pharmaco-metabolomics as it could identify, qualitatively and quantitatively analyze a set of metabolites in biological matrices involved in biochemical pathways (metabolome), and monitor the interaction

of genes and environment. The value of metabolomics is the possibility of discovering and determining biological markers as indicators, for example in the development of the disease, the effects and toxicity of the drug. In the last decade, intensive work has been done to discover metabolome which will be specific to hepatotoxicity or even DILI. Additionally, rapid detection of metabolites in biological fluids using nuclear magnetic resonance and mass spectrophotometry, as well as metabolomics will introduce the method in the early diagnosis and prognosis of DILI in the future.[20]

Conclusion

tDespite the large number of drugs with proven hepatotoxic potential and the development of diagnostic methods and criteria for assessing causal relationship and monitoring, definitive diagnosis of drug-induced liver injury is still a challenge and is an excluding diagnosis. In order to prevent DILI, it is suggested that doctors and pharmacists are educated about the safe drug use and identification of clinical symptoms of liver damage, risk factors, monitoring of liver function in the treatment with hepatotoxic drugs, updating instructions for use of medicines in terms of drug hepatotoxicity, continuous monitoring and reporting of adverse drug reactions.

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Lijekovima izazvana oštećenja jetre: patogeneza, kliničke karakteristike i monitoring

SAŽETAK

Uvod: Lijekovima izazvana oštećenja jetre (drug induced liver injury-DILI) su po učestalosti rijetke, ali potencijalno životno ugrožavajuće neželjene reakcije na lijekove. DILI, patofiziološki i histopatološki, se teško razlikuju od akutnih ili hroničnih oboljenja jetre izazvanih drugim etiološkim uzročnicima. Oštećenje jetre može nastati direktno, dejstvom aktivne supstance ili indirektno, preko metabolita, a najčešće je dozno-zavisno i predvidljivo, ili nepredvidljivo, nastalo reakcijom idiosinkrazije, imunološke i neimunološke patogeneze i najvjerovatnije nezavisno od doze primjenjenog lijeka.

Metode: U ovom specijalnom članku smo prikazali rezultate istraživanja o lijekovima koji najčešće izazivaju oštećenje jetre, dijagnostičke procjene, monitoring i ishode DILI, objavljene u publikacijama citiranim u naučnoj medicinskoj bazi MEDLINE/ PubMed, u periodu od 2006. do 2015. godine.

Rezultati: Incidenca DILI je u različitim regijama u svijetu i dalje nepoznata, ali se procjenjuje na 2-19 slučajeva/100.000 stanovnika/ godišnje u evropskim i američkim istraživanjima, odnosno preko 90 slučajeva/100.000 stanovnika/godišnje u azijskim zemljama. Antimikrobni lijekovi (amoksicilin/klavulonat, eritromicin, flukloksacilin, izoniazid), antiinflamatorni i analgo-antipiretici (diklofenak, paracetamol), hipolipemijski lijekovi (lipofilni statini) i različiti antiepileptici predstavljaju najčešće lijekove koji izazivaju oštećenje jetre.

Zaključak: Savremenim analitičkim postupcima do danas je otkriveno nekoliko pouzdanih biomarkera, iako nijedan nije dovoljno specifičan i senzitivan za DILI, tako da se dijagnostička i prognostička procjena DILI i dalje zasniva na kliničkoj i farmakološkoj anamnezi, važećim RUCAM kriterijima za DILI, te laboratorijskim nalazima jetrene funkcije.

Ključne riječi: lijekovi, hepatotoksičnost, idiosinkrazija, farmakogenetika, RUCAM kriterijumi

REVIEW ARTICLE

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Caesarean Section - before and now

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ABSTRACT

Introduction: Caesarean section (CS) is one of the most common obstetric surgeries and often it is the only method to save mother's life and life of the fetus in various pregnancy and delivery complications. Each obstetric surgery, especially CS, implies professional valuation of prognostic valid parameters, i.e. existence of an accurate indication. The aim of the paper is to get a retrospective review of Caesarean section, its evaluation in the sense of frequency, indications and risk for mother and fetus. Frequency of Caesarean section was analyzed retrospectively and it has been noted that it grew significantly in past decades, which could be recognized as a new trend in the world in almost all countries, especially in the last decade. According to information from the WHO for 2010, CS percentage is as follows: USA 30.3%, Cuba 35.6%, Italy 37.4% and Germany 27.8%.

In the first 6 months of 2006, at the Clinic of Gynecology and Obstetrics of the University Clinical Centre of the Republic of Srpska, CS percentage was 20.54%, whereas in the same period of 2016, CS percentage is 31.58%. Nowadays, the World Health Organization suggests adoption of classification per Robson in order to decrease the CS percentage down to between 15% and 25%. This surgery carries certain risks; maternal mortality is 2-4 times higher while morbidity is 5-10 times higher after Caesarean section in comparison to vaginal delivery. Caesarean section is connected to lower risk of fetal traumas and this is one of the essential reasons affecting the selection of Caesarean section over vaginal delivery. Thanks to the development of modern perinatology and surgery techniques as well as development of modern anesthesia, maternal morbidity, and especially mortality, is reduced to minimum.

Key wordsi: Caesarean section, incidence, indications, vaginal delivery.

