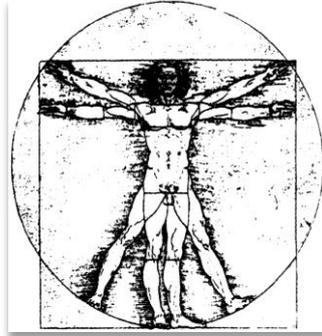


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SEX AND ETHNIC DIFFERENCES OF SOMATOTYPE IN MACEDONIAN ADOLESCENTS

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ABSTRACT

Objectives. The aim of this study was to evaluate sex-specific and ethnic differences of somatotype in Macedonian adolescents at the age of 18 years.

Methods. In this study 269 adolescent students (137 males and 132 females), from Macedonian and Albanian nationality at age of 18 years were included from secondary schools in three cities (Skopje, Ohrid and Strumica) in R. Macedonia. Ten anthropometric parameters were measured using standard equipment and measurement technique to assess the somatotype according to Heat-Carter somatotyping method.

Results. There were significant sex differences for mesomorph component in both ethnic groups in favor of male adolescents, and significant sex differences for endomorph component in favor of females from Albanian nationality. Males from both ethnic groups were more mesomorphic than females and belonged to mesomorph-endomorph, endomorph mesomorph, balanced ectomorph and central somatotype. Females were more endomorphic and belonged to endomorph-ectomorph, ectomorphic endomorph, balanced endomorph, mesomorph endomorph.

Conclusion. Our findings suggest that ethnic groups should be taken in mind for easier evaluation and understanding of differences in anthropometric parameters of growth, body shape and composition in Macedonian adolescents.

Key words: adolescents, somatotype, endomorphy, anthropometry.

INTRODUCTION

Somatotype is physical expression of long-term interaction between personal genotype and external factors. Anthropometric somatotyping is one of the methods which describes the body shape and composition. The term somatotype and its three components (endomorph, mesomorph and ectomorph) were described in 1940 by Sheldon and his co-workers. According to him, endomorphy means relative predominance of soft roundness throughout the various regions of the body; mesomorphy means the relative predominance of muscle, bone and connective tissue and ectomorphy means relative predominance of linearity and fragility. Later Heat and Carter introduced the simplified method for somatotyping and in the last few decades it has been widely used for studying body physics variations in children, adolescents and adults among populations, age changes and sex differences [1,2].

Somatotype in adults is relatively stable and the most common factors that can influence on the changes of body shape and structure are the eating habits and physical activity, but in the period of childhood and adolescence somatotype changes due to different time when puberty begins and sexual maturity [3-6]. In many anthropological studies that have examined the growth and development in children and adolescents, the knowledge about changes in somatotype during growth has contributed to better understanding of sex and age differences and changes in body composition [7-12].

Macedonia is a multiethnic country in which a heterogeneous population composed of mixture of different religious and linguistic affiliations lives on a small space with limited resources. Albanians are the largest ethnic minority in the Republic of Macedonia. Of the 2,022,547 citizens of Macedonia, 509,083, or 25.2%, are Albanians according to the latest national census in 2002 [13]. The Albanian population in the country is largely rural with ethnic Albanians forming a majority or plurality in only 3 of the country's 34 cities. Macedonians and Albanians differ in some aspects of lifestyle, eating habits, socioeconomic and cultural aspects, hence differences in body constitution are to be expected.

There are not enough studies on the somatotype of the adolescents in R. Macedonia of both ethnic groups. Thus, the aim of our study was to examine one, until now, not investigated issue, to assess the sex and ethnic differences of anthropometric characteristics and somatotype of two ethnic groups of Macedonian adolescents both males and females, at the age of 18 years.

SUBJECTS

Data were obtained from a cross-sectional sample of students of four high schools in three cities in R. Macedonia: Skopje, Strumica and Ohrid. The sample included 269 healthy students (137 males and 132 females) at the age of 18 years, from selected schools and classes, which gave their consent for participation in the research. In order to avoid mistake in the selection of the sample, volunteer students were not included. Subjects were grouped according to sex and ethnicity. The University Human Research Ethics Committee approved the experimental protocols.

ANTHROPOMETRY AND SOMATOTYPING

For evaluation of somatotype ten anthropometric variables were selected and measured according to the International Biological Program (IBP): body height, elbow diameter and knee diameter; body weight, four skinfolds (triceps, subscapular, supraspinale and calf); and two circumferences (arm and calf). The following standard anthropometric instruments were used: for measuring body height anthropometer by Martin, with 1 mm reading accuracy; decimal weight scale; "John Bull" caliper square for determination of skin-folds with pressure of 10 g/cm² and precision of 0.1 mm; elastic band, also with 1 mm reading accuracy, for measuring circumferences; and caliper square for measuring of diameters with reading precision of 1 mm and weight scale for measuring body weight. Anthropometric measurements were made during school hours, not interrupting the lessons. Subjects were standing, facing ahead, and body height was measured as maximum distance from the floor to the highest point on the head. Shoes were off, both feet together, and arms at the sides. Heels, buttocks and upper back were in contact with the wall. Body height measurement can vary throughout the day, usually being higher in the morning, so to ensure reliability we measured height at the same time of the day.

Somatotype components were assessed using the Carter Heat somatotyping method. The anthropometric somatotype was calculated by the following equations [14]:

Endomorphy = $-0.7182 + (0.1451 \times X) - (0.00068 \times X2) + (0.000014 \times X3)$, where X = (sum of triceps, subscapular, and supraspinal) \times (170.18/height, cm).

Mesomorphy = $(0.858 \times \text{humerus breadth}) + (0.601 \times \text{femur breadth}) + (0.188 \times \text{corrected arm girth}) + \text{Postural Stability in Children } 175$ $(0.161 \times \text{corrected calf girth}) - (\text{height} \times 0.131) + 4.5$, where corrected arm and calf circumferences are the respective limb circumferences minus the triceps and medial calf skinfolds.

Three equations were used to calculate ectomorphy according to the height weight ratio (HWR): If HWR is ≥ 40.75 , then ectomorphy = $(0.732 \times \text{HWR}) - 28.58$; if HWR is less than 40.75 but greater than 38.25, then ectomorphy = $(0.463 \times \text{HWR}) - 17.63$; if HWR ≤ 38.25 , and ectomorphy = 0.1.