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Introduction

Caesarean section (CS) is one of the most common obstetric surgeries, where we use cut through mother's abdominal wall and uterus to extract fetus, most often in late stages of pregnancy when there is a possibility for the fetus to survive, and it is often the only method to save mother's life in various pregnancy and delivery complications. Each obstetric surgery, especially CS, implies professional valuation of prognostic valid parameters, i.e. existence of an accurate indication. Surgery is performed with the aim of avoiding or removing supposed or diagnosed pathological state resulting from pregnancy or delivery. Caesarean section was and, undoubtedly, still is one of the most important obstetric surgeries, which, in certain situations, saves lives of mother or fetus, or both mother and fetus.[1]

Caesarean section incidence

The frequency of this obstetric surgery has grown extremely in the past decades, which could be recognized as a new trend in the world in almost all countries, especially in the last decade.

The percentage of CS in Great Britain grew from 12% to 29% during the period from 1990 to 2008. According to

information from the WHO for 2010, CS percentage is as follows: USA 30.3%,Cuba 35.6%, Italy 37.4%, Germany 27.8%, Spain 25% and France 18.8%. In 1973, the percentage of CS in Sweden was 5%, while in 1990 it was 10.84%, and it is one of rare countries, along with Norway (16.3%), where growing trend of the CS percentage is not significantly increased.[2] Lately, increase of CS has been noted in the country with the largest population, China, as high as 50%. There is an extremely high CS percentage noted in Brazil, 50.1%, whereas in some private clinics it goes up to 85%. In Serbia, in 2010, the CS percentage was 24.3% and it has been constantly growing in the last two years and, and according to incomplete data, it is about 35%.[3] According to the report by the WHO, about 18.5 million Caesarean sections are performed in the world. In 50.4% of the countries, CS percentage is over 15%. WHO recommends that CS percentage is to be between 15 and 25% and that higher percentage has no justified grounds since it does not lead to a decrease in total perinatal mortality. It is necessary to calculate and find optimal model of expected CS percentage at the level of national obstetrician associations.[2]

The incidence of Caesarean section (CS) and Apgar score (A/S) of the Caesarean section for the first 6 months of 2006 and the first 6 months of 2016 were analyzed at the Clinic of Gynecology and Obstetrics of the University Clinical Centre of the Republic of Srpska.

As for the first 6 months of 2006, CS percentage was 20.54%, and in 2016, it was 31.58%. Analyzing Apgar score at birth for CS, in first half of the year 2016, the percentage of children with lower Apgar score (1-3) is smaller (2.7%) in comparison with the year 2006, when it was 3.2%. Apgar score from 4 to 7 was found in 13.8% children in the first half of the year 2006, and in 2016, there were 6.9% children delivered by Caesarean section. (Table 1)

2016. godine 6,9% djece rođene carskim rezom. (Tabela 1)

Table 1. The incidence of Caesarean section and Apgar score at the Clinic of Gynecology and Obstetrics of the University Clinical Centre Banja Luka for the period from 1.1.2006 to 30.6. 2006 and from 1.1.2016 to 30.6.2016

Year	1.1.2006.-30.6.2006.	1.1.2016-30.6.2016
Total number of deliveries	1329	1545
Caesarean section (CS) %	273 (20,5%)	488 (31,6%)
Apgar Scor at birth (CS) 1-3	9 (3,2%)	13 (2,7%)
Apgar Scor at birth (CS) 4-7	36 (13,8%)	34 (6,96%)
Apgar Scor at birth (CS) 8-10	228 (83,5%)	441 (90,3%)

Significant increase of number of Caesarean sections, both primary and repetitive (iterative), is a trend in the world[4-8], and reasons for this are not quite understandable. Some explanations could be summarized as follows:

- There is a growing number of primiparas and they are exposed to increased risk for Caesarean section.
- A woman delivers at late age nowadays, and, especially if it is primipara, then a woman is under an increased risk for CS.
- Increase of CS is directly connected to ever growing use of electronic fetal monitoring in modern times compared to fetal auscultation earlier, and more current discovering of fetal distress.
- Most of deliveries by pelvic presentation are performed by CS as prevention from fetal injuries.
- Delivery by vacuum and forceps is in decline in the world, which is one of the reasons for the increase of CS.
- There is an increase in induced deliveries,which statistically have higher CS percentage.
- There is an increase in obese people, hence pregnant women – obesity is modern times disease and increases risk for CS.
- Development of modern neonatology brings increase in abortions with preeclampsia, being final and permanent solution for mother or for fetus or for both, and is one of causes of CS increase in the world and of iatrogenic prematurity.
- There is an increase of planned (elective) CS due to new–non-obstetric indications (eye indications, various mother's chronic diseases, premature delivery, Caesarean section desired by mother, previous Caesarean section-one or more, fear from delivery pain and delivery outcome, forensic medicine aspect of delivery outcome –fear for mother and fetus risk).

Caesarean section indications

Caesarean section is obstetric surgery saving the health and lives of mothers and children, which justifies this surgery in the majority of indications. In our region, Caesarean section is performed on medically justified indications. There are several accepted classifications, and the most accepted is the one for absolute, relative and extended Caesarean section indications. Nowadays, the World Health Organization (WHO) suggests adoption of Robson classification in order to decrease CD percentage down to between 15% and 25%.[5]

According to Robson classification, pregnant women are classified in 10 groups. Pregnancy characteristics used in this classification are as follows: singleton or multiple pregnancies, nulliparous, multiparous, or multiparous with previous CS, head precedence, pelvic presentation or other abnormal mal-presentations, spontaneous or induced delivery, due or preterm delivery. Studies conducted so far have shown that more than 85% of all Caesarean section indications are: previous Caesarean section, fetal distress, distortion and abnormal fetal presentation.[4]

Wide use of cardiotocography have increased frequency of Caesarean sections due to earlier and more frequent discovery of fetal distress compared to the period of periodic auscultation of fetal heart tones. Pelvic presentation has significantly increased as CS indication, being the consequence of obstetrician's inexperience, lack of patience and pressure of wider social community.