STATISTICAL ANALYSIS

The data were analyzed with descriptive statistics represented by measures of central tendency and its deviation (arithmetic mean value and standard deviation). The significant differences between groups, were evaluated with ANOVA, the level of significance set at $p < 0.05$. The statistical package for the social sciences (version 20.0, SPSS Inc, Chicago, IL) was used for all statistical analyses. Somatotype-Calculation and Analysis V1.1. Monte Goulding, Sweat Technologies, Mitchell Park, South Australia software was used to determine somatotypes.

RESULTS

The study included 269 adolescents (137 females and 132 males) from two ethnic groups, Macedonians and Albanians, at the age of 18 years, from Skopje, Strumica and Ohrid. Anthropometric measurements of both Macedonian and Albanian adolescents at the age of 18 years are given in Table 1. Males of both ethnic groups had higher values for height and weight than females, and males and females from Macedonian nationality had higher values for height and weight compared to Albanians.

The frequency and distribution of 13 categories of somatotype (Carter, 1980) are shown in Table 2. At the age of 18 years male examinees of Macedonian nationality belonged to three somatotype categories: endomorphic-mesomorph (20%), central type (17%) and mesomorph-endomorph (16%), while other adolescents belonged to other categories. Males from Albanian nationality belonged predominantly to endomorphic mesomorph (27%) and balanced mesomorph (20%) contrary to other ethnic groups who were represented by a very small number or only 7%. Females of Macedonian nationality belonged to balanced endomorph (18%) and mesomorph-endomorph (28%) and the rest of examinees belonged to other somatotypes: balanced ectomorph (12%), central type (10%), mesomorph-endomorph (9%), endomorph-ectomorph (11%) and ectomorph-endomorph (10%). Females from Albanian nationality differed from their peers of other ethnic groups in their somatotype and they mainly belonged to mesomorphic endomorph (20%), balanced ectomorph (20%) and endomorph-ectomorph (17%). We can conclude that males of both ethnic groups at the age of 18 years were more mesomorphic than females. Albanian males were more mesomorphic than Macedonians, and Albanian females are more ectomorphic than Macedonian females.

Sex and ethnic differences of somatotype components (mean values and standard deviations) are shown in Table 3. Results obtained showed that males of both ethnic groups were more mesomorph than females, who are more endomorph. There are statistically significant sex differences for mesomorph component in favor of males of both ethnic groups, and for endomorph component in favor of females of Macedonian nationality. Although our results have shown that Albanian adolescents are more mesomorph and more ectomorphic than their peers from Macedonian nationality, there were no significant ethnic differences between the groups.

Table 1. Anthropometric variables in 18- year-old adolescents by sex and ethnic group

Age 18 years Variable	Males		Females	
	Macedonian Mean \pm SD	Albanian Mean \pm SD	Macedonian Mean \pm SD	Albanian Mean \pm SD
HWR	42.59 \pm 1.91	42.90 \pm 2.06	42.70 1.79	43.27 2.25
Height	179.70 \pm 6.74	177.60 \pm 7.92	165.31 6.01	163.00 5.80
Weight	75.99 \pm 11.16	72.00 \pm 12.60	58.54 7.75	54.03 7.23
Triceps SF	12.46 \pm 5.17	10.79 \pm 3.17	16.20 4.46	16.09 5.32
Subscapular SF	11.87 \pm 4.12	11.76 \pm 4.65	12.83 4.55	11.92 4.11
Supraspinale SF	13.02 \pm 6.27	11.33 \pm 6.61	14.08 5.24	13.73 4.70
Calf SF	10.87 \pm 4.76	10.09 \pm 4.09	13.65 4.76	14.93 4.95
Arm Girth	31.52 \pm 3.41	31.30 \pm 3.45	26.17 2.45	25.62 2.23
Calf girth	37.08 \pm 3.17	36.89 \pm 2.94	35.03 2.58	34.56 3.01
Humerus B	6.84 \pm 0.44	6.99 \pm 0.41	5.77 0.35	5.90 0.33
Femur B	9.61 \pm 0.67	9.40 \pm 0.55	8.64 0.46	8.42 0.46
n	107	30	102	30

Table 2. Somatotype categories (%) in adolescents at the age of 18 years by sex and ethnic group

Somatotype categories (%)	Males		Females	
	Macedonian	Albanian	Macedonian	Albanian
Endomorph-ectomorph	3	3	11	17
Ectomorphic endomorph	2	0	10	10
Balanced endomorph	3	0	18	13
Mesomorphic endomorph	8	3	28	20
Mesomorph-endomorph	16	13	9	7
Endomorphic mesomorph	20	27	2	3
Balanced mesomorph	7	23	0	0
Ectomorphic mesomorph	4	3	0	0
Mesomorph-ectomorph	5	3	1	0
Mesomorphic ectomorph	6	7	0	0
Balanced ectomorph	11	10	12	20
Endomorphic ectomorph	0	0	0	0
Central type	17	7	10	10
N	107	30	102	30

Table 3. Somatotype components in 18-years-old Macedonian adolescents by sex and ethnic group

Age 18 years Variable	Males		Females	
	Macedonian Mean \pm SD	Albanian Mean \pm SD	Macedonian Mean \pm SD	Albanian Mean \pm SD
Endomorphy	3.52 \pm 1.32	3.26 \pm 1.28	4.44 \pm 1.14 ^b	4.33 \pm 1.17 ^b
Mesomorphy	4.08 \pm 1.40 ^b	4.30 \pm 1.45 ^b	3.04 \pm 1.09	3.04 \pm 1.36
Ectomorphy	2.65 \pm 1.27	2.83 \pm 1.51	2.72 \pm 1.19	3.19 \pm 1.47
n	107	30	102	30

Significant differences were found ($p < 0.05$) ^a $p < 0,05$ (ethnic differences) , ^b $p < 0,05$ (sex differences)