The percentage of Caesarean section with pelvic presentation in 1970 was 11.6%, whereas in 1978, it grew to 60.1%.Twin pregnancy has extremely increased as indication for Caesarean section in the world and in our country. According to the literature data (ACOG) for 1995, Caesarean section percentage with twin pregnancy was 53%, and in 2008, it was 75% (even in head precedence it increased from 45% to 68%.6-10). Increase of Caesarean section with twin pregnancies is also a consequence of a large number of pregnancies with in vitro fertilization pregnancies and sterility treatment, increased number of complications following twin pregnancy, delivery at later age, higher percentage of preterm delivery and pelvic presentation, as well as obstetrician's fear from possible complications at delivery since these are "two fetuses".

The highest trend of CS increase has lately been noted with the following: condition after CS, preterm delivery, pelvic presentation, twin pregnancy, diabetes mellitus and post term pregnancy. Study by Brennan from 2009, which analyzed 47402 Caesarean sections from 9 world centers, has come to the conclusion that there is an increase of the condition after CS as an indication from 51.4% to 80.79%, nulliparous pelvic presentation from 69.9% to 98.6%, twin pregnancy from 34.7% to 74.6%, preterm delivery from 22.2% to 46.6%.7 Following are the reasons: decreased risk from fetal injuries, fear of pain and uncertainty, protection of pelvic bottom muscles. What is certain is that planned CS upon mother's request should not be performed before 39th gestation week and without a proof of fetal lung maturity. Study by the American College of Obstetrics and Gynecologists from 2013 showed no significant difference in the outcome of planned vaginal delivery and planned CS upon mother's request.[4]

Caesarean delivery risks

Risks and complications of Caesarean section refer to mother and fetus. It is necessary to provide informed consent from mother with previously detailed explanation of pros and cons of the surgery intervention itself, which is applied with all surgery interventions nowadays. Generally, CS has higher percentage of surgery complications by mother for current and all the upcoming pregnancies compared to the vaginal delivery, and smaller degree of perennial injuries and disturbances of pelvic floor.[4]

Maternal mortality and morbidity

This operation is also followed by certain risks; maternal mortality was 2-4 times higher, and morbidity 5-10 times after Caesarean section in comparison to vaginal delivery. 1Thanks to the development of modern perinatology and surgery techniques as well as development of modern anesthesia, maternal morbidity, and mortality in special, has been reduced to minimum. Incidence of maternal mortality in developed countries of the world (USA) amounts to 13.3 for 100 000 and with vaginal delivery it amounts to 3.6 for 100 000, whereas total maternal mortality amounts to 2.7%.8 In Guise meta analysis from 2010, mother's death was reported 13 times for 100 000 repeated elective CS compared to mortality of 4 for 100 000 CS in trying vaginal delivery preceded by CS.4 In the study conducted in Canada during the period from 1991 to 2005, frequency of maternal complications is also significantly higher compared to vaginal delivery, where percentage of all listed complications in CS is obvious in comparison to vaginal delivery (Table 2).[9]

Table 2. Complications of Caesarean section and vaginal delivery

Complications	Caesarean section n-46766	Vaginal delivery n-2 292 420
Global morbidity	2,73%	0,9%
Hysterectomy	0,09%	0,01%
Infection	0,60%	0,21%
Venous thromboembolisms	0,06%	0,03%
Early hematoma	1,3%	0,27%
Cardiac arrest	0,19%	0,04%
Anaesthetic complications	0,53%	0,21 %

Study by Villar and associates from 2010 reported double higher number of maternal morbidity with CS compared to vaginal delivery.4 Generally, all CS complications are more common in conditions after one or more Caesarean sections, performed in line with study by Marschal from 2011 and Silver from 2006.[4]

This conditioned the increase of attempts for probe vaginal delivery preceded by CS. To make the best decision about the way of delivery after one precedent Caesarean section,

we need an exact risk evaluation and benefit from each delivery method. Special attention is paid to evaluation of scar quality of the previously performed Caesarean section, done by ultrasound, which decreases a risk of uterus rupture, being one of the most difficult complications. At the conference held in 2010, the National Institutes of Health tried to make consensus on long-term and short-term benefits and side outcomes with trying probe vaginal delivery preceded by CS and vaginal delivery itself preceded by CS.[10]

Fetal morbidity and mortality

Caesarean section is connected to lower risk of fetal traumas and this is one of the essential reasons affecting the selection of Caesarean section over vaginal delivery. In Caesarean section, we have significantly lower percentage of fetal injuries and lethal outcomes, but also a higher number of respiratory disturbances compared to vaginal delivery. The most common complications are skin injuries– skin lacerations, clavicle fracture, injury of plexus brachialis and skull fracture as well as facial nerve paralysis. Although risks for physical injuries are lower in Caesarean section, analyses showed that it did not significantly affect neurological development of an infant. Incidence of neonatal convulsions and cerebral paralysis has not been significantly decreased, according to study by Muller from 2008, although the CS rate has significantly increased.[4] Neonatal depressions are more common due to general anesthesia, respiratory distress with term children, and transitory tachypnea of newborn and fetus injuries during surgery. Simultaneously with CS increase trend in the world, there is a trend of diseases such as autoimmune, allergic (asthma, allergic rhinitis, atopic dermatitis), diabetes mellitus type1 and multiple sclerosis. It has been noted that nowadays these diseases have been more frequent in highly developed countries. This, exactly, was a base for development of several theories suggesting that environmental factors, excessively clean environment could affect occurrence of these diseases in early childhood, which has been confirmed by a large number of epidemiological studies. Studies by Bager from 2008 and Decker from 2011 suggest that children born in Caesarean delivery have an increased risk for development of disease in later life such as: allergic diseases, diabetes mellitus type 1, celiac disease, with assumption that this increased risk could be a consequence of a lack of contact with maternal vaginal and intestinal flora at birth, which could affect delivery and formation of their immune system.[11,12]

Cesarean delivery techniques

It is known that surgery techniques vary and depend on surgeon, and, in our clinical work, we are governed by already learned operative technique. Decrease of morbidity is greatly affected by the knowledge of basic surgery principles and use of acknowledged surgery methods. There is a trend in the world in the development of surgery techniques of Caesarean section both as for incision on skin and opening and closing cut on uterus.

Conclusion

Making decision on surgery completion of delivery regardless gestation has to be supported by valid and accurate indications, good preparation of patient and the team performing it, as well as multidisciplinary cooperation, just before, during and after surgery-Caesarean section. In the Republic of Srpska and surrounding regions there is a trend of increased Caesarean deliveries which did not provide expected decrease of total perinatal mortality. Although CS is a relatively safe surgery, we should never forget we are talking about a very serious surgical procedure.

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Carski rez – prije i sada

SAŽETAK

Carski rez (CS) predstavlja jednu od najčešćih akušerskih operacija i često je jedina metoda kojom se može spasiti život majke i ploda kod raznih komplikacija trudnoće i porođaja. Svaka akušerska operacija, a pogotovo CS, podrazumijeva stručno vrednovanje prognostičkih validnih parametara, odnosno postojanje tačne indikacije. Cilj rada je da se retrospektivno sagleda carski rez, njegova evaluacija u pogledu učestalosti, indikacija i rizika po majku i plod. Retrospektivno je analizirana učestalost carskog reza i uočeno je da je u posljednjim decenijama u velikom porastu, što se može nazvati novijim trendom u svijetu u skoro svim državama, a naročito u posljednjih deset godina. Prema podacima SZO za 2010. godinu, procenat CS u navedenim zemljama je: SAD 30,3%, Kuba 35,6%, Italija 37,4%, Njemačka 27,8%. Na Klinici za ginekologiju i akušerstvo UKC RS, u prvih 6 mjeseci 2006. godine, procenat CS iznosio je 20,54%, dok u istom periodu 2016. godine procenat SC iznosi 31,58%. Danas Svjetska zdravstvena organizacija predlaže usvajanje klasifikacije po Robsonu, kako bi se procenat CS smanjio između 15% i 25%. Ova operacija nosi i određene rizike; maternalni mortalitet je 2-4 puta veći, dok je morbiditet 5-10 puta veći poslije carskog reza u poređenju sa vaginalnim porođajem. Carski rez je povezan sa nižim rizikom od fetalnih trauma i to je jedan od ključnih razloga koji utiču na izbor za carski rez u odnosu na vaginalni porođaj. Zahvaljujući razvoju savremene perinatologije i operativnih tehnika, kao i razvoju savremene anestezije, maternalni morbiditet, a pogotovo mortalitet, je sveden na minimum.

Ključne riječi: carski rez, incidencija, indikacije, vaginalni porođaj.

CASE REPORT

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Acute Pancreatitis in Pregnancy

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ABSTRACT

Introduction: Acute pancreatitis in pregnancy is usually diagnosed in the third trimester. The most common etiology factors are cholelithiasa and choledocholithiasa. The most severe consequence is perinatal and maternal mortality. The lethal outcome is largely reduced due to the widespread use of the following: contemporary diagnostics (ultrasound, magnetic resonance imaging, endoscopy and laparoscopy) and multidisciplinary approach to problem solving.

Key words: acute pancreatitis, pregnancy

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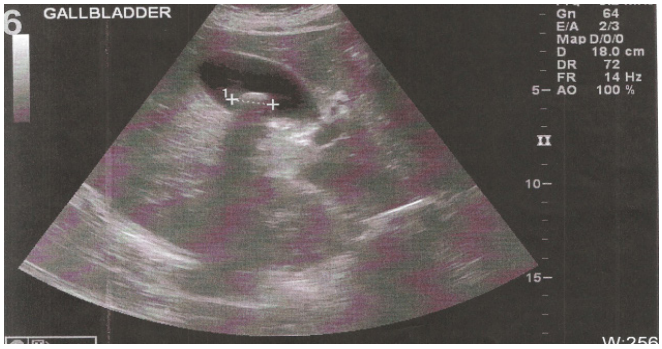
Introduction