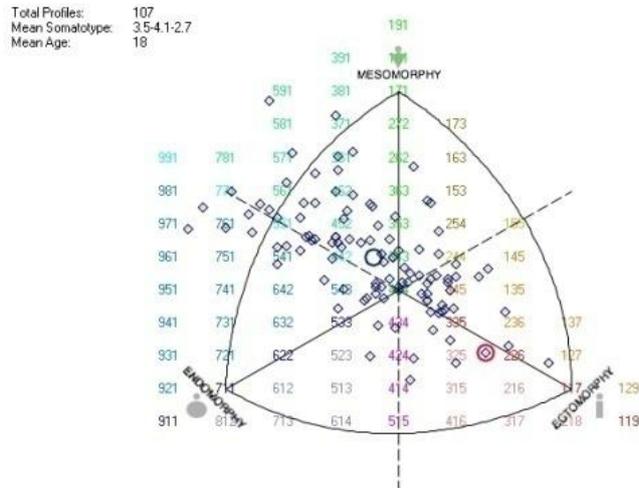


Fig.1. Somatochart, displaying somatotype categories in male adolescents by Macedonian nationality -18 years old

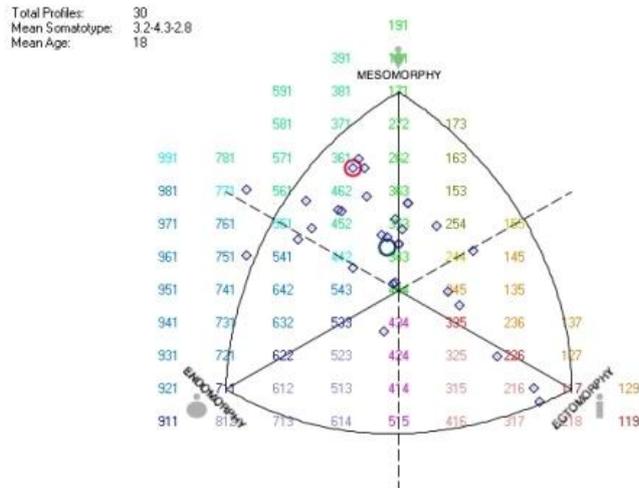


Fig. 2. Somatochart, displaying somatotype categories in male adolescents by Albanian nationality -18 years old

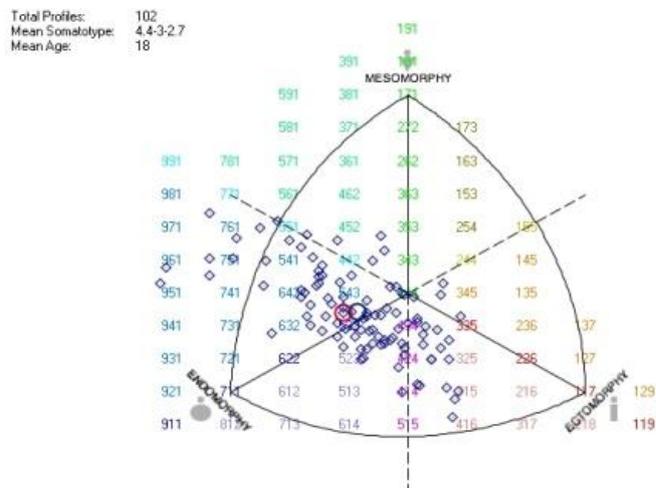


Fig. 3. Somatochart, displaying somatotype categories in female adolescents by Macedonian nationality -18 years old

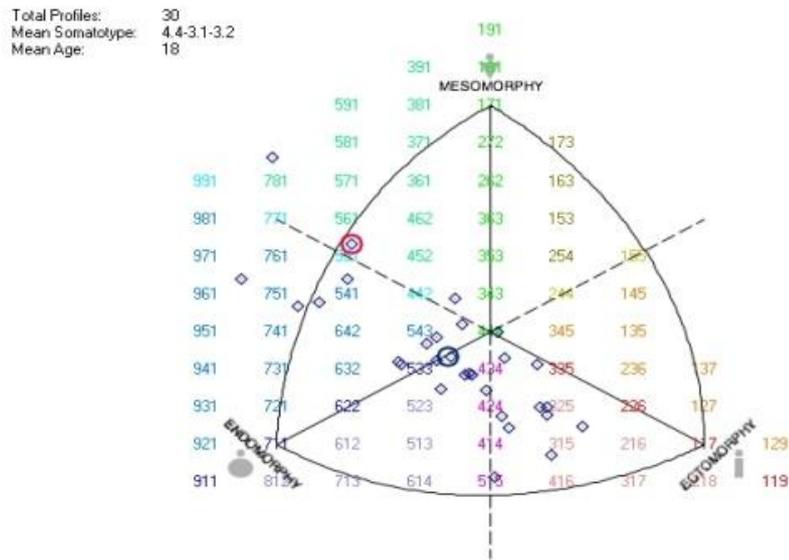


Fig. 4. Somatochart, displaying somatotype categories in female adolescents by Albanian nationality -18 years old

DISCUSSION

Anthropometric somatotype of Heat-Carter is one of the most used methods for evaluation of the relation between body composition and physical performance in different sports, but also is very often applied in the studying of body composition, during the period of growth and development which is marked with rapid changes in body composition and body constitution [15-18]. According to the studies on somatotypes of children and adolescents there are differences in body structural components which are specific for every age and for both sexes.

Although genetic factor is the key factor for body shape and composition, when determining somatotype, ethnicity and sex should be considered. The aim of this study was to assess the sex and ethnic differences of somatotypes of Macedonian adolescents of two ethnic groups, Macedonians and Albanians, at the age of 18 years, and to compare the results with other populations. The study of Gakhar I and Malik SL, on the age and sex differences in somatotypes of the adolescents at the age of 10 to 18 years from Jats, New Delhi, suggest that after the age of 14 years the differences of somatotypes are increasing between the sexes [5]. Indian male adolescents at the age of 18 years in their study belonged to meso-ectomorphs and balanced ectomorph, and our results showed that male adolescents of both ethnic groups belonged to mesomorph-endomorph, endomorph-mesomorph and balanced ectomorph, which indicates that there are certain differences in body composition in our adolescents compared to their Indian peers. Females at the age of 18 years in the study of Gakhar I and Malik SL were more of a central type, while Macedonian females of both ethnic groups belonged to endomorphic types and mesomorphic endomorph. As many studies suggests the endomorph component or the first component in the somatotype (which is a rating on a continuum of relative fatness of a physic) in females increases it is values from the age of 10 to the age of 18 years while in males shows little increasment with the age untill the age of 14 years. Contrary to endomorph component mesomorph component or the second component in the somatotype (which is a rating on a continuum of musculoskeletal robustness relative to stature after the age of 13 years) had higher values in males and the values increased until the age of 18 years, which results in higher mesomorphism in males at the age of 18 years [2, 5,12,19].

The results of our study clearly suggest that in physique investigations, the somatotypes need to be studied at each age and sex separately, and considering the ethnicity of the population.

CONCLUSION

Our study had a goal to examine one, until now, not investigated issue, to assess sex and ethnic differences on somatotype of the population group of adolescents at the age of 18 years from Republic of Macedonia. According to our study we found sex and ethnic differences which might be used in clinical practise when evaluating the growth and development as indicators of health of youth population. Ethnic group should be taken in mind for easier evaluation and understanding of differences in anthropometric parameters of growth, body shape and composition. Due to a smaller sample size included, particularly participants of Albanian nationality, future studies are needed comprising a larger cohort by including more variables as well as social determinants for both ethnic groups for better understanding of differences between the groups.

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TROPONIN – FACTOR FOR DETERMINATION OF MYOCARDIAL ISCHEMIC DAMAGE IN POSTOPERATIVE PERIOD OF CARDIAC SURGERY IN PEDIATRIC POPULATION

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ABSTRACT

Background. Troponin is an important biomarker for early evidence of ischemic damage to the heart tissue after a cardiac surgery conducted in the pediatric and adult populations. Elevated values correlate with perioperative and postoperative procedures and practices and are a significant factor for possible later complications.

Methods. The study included 30 operated children divided into two groups, the first group of operated children without a cardiopulmonary bypass (CPB), and the second group of operated children with a cardiopulmonary bypass. The correlation between elevated troponin and perioperative and postoperative parameters was monitored (duration of CPB and aortic cross-clamping time, stay in the intensive care and therapy during respiratory support, during inotropic support, the presence of renal or hepatic failure, postoperative complications).

Results. In both groups of operated children troponin was elevated. In the first group of children operated without cardiopulmonary bypass, the average value of troponin was 9.5 ng/ml (range 6.5-16.8 ng/l). In the second group of operated children (27 children) with cardiopulmonary bypass, the mean value of duration was 81.5 minutes (range 18 to 296 minutes), and X-cross time (aortic cross-clamping time) in the same group of children was with a mean value of 28.2 minutes (range of 0-86 min.). In the first group of children the mean value of troponin was 9.5ng/ml and in the second group 23.0 ng/ml. The obtained values of troponin have confirmed a highly significant correlation with perioperative and postoperative procedures.

Conclusions. Troponin is a prognostic marker for early evidence of ischemic and necrotic changes of cardiac infarction in the pediatric population in cardiac surgery. Elevated values in the first 24-48 hours are significantly correlated with perioperative and postoperative procedures and are an important indicator of the extent of damage to the heart tissue. But its prognostic significance of myocardial ischemic changes is lost in a period between 2-6 months after cardiac surgery.

Keywords: troponin, cardiac surgery, myocardial ischemic changes

INTRODUCTION

Troponin is a highly specific biomarker for early evidence of ischemic changes in the heart tissue. It is a part of the tropomyosinprotein complex composed of three subclasses: troponin c TnC (calcium-binding molecule), cTnI (inhibitory molecule), cTnT (tropomyosin-binding molecule). Troponin TnI is the most frequently used in the clinical practice.

In the literature there is a small number of studies that have examined troponin I in the pediatric population in cardiac surgery, with a special emphasis on the early postoperative period. A correlation is found between elevated troponin and perioperative and postoperative procedures (duration of CPB and cross-clamping time, the EIT stay, duration of ventilator and inotropic support, renal and hepatic failure and so on). Ischemic changes occurring during the cardiac surgery represent a significant factor of postoperative changes in cardiac function which can be confirmed by elevated troponin. Therefore, it is considered as a prognostic biomarker of early morbidity and mortality.

MATERIALS AND METHODS

In this prospective study 30 children with congenital heart defect were examined, in whom the cardiac surgery was carried out in the period from September 2014 to May 2016.

The basic anamnestic data were taken, including history, age, gender, type of congenital heart defect, etc. Most children were in the infancy period.

Operated children were divided into two groups depending on the severity of congenital heart defect and the use of cardiopulmonary bypass (CPB). The first group consisted of operated children without use of CPB diagnosed with a coarctation of the aorta and ligation of DAP, and the second group included operated children with a complex congenital heart defects in which cases a cardiopulmonary bypass was carried out.

According to the type of the operated congenital heart defects, the highest percentage (20%) belonged to the Atrial Septal Defect (ASD) and Tetralogy of Fallot (TOF) (6/30), then the Ventricular Septal Defect (VSD) with 16.6% (5/30) followed by complex cardiopathies, Transposition of Great Arteries(TGA), Double Outlet Right Ventricle (DORV).

The correlation between the values of troponin and perioperative and postoperative parameters was monitored (duration of CPB and aortic cross-clamping time, stay in the intensive care and therapy during respiratory support, time of inotropic support, the presence of renal or hepatic failure, postoperative complications).

During cardiac surgeries a continuous sedation with opiates Fentanyl and neuromuscular blocking agent Pancuronium bromide was used and also myocardial protection with cardioplegia were implemented.

In three children with CoAo - coartation of the aorta and DAP-ductus arteriosus persistens a cardiac surgery without cardiopulmonary bypass was performed. In 2 children a surgery was carried out- correction of CoAo, and in one child, a ligation of DAP.

In 27 children a cardiac surgery with thoracotomy and cardiopulmonary bypass was made. In 6 children a surgery for closure of the atrial septal defect, in 5 children closure of ventricular septal defect, in 5 children correction of TOF, in 4 children correction of transposition of the great vessels (arterial switch operation), in 2 children correction CAV and DORV were realized.