Acute pancreatitis in pregnancy is not an uncommon problem. Annual incidence is from 5 to 80 per 100.000 citizens. However, during pregnancy it varies and ranges from 1 in 1.000 to 1 in 10.000 pregnant women.[1-3] More than 50% of cases are diagnosed in the third trimester of pregnancy. The most common cause of acute pancreatitis in pregnancy is gallstones.[1]

Case report

A pregnant woman in the 34th/35th week of pregnancy, age 33, was hospitalized at the Clinic of Gynecology and Obstetrics in Banja Luka on the 6th of September 2015 due to the abdominal pain. Aware, afebrile, subicteric, TA=110/80mmHg, f=120/min., pale. She normally felt fetus movements. Obstetric result: Gestational age 34|35 NG, PVU disappeared, dilation 3-4 cm, edges of medium thickness, medium elastic, fetal membranes whole, the head of the fetus in the forefront, loosely fixed above the pelvic inlet, did not feel contractions, FSF (+) positive, CTG attached. Examined by an abdominal surgeon and moved to the Clinic of General and Abdominal Surgery. In the laboratory: pancreatic amylase=2664U/L, Ca=2.09 mmol/L, total bilirubin=63μmol/L., direct bilirubin=58.7, hemoglobin=88g/L. Ultrasonically, distinctly distended gallbladder, wall thickened with visible intraluminal calculi and suspected calculi in the cystic duct. (Picture 1.)

Picture 1. **The ultrasound findings of the gallbladder with clearly identifiable intraluminal stone**



RTG pulmo was clean. On September, 6th 2015, in agreement with the attending gynecologist, a surgical procedure was indicated. In the introduction of anesthesia TA=140/80 mmHg, f=130/min. The patient was introduced into a general endotracheal anesthesia (OEA), according to the protocol for obstetric anesthesia. The patient was intubated and put on controlled mechanical ventilation with a mixture of gases 02, Nitrogen oxide (N2O) and Sevorane. Relaxation was continued with Tracrium. After laparotomy, Dorfler's variant of the section

was performed. Live premature male child 2720g/48cm was born, AS 9/9, accompanied by a neonatologist and a midwife and relocated to the Department of Pediatrics. After the childbirth, anesthesia was continued with opioid analgesic, fentanyl in a dose of 400mcg (8 ml). During OEA, the patient was profusely rehydrated (4500ml 0.9% NaCl), TA around 140/85mmHg, ventilation parameters: VT=560ml, fr.12|minute, SpO2=100%, diuresis after the end of surgery - 100ml. After the delivery, cholecystectomy was performed. Choledochotomy with T drainage was done after the dilation of the papilla of Vater. Due to the low hemoglobin, blood products were transfused. Postoperative treatment was continued in JILa (three days, from September, 6th to September, 9th 2015). Upon the reception to the Intense Care Unit: hemodynamicly unstable, hypotensive (TA=90/65mmHg), tachycardia, fr.=120/min. During the treatment in intensive care, 13500ml of crystalloid solution was given, diuresis during 24 hours was on average of 1500 ml, respiratory condition was stable, SpO2=97%. Laboratory biochemical findings were as follows: September, 6th 2015: E=3.7 HGB=86 HCT=0.27 L=13.3, Platelets=29 and 24 in the repeated report. Amylase in serum=2664, Amylase in urine 234, total bilirubin=63.7 Direct bilirubin=58.3. Correction of CSF was done, treated with: red blood cell concentrate erythrocytes in a dosage of 330 ml, re-suspended erythrocytes in a dosage of 380ml, a 240ml dose of SSP, platelets in an amount of 7 doses. On September, 7th 2015 Albumins=22, K=2.8, Ca=1.6 (total). The patients was given 80mEq 7.4% KCl, 20ml $MgSO_4$, 5 ampoules Ca-gluconate (50 ml), 100 ml of 20% albumin. Losses through drains: abdominal=400ml, T-drain=200ml. On the second postoperative day, the patient was gynecologically checked and Bromergin was introduced to therapy. The postoperative course was normal. In laboratories, on September, 16th 2015, it was observed that the pancreatic amylase 109 U/L and lipase 179 U/L declined. Hemoglobin was 96g/L. On September, 17th 2015, the patient with clement T drain was relocated to the Clinic of Gynecology and Obstetrics, where the treatment was completed. With good general condition, the patient was discharged with further recommendations on treatments and checkups.

Discussion

Acute pancreatitis (AP) in pregnancy is usually related to gallstones, which makes more than 70% of all cases of pancreatitis in pregnancy.[1] Hypertriglyceridemia in the third trimester of pregnancy is a more common cause of acute pancreatitis than gallstones.[2] AP in pregnancy can be associated with HELLP syndrome or preeclampsia, leading to high mortality of the fetus or premature birth.[3] Other causes include medications containing metformin and sitagliptin.[4] Diabetes mellitus type 2 increases the risk of acute pancreatitis 2.8 times.[5] Due to physiological changes, pregnancy itself contributes to the development of AP. Hyperthyroidism, connective tissue diseases, infections and trauma are other rare causes of acute pancreatitis. However, the primary diseases are absent in most cases (57.89%).[6] AP in pregnancy is difficult to diagnose in the first trimester compared to the third trimester. The most common clinical symptomatology are abdominal pain (89.47%) and emesis (68.42%).[3] When assessing patients with AP these four questions should be answered:

1. Does the patient has acute pancreatitis?
2. If there is an acute pancreatitis, which form? The seriousness (whether it is mild or severe form of acute pancreatitis)?
3. Is there a biliary etiology?
4. Which trimester of pregnancy is it?