Moderate hypothermia was conducted in an interval of 30-34 degrees.

Postoperatively all children stayed in the intensive care unit, and treatment, vital parameters and clinical sings were continuously monitored. Due to complications and respiratory failure three children were intubated again.

Examination of troponin was realized with Imulight 2000 which uses enzyme amplified chemiluminescence and verifies the subclass of troponin I. It examines the venous blood three times preoperatively, postoperatively within 12-48 hours as well as 2-6 months after surgery.

RESULTS

In this prospective study 30 children were examined and most of them were in the infancy period. The average age of the operated children was 10.2 months (range 10 days - 84 months). There were 19/30 (63%) boys and 11/30 (37%) girls.

Table 1. Age of children operated on

0-1 month	5
1-12 months	20
12-24 months	3
from 24 months	2

According to the type of operated congenital heart defects, the highest percentage belonged to ASD, VSD followed by complex cardiopathies TOF, TGA, DORV etc. (Table 2).

Table 2. Types of congenital heart defects

Congenital heart defect	Number of children operated on	Rate
DAP	1	3.3 %
CoAo	2	6.6 %
VSD	5	16.6 %
ASD	6	20.0 %
CAV	2	6.6 %
TGA	4	13.3 %
TOF	6	20.0 %
Stenosis aortae	1	3.3 %
DORV	2	6.6 %
Anomal.Pulmonary venous return	1	3.3 %

DAP- Ductus arteriosus persistens, ASD-Atrial septal defect, VSD- Ventricular septal defect, CoAo - coartation of the aorta, TOF-Tetralogy of Fallot, TGA – Transposition of the great arteries, DORV - Double outlet right ventricle.

Troponin I was measured three times, preoperatively, postoperatively in a period of 12-48 hours and 2-6 months after surgery. Preoperative values of troponin in all children were in the normal range of 0.20-0.30 ng/ml.

In the postoperative period the elevated values of troponin I in the period of 12-48 hours were correlated with the duration of cardiopulmonary bypass and aortic cross-clamping time ($p = 0.01$).

In the second group of operated children (27 children) with cardiopulmonary bypass, the mean duration was 81.5 minutes (range 18 to 296 minutes), and X-cross time (aortic cross-clamping time) in the same group was with a mean duration of 28.2 minutes (range of 0-86 min.). In 10 children from this group where cardiopulmonary bypass lasted for more than 100 minutes, troponin values were over 20 ng/ml (range 22 to 293 ng/ml).

In the remaining 20 children troponin was below 20 ng/ml (range from 0.5 to 18.6 ng/ml).

Prolonged cardiopulmonary bypass was the result of perioperative complications, intracranial hemorrhage, arrhythmias, systemic bleedings with hypotension and bradycardia, etc. The average value of troponin was 23.0 ng/ml (range 8.5-54.8 ng/ml). This ratio between values of troponin and CPB is shown in Figure 1.

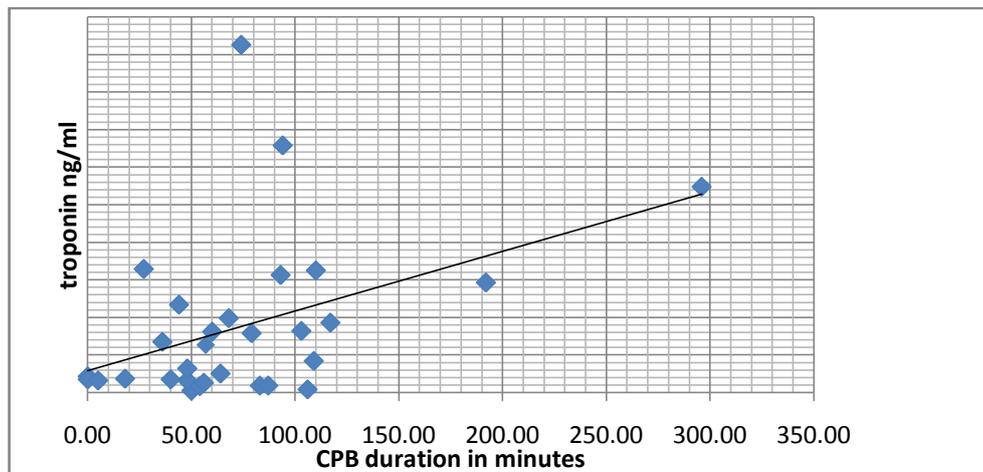


Fig. 1. Relationship between elevated troponin and duration of CPB

The duration of X-cross time (aortic cross-clamping time) was also correlated with the elevated values of troponin. In the first group the X-cross time (aortic cross-clamping time) at coarctation of aorta was 16.9 minutes (range 15,5 -18 minutes) ($p = 0,1$). In the second group the X-cross time (aortic cross-clamping time) was with a mean value of 29.2 minutes (range 0-60 min.).

Figure 2 shows the linear relation between values of troponin and duration of the X-cross time - aortic cross-clamping time.

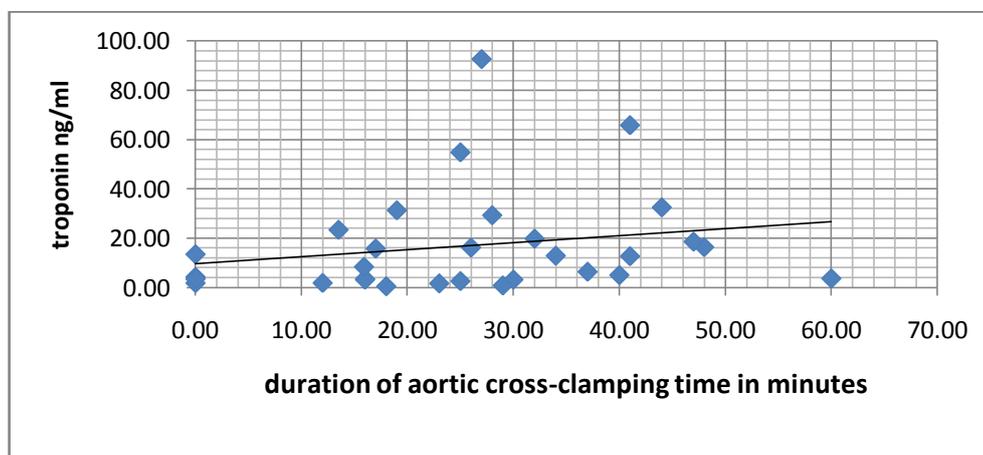
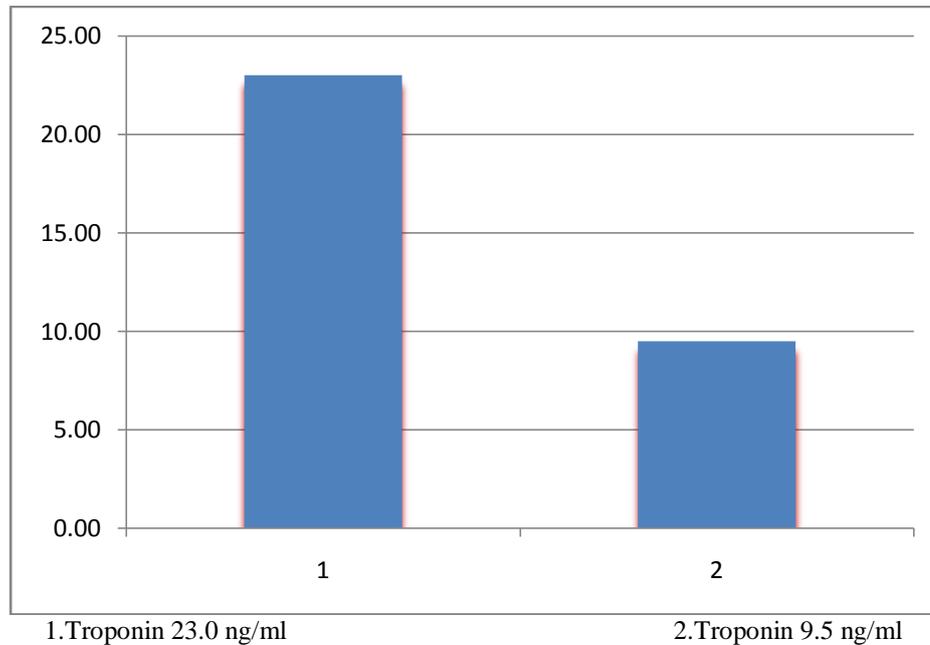


Fig. 2. Correlation between elevated values of troponin and duration of aortic cross-clamping time

In the first group of operated children without a cardiopulmonary bypass, troponin was elevated, but with lower values compared to the operated children with a cardiopulmonary bypass. The average value of troponin was 9.5 ng/ml (range 6.5-16.8 ng/l). The differences in the values of troponin were a result of the absence of cardiopulmonary bypass.

Comparison between the mean values of troponin in both groups



Elevated values of troponin correlated with the stay at the Department of intensive care and therapy, with the duration of mechanical ventilation and the inotropic support.

The duration of the stay at the Department was 4.2 days (range 1-20 days). Children who stayed longer at the Department of intensive care had higher troponin values than other children. At the same time, because of the longer stay at the Department, they needed a longer inotropic support. It took an average of 3.2 days (range 1- 10 days) ($p = 0.1$).

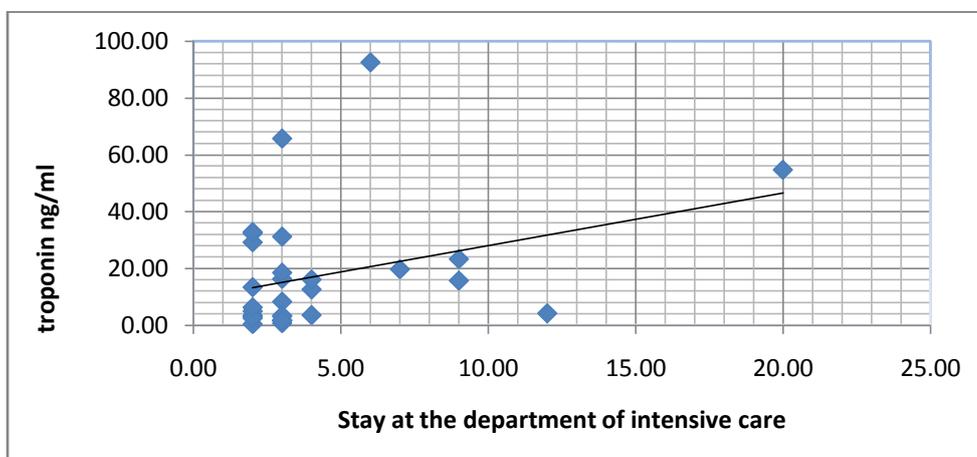


Fig. 3. Correlation between elevated troponin and stay at the Department of intensive care

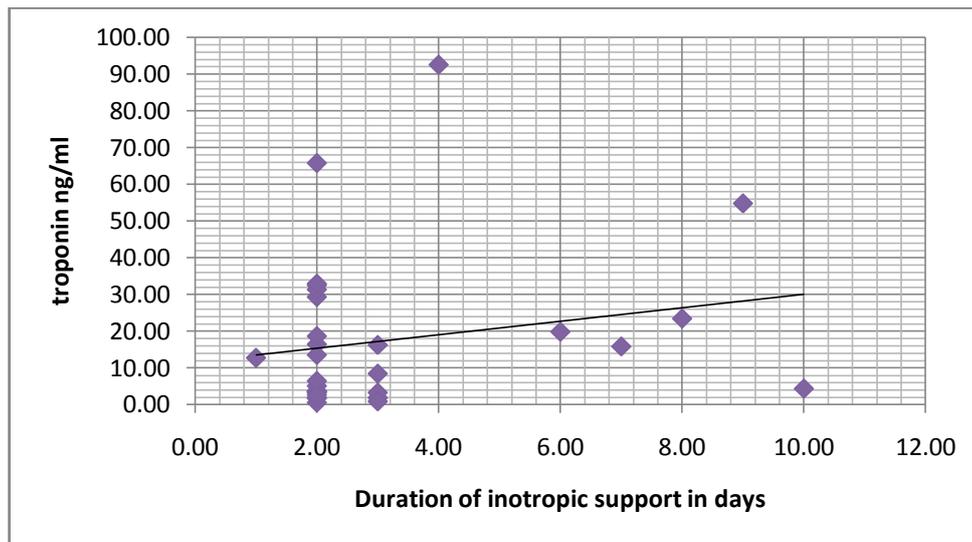


Fig. 4. Correlation between elevated troponin values and inotropic support

In all operated children, the hepatic and renal functions were normal with normal liver enzymes and degradation products urea and creatinine.