This last question will determine the selection of diagnostics and therapy regimen.[7] Ultrasound diagnosis is safe and inexpensive, but it has a low diagnostic value for the AP. Cholangiopancreatography (MRCP) without contrast is another diagnostic method and has over 90% sensitivity. A mild form of acute pancreatitis (MAP), as the most common, is usually treated in the first week and runs without complication. Severe acute pancreatitis (SAP) is defined by a dysfunction of the pancreas, which lasts longer than 48 hours.[8]MAP is mainly treated conservatively.[1] The treatment consists of restoring fluid, oxygen support, analgesics, and the cessation of food intake to suppress exocrine pancreatic function, which prevents its autodigestion.[9] The treatment of acute pancreatitis due to gallstones and gallbladder disease during pregnancy depends on gestational age, presence or absence of choledohal diletation, the presence of cholangitis and severity of acute pancreatitis.[1] Indications for surgical treatment are: obstructive jaundice, acute cholecystitis resistant to treatment and peritonitis.[1] In MAP, enteral nutrition is not necessary and fat-free diet can begin within 3-5 days.[10] In SAP, enteral nutrition should be carried through nasojejunal probe. Prophylactic use of antibiotics in acute pancreatitis is controversial.[11] Meta analyzes have shown that antibiotic prophylaxis does not reduce mortality nor it reduces the incidence of surgical interventions.[11] Prognosis for mild forms of acute pancreatitis (MAP) is excellent without adverse effects on the fetus or the mother. In 2009, no cases of perinatal mortality have been reported in 73 patients with acute pancreatitis in pregnancy during the second and third trimester of pregnancy, and all babies were born full term.[10] Despite the abovementioned, fetal risks in AP during pregnancy, including preterm delivery and intrauterine fetal death, still exist.[1]

Conclusion

The incidence of acute pancreatitis (AP) in pregnancy varies and ranges from 1 in 1.000 to 1 in 10.000 pregnant

women. More than 50% of cases are diagnosed in the third trimester of pregnancy. The most common cause of AP in pregnancy is gallstones. Given the course of the disease, there is a mild and severe form of acute pancreatitis. The selection of diagnostic and treatment regimen determines the trimester of pregnancy (gestational age). Conservative treatment of mild forms of acute pancreatitis in pregnant women is the first method of treatment, especially if the fetus is not in full maturity. Conservative treatment, which replaced the earlier position on the surgical treatment, as the first method of treatment may be associated with reduced mortality compared to the previous period. Treatment of acute pancreatitis due to gallstones and gallbladder disease in pregnancy depends on gestational age, presence or absence of choledohal diletation, the presence of cholangitis and severity of acute pancreatitis. Indications for surgical treatment are: obstructive jaundice, acute cholecystitis resistant to treatment and peritonitis. In our case, given the progress of the pregnancy and fetal maturity, it was decided to perform a Caesarean section (Sectio Cesare) and surgically treat the disease (Laparatomia mediana expl., Holecystectomio,Holedochotomiom cum T-drainagae,Dilatatio papilae Vaterii).

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Akutni pankreatitis u trudnoći

SAŽETAK

Uvod: Acute Akutni pankreatitis (AP) u trudnoći se najčešće dijagnostikuje u trećem trimestru. Najčešći etiološki faktori su kolestaza i koledokoltijaza. Najteža posljedica je letalni ishod po majku i dijete. Letalni ishod je u velikoj mjeri smanjen upotrebom: savremene dijagnostike (ultrazvuk, magnetna rezonanca, endoskopija, laparoskopija), ranim započinjanjem terapije i multidisciplinarnim pristupom rješavanju problema.

Ključne riječi: akutni pankreatitis, trudnoća

CASE REPORT

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Tibial Intercondylar Eminence Fracture

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ABSTRACT

Introduction: Tibial intercondylar eminence fractures are uncommon injuries, occurring mainly in adolescents and young adults. When necessary, regardless of patient age, anatomic reduction and stable internal fixation are mandatory for fracture healing and accurate restoration of normal knee biomechanics. There are various arthroscopically assisted fixation methods (sutures, anchors, wires, or screws). We present a case, in which we reduced the fracture using fiber wire suture, fixing it with EndoButton® on the medial tibial tuberosity, with a clinical and radiological follow-up of three months.

Key Words: tibial intercondylar eminence fracture, anterior avulsion, Endobutton®, knee arthroscopy.

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Introduction

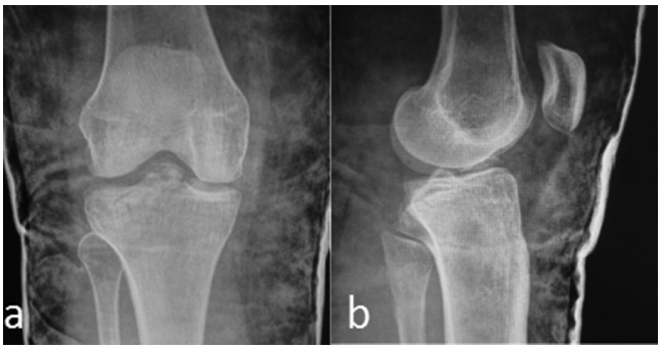
Tibial intercondylar eminence fractures, characterized by fractures at the insertion site of the anterior cruciate ligament (ACL) on the tibia, lead to joint dysfunction. These injuries are rare, affecting only three in every 100,000;