The correlation between elevated troponin and postoperative complications was not confirmed (pleural effusion, chylothorax, sepsis, A-V block). They were treated with appropriate procedures and adequate therapy.

Troponin values in the period of 2-6 months were in the normal range of 0.20-0.30 ng/ml. All children were operated in good general condition. The findings of the echocardiography were unremarkable with good kinetics, without pericardial effusion.

DISCUSSION

Troponin is an important biomarker for diagnosis of early ischemic changes in the myocardium after a cardiac surgery.

In the past, a small number of studies examined a group of cardiac markers (together with a natriuretic peptide, creatine kinase, myoglobin) where obtained postoperative results were related mainly to the adult population [1-6]. The study conducted by Franz F, Franco Stocer et al. demonstrated elevated troponin values that occurred 4 hours after the intervention and reached a peak 24-48 hours after the cardiac surgery. It should be noted that this study included neonatal and pediatric patients, and a statistically significant correlation was found between elevated troponin values and [7] the duration, the manner of implementation of CPB, the X-clamp time (aortic X-cross clamping time), the stay at the department of intensive care and therapy, the duration of respiratory and inotropic support, the presence of renal and hepatic impairment. Prolonged duration of CPB and X-clamp time causes more damage to the myocardium and is reflected through the elevated troponin values. This has been confirmed in several studies performed in adults [8-16].

In our study the operated children were divided into two groups, with and without cardiopulmonary bypass and X-cross time in order to identify groups of children with a high and low risk after a cardiac surgery. There was a statistically significant correlation between the duration of CPB and X-cross time and troponin values that were over 20 ng/ml. Statistically significant correlation was found between elevated troponin values and the stay at the Department of intensive care and therapy, the duration of the mechanical ventilation, the length of the respiratory and inotropic support. There was no statistically significant correlation with postoperative complications (chylothorax, sepsis, pleural effusion, A-V block) because the invasive procedures, extension of inotropic support, antibiotics etc., had begun in due time.

Several studies have shown that elevated troponin does not correlate with the age of the operated children. However, it should be borne in mind that a small number of studies has confirmed this.

In our study there was a statistical correlation between elevated troponin values and age, because all children that had higher troponin values were in the infant group up to 1 year old. However, it has been taken into consideration that this study comprised a small number of children.

CONCLUSION

Troponin is a sensitive early biomarker that has prognostic significance in the occurrence of ischemic damage to the myocardium in the early postoperative period in the pediatric population. Elevated values between 24-48 hours are an important factor for predicting the possible postoperative complications that can be treated and eliminated if the treatment is started on time. Its prognostic significance for long-term monitoring of myocardial ischemic changes has not yet been confirmed.

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TREATMENT OF TIBIAL PLATEAU FRACTURES – COMPARATIVE ANALYSIS OF TWO OPERATIVE TECHNIQUES

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ABSTRACT

The knee is one of the three main joints in the human body that helps distribute the weight of the body. Fractures occurring in this area affect the function and stability of the knee. Of late, as regards the treatment of these fractures, emphasis is being placed on surgical treatments with minimally invasive approaches, anatomically, which are focused on preservation and no additional major damage to the soft tissue.

The aim of this article is to make a comparison between the minimally invasive surgical treatment of tibial plateau fractures with contralateral elevation of the tibial plateau and its fixation with screws, and the open surgical approach to these fractures and fixating the tibial plateau with plates and screws. The comparison is made on the basis of the Schatzker classification type I, II, III and IV of tibial plateau fractures, comparing the duration of surgical interventions and the functional results at the 6-month follow-up, as well as the occurrence of any potential postoperative complications.

Methods. In the period from April 2011 to July 2015, twenty-three patients (12 male and 11 female patients) were treated at the University Clinic of Traumatology. Twelve of the patients were treated with the contralateral approach and the minimally invasive treatment, while eleven of the patients were treated with open surgical treatment and osteosynthesis with plates. All of the patients were evaluated at the 6-month follow-up using the Lysholm score / Tegner activity scale, and Rasmussen functional score. These two scoring scales are compatible and together they give a complete picture of the function of a knee joint.

Conclusion. The contralateral minimally invasive approach of Schatzker classification I, II, III, and IV of tibial plateau fractures is a surgical treatment that results in a small number of complications and has its advantages over the open surgical approach used in patients with these types of injuries. The main benefit of this surgical treatment is preservation of the soft tissue which, of course, affects the end results as well. The minimally invasive surgical treatment allows for a shorter hospital stay of the patients, their quicker verticalization, and faster healing of the fracture, which in turn makes the effective return to everyday activities possible. On the other hand, the standard procedure of open surgical approach provides a direct visualization of the traumatised structures, making it easier to anatomically reconstruct the fractured bone fragments of the tibial plateau and to repair the soft tissue trauma.

Key words: tibial plateau fractures, minimally invasive treatment, quick verticalization.

INTRODUCTION

Tibial plateau fractures are fractures that occur in the area of the knee joint. The knee joint is one of the three main joints in the human body that helps distribute the weight of the body. Fractures occurring in this area affect both the stability of the knee and the function of the knee joint. The tibial plateau is the upper part of the tibial bone which joints with the lower part of the femoral bone, and together they comprise the knee joint. The two articular surfaces are incongruent and so, in order for the joint to have the necessary stability and strength, there are cartilaginous and ligamentous structures incorporated into the knee joint. Cartilaginous structures are the lateral and medial menisci. Ligamentous structures are the anterior and posterior cruciate ligaments, and lateral and medial collateral ligaments. And as they are all attached to the tibial bone, a fracture to the tibia can also result in trauma to some of the soft tissue structures. According to Colletti, Greenberg, and Terk, there is a possibility of anterior cruciate ligament rupture in 34% of the tibial plateau fractures, lateral meniscus damage occurs in 45% of these fractures, and medial meniscus damage in 21% of these cases.