These injuries are commonly seen in children age between 8-13 years and are usually sport related injury, occurring especially during skiing or cycling. These injuries are correlated to high energy trauma, such as road traffic accidence. The anterior tibial spine is injured ten times more frequently than the posterior tibial insertion.[3] In 1959, Meyers and McKeever[4] proposed a classification system for these fractures as follows: type I fractures are not displaced; type II, angular elevation of the anterior portion with full posterior hinging, resembling a "bird- beak"; and type III fractures are completely displaced. Later, Zaricznyj[5] added type IV - complete multifragmental fracture. Fractures of the intercondylar eminence are more thoroughly described in the paediatric orthopaedic literature and occur at lower frequency in adults. Optimal treatment methods remain controversial and are varied by classification type, surgeon preference, and patient age. Furthermore, the evolution of arthroscopic techniques and the possibility of extension loss after conservative treatment of type II fractures have increased the tendency toward operative treatment of these fractures. Unfortunately, the bibliography on this subject is quite limited.

Case report

We described a 28-year-old woman who fell in a hole with direct trauma to her right knee. She was initially admitted to the emergency service, where the initial radiographs were obtained (Fig.1a-b). They showed a tibial avulsion fracture of the anterior and cruciate ligament.

Figure 1. Tibial intercondylar eminence fracture(a) with LCA dysfunction(b)



Upon the admission, clinical examination showed the Tegner–Lysholm skore of 35 points. The knee was painful, effusion ++/4, Lachmann ++, anterior drawer + and posterior drawer ++, and was negative for varus and valgus stress. Computed tomography (Fig.2a-b) was requested. The diagnosis was confirmed and the avulsion was classified as Meyers and McKeever type III.

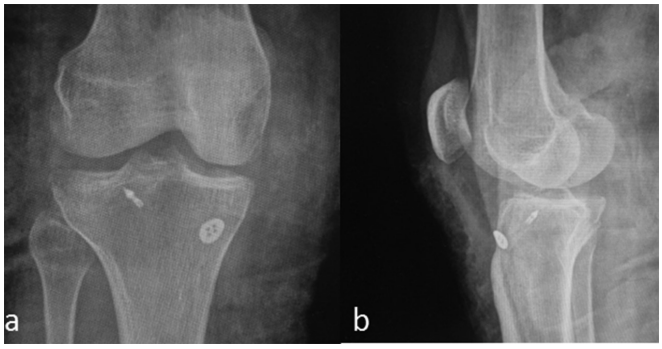
Figure 2. Computed tomography confirmed the tibial intercondylar eminence fracture



Afterwards, the decision was made to conduct a surgery treatment.

The patient was positioned supine with a thigh tourniquet. Using a 30,4.0- mm arthoscope, three arthroscopic portals were used: a standard lateral portal, an anteromedial portal medial to the patellar tendon and a far medial portal. A diagnostic arthroscopy was performed, hemartrosis was evacuated from the joint and the fracture was visualized. The underlying tibial cancellous bone was cleaned with a shaver and slightly deepened, allowing for a slight over reduction of the fracture. Fracture was reduced using fiber wire suture, fixing it with EndoButton® on the medial tibial tuberosity. The patient was discharged from hospital two days after the surgery, with an immobilizer, prophylactic antibiotics (amoxicillin 1 gr a day for 7 days) and prophylaxis for deep vein thrombosis (enoxaparin sodium, 4000 U.I., 1fl/die per 15 days), and was instructed not to put her body weight on the operated limb. Ten days after the operation, physiotherapy programme, consisting of isotonic and isometric exercises and flexion-extension, started. On the 30th day after the operation, the patient attained range of motion of 0–90◦. On the 60th day of follow-up, the patient presented range of motion of 0–100◦, with radiographs that showed consolidation of the fractures and absolutely anatomical reduction of the spine (Fig.3).

Fifure 3. Three months after the treatment, consolidation of fracture



The patient was then advised to partially bear weight on the limb, with crutches. After 10 weeks of follow-up, she was suggested full weight-bearing, while continuing with the rehabilitation protocol. From then on, the patient was controlled every month. Three months after the treatment, radiography showed that the patient was free from symptoms. She had already returned to her habitual working activities. The Tegner–Lysholm knee evaluation score was 94 (good result); her range of motion was 0–115◦; she was negative for Lachmann tests, negative for anterior and posterior drawers, negative for pivot shift and negative for varus and valgus stress.

Discussion

Tibial intercondylar eminence fractures are not common. They occur mainly in adolescents or young adults during sporting activities or even bicycle or car accidents. When not fixed, these fractures cause knee disability and reduce working ability. Their management has evolved from traditional conservative treatment to surgical treatment using different techniques. Several surgical treatments have been proposed for these injuries, going from the conventional open procedure to inclusion of arthroscopic methods, which were first described by McLennan[6] in 1982 with a number of fixation methods: Kirschner

wires, cannulated screws, sutures with steel or polyester wires, anchors and EndoButton®. While the results from primary fixation in skeletally immature patients are good, the treatments in adults present variable results and some authors have reported high rates of incidence of postoperative complications[7]. According to classification of Meyers and McKeever[8] proposed in 1970, and subsequently modified by Zaricznyj,[5] we can predict the best treatment in relation to each type of fracture. It is recommended that fractures without displacement (Type I) should be treated conservatively; moderately displaced fractures (Type II) can be managed conservatively or surgically; and displaced fractures (Type III) and comminuted fractures (Type IV) have surgical indications. The type of surgical treatment depends on the position and size of the avulsed fracture.

In 2011, Shelbourne et al.[9] reported that the most common forms of treatment for this type of injury might equally be open or arthroscopic reduction, although controversy remained regarding which treatment method was best. In 2012, Hapa et al.[10] conducted a biomechanical study on sheep and affirmed that fixation using EndoButton for fractures of the tibial eminence produced initial fixation strength that was greater than with fixation using anchors or other types of suture. For functional evaluation, Lysholm and Gillquist developed a scale of knee symptoms. The Lysholm scale includes basic aspects of the Larson scale, but introduces the criteria of instability and correlates it with activity. This scale was modified by Tegner and Lysholm. These authors recognized the difficulty in having a score for ligament injuries and decided at that juncture to investigate clinical findings and evaluate symptoms and functions. This scale or questionnaire by Lysholm is composed on eight questions, with options for closed responses, in which the final result is expressed in nominal and ordinal form, such that “excellent” is 95–100 points, “good” is 84–94 points, “fair” is 65–83 points and “poor” is less than or equal to 64 points.

Conclusion

To conclude, we can say that the treatment of the avulsion fractures of the ACL is one of the most complex procedures in orthopaedic surgery. Unfortunately, both conservative and surgical treatments have no guarantees of complete success. The choice of the type of treatment has to be evaluated considering the age, the anatomical congruence and the functional request of the patient.

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Prelom interkondilarne eminencije tibije

SAŽETAK

Uvod: Prelom tibijalne interkondilarne eminencije je rijetka povreda koja se javlja uglavnom kod mladih sportista u adolescentno doba,. Bez obzira na starosnu dob pacijenta, narušena je anatomska stabilnost koljena. Obaveza hirurškog liječenja preloma je anatomska repozicija i stabilna fiksacija preloma. Anatomskom repozicijom i stabilnom osteositezom se postiže fiziološka funkcionalnost i stabilnost koljena. Postoje različita sredstva (konac, žice, zavrtnji) kojima se stabilizuje interkondilarna eminencija. Prikazujemo slučaj gdje smo stabilizovali tibijalni prelom interkondilarne eminencije upotrebom EndoButton® uz kliničko i radiološko praćenje od tri mjeseca.

Ključne riječi: prelom tibijalne interkondilarne eminencije, EndoButton®, artroskopija

Instructions for Autors

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Abstract and key words. Structured abstracts should be included in papers that report original research. Abstracts are limited to 250 words in four labeled paragraphs: Introduction, Materials and Methods, Results, and Conclusion. The abstract should state concisely the question that was asked or the objectives of the study, the methods that were used, the results obtained, and adequately answer the question posed in the introduction. The abstract should provide pertinent information when read alone. Below the abstract, authors should provide 3-6 key words or short phrases, according to terms from the Medical Subject Headings—MeSH (www.nlm.nih.gov/mesh).

Introduction. Generally, this section provides the motivation for the paper (i.e., what is missing or unknown in the research literature at this time), an overview of the scientific theory or conceptual models on which the research was based, and the purpose of the study and why it is important. Cite only relevant references.

Materials and methods. This section accurately describes the procedures used to carry out the study; it should be complete enough to permit others to replicate the study. Describe the methodological design, subjects, data sources, data collection methods, and any statistical and analytical procedures. These five parts may not be needed in all papers. Short papers may include these details in different paragraphs, but titled subsections may be used in longer papers. The Methods section should describe how the research was structured, how subjects or groups of subjects (defined by sex, age, and other characteristics) and how the subjects were chosen and assigned to these groups. Identify all drugs and chemicals by generic names, exact drug dosages and routes of administration. Variability should be expressed in terms of means and standard deviations (SD). Because SD and SEM are positive numbers, we recommend elimination of a +/- sign; instead, the SD may be given in brackets. For example, "systolic blood pressure in group of healthy students was 129 mm Hg [SD = 6, n = 87]." A p-value can be used to disprove the null hypothesis, but the authors should also give an estimate of the power of the study and state the exact tests used for statistical analysis.

Results. This section presents findings in logical sequence using the text, tables and illustrations. This section should show how the results of the study answer the research question. This may be shortest part of the entire paper. Details may be presented concisely in one or more tables or figures. Do not repeat the data presented in tables or illustrations in the text. Emphasize or summarize only important observations and how these answer the question posed in the introduction.

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Acknowledgments. List all persons as well as financial and material supporters who helped to realize the project, even if they did not meet the criteria for authorship.

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De Lacey G, Record C, Wade J. How accurate are quotations and references in medical journals. BMJ 1985; 291:884-6.

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Croat Med J 2003; 44:770-83.

Huth EJ. How to write and publish papers in the medical sciences. Philadelphia: ISI Press, 1982.

Davidović L, Marković M, Čolić M, et al. Treatment of traumatic rupture of the thoracic aorta. Srp Arh Celok Lek 2008; 136: 498-504.

Curtis MJ, Shattock MJ. The role of the manuscript assessor. In: Hall GM, ed. How to write a paper. London: BMJ Publishing Group; 1994: 89-95.

Electronic publications:

International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info Accessed March 20, 2012.

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfi eld.libraryupenn.edu/ essays/v13p019y1990.pdf. Accessed April 25, 2012.

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