The tibial plateau is comprised of three parts or plateaus – lateral, central and medial plateaus. The lateral plateau is the outer part of the upper tibial bone to which the lateral meniscus and the lateral collateral ligament are attached. The upper part of the fibular bone (the head of the fibula), around which the peroneal nerve passes, sits on the posterior outer part of the lateral plateau. The central plateau is the elevated rough medial part represented by the intercondylar eminence to which the cruciate ligaments and menisci attach. The vascular structures of the knee joint pass behind this central plateau. The medial plateau is the inner part of the upper tibial bone to which the medial meniscus and the medial collateral ligament are attached.

One should always have in mind the aforementioned when deciding on the appropriate treatment of a tibial plateau fracture. Considering the intricate structure of the knee joint, deciding on the appropriate treatment of any injury to the structure is a complex task that requires great caution and precise planning before starting any treatment as it can lead to a number of early and late complications.

The tibial plateau fractures in this study are classified according to the Schatzker classification: I – lateral split in the tibial plateau; II – lateral split in the tibial plateau with depression; III – depression of the lateral tibial plateau; and IV – medial split of the tibial plateau.

According to the rules for the minimally invasive treatment, it is best not to damage the periosteum and to make incisions as small as possible with a minimal but adequate fixation. The new minimally invasive treatments with contralateral elevation and fixation with screws, as well as the treatment with small incisions and fixation with locking plates, follow these new trends. A patient's hospital stay is significantly shortened due to the small surgical incisions. And because the duration of one's postoperative recovery is shortened, the physical therapy can begin earlier which in turn leads to one's full recovery faster.

The aim of this article is to make a comparison between the minimally invasive surgical treatment of tibial plateau fractures with contralateral elevation of the tibial plateau and its fixation with screws, and the open surgical approach to these fractures. The comparison is made only on the Schatzker types I, II, III and IV tibial plateau fractures, and it compares the duration of surgical interventions and the functional results at the 6-month follow-up.

MATERIALS AND METHODS

The study was conducted at the University Clinic of Traumatology in the period from April 2011 to July 2015. Twenty-three patients (12 male and 11 female patients) were treated in this period. For the patients to be part of our research, the following inclusion criteria were used: patients with Schatzker I, II, III, and IV tibial plateau fractures. The following criteria were used as exclusion criteria: patients with Schatzker I, II, III, and IV tibial plateau fractures with comorbidities (inadequately regulated diabetes mellitus, cardiomyopathia chronica, patients over 70 years of age), patients with Schatzker V and VI tibial plateau fractures.

The tibial plateau fractures in this study are classified according to the Schatzker classification: I – lateral split in the tibial plateau; II – lateral split in the tibial plateau with depression; III – depression of the lateral tibial plateau; and IV – medial split of the tibial plateau.

Twenty-three patients were treated at the University Clinic of Traumatology. Twelve of the patients were treated with the contralateral approach and the minimally invasive treatment, while eleven of the patients were treated with the standard open approach. The male patients were between the ages of 31 and 68 (mean age of 47). The female patients were between the ages of 25 and 68 (mean age of 51.4). CT and x-ray investigations were made at the time of admission of all the patients with the aim of determining the type of fracture in each patient so that the appropriate intervention can be decided on. In addition, ECG investigations and laboratory tests were also done in order to determine whether the patients could be included in our research. Upon completing the x-ray and CT investigations, it was established that three of the patients had the Schatzker type I fracture, two had the Schatzker type II fracture, fifteen had the Schatzker type III fracture, and three patients had the Schatzker type IV fracture.

All of the patients were treated surgically either within the first 24 hours or between the seventh and the tenth day after the initial trauma, depending on the condition the local area of the fracture was in. All of the patients were operated on using a spinal anaesthesia and placed on an extension table. Twelve patients were treated with the contralateral approach and the minimally invasive treatment where traction was applied to the injured leg while it was placed in a neutral position so as to achieve an indirect reduction of the fracture, which was controlled by a C-arm. After all the preparations for surgery were made, a small incision of 1.5 to 2 cm long was made (parallel to the tuberositas tibiae) and another one of 1.5 cm in length on the opposite side of the fracture. On reaching the bone, a hole was drilled in the bone by using four drill bits successively (ranging from 2.8 mm to 6 mm) through which the elevator could be inserted and the calcium hydroxyapatite placed.

Before inserting the elevator through the hole made in the bone, a reduction of the bone was made using a device for temporary fixation. After identifying the depressed part, it was pushed back into place by using the elevator and the gap in the fracture was filled with calcium hydroxyapatite. In the end, the fracture was fixated with either cannulated or spongiosis screws. The entire intervention was controlled using a C-arm for fluoroscopic evaluation.

Postoperatively, the injured leg was immobilised in either a splint or a cast. The patients were given analgesics, antibiotics and tromboprophylaxis. A blood test analysis was made on the first postoperative day so as to evaluate any significant blood loss. On the second postoperative day, a control x-ray was made. On the seventh postoperative day, the surgical sutures were removed.

Eleven patients were treated with the open approach with a plate. They were all placed on the operating table in a supine position with the injured leg slightly elevated. After all the preparations for surgery were made, the open parapatellar approach was used. Depending on the condition the local area of the fracture was in, the surgical intervention was done either within the first 24 hours after the trauma or, if there was a significant local swelling, it was postponed for seven to ten days later. After reaching the bone by way of incision on the capsule, an anatomical reduction of the bone fragments was carried out.

Any eventual defects were filled either with calcium hydroxyapatite or with spongiosis from a donor bone. The fixation was made with free screws and a T-plate, or with anatomical locking plates for the upper part of the tibial bone. It was followed by restoration of the traumatised soft tissue of the knee. The wounds were closed in layers.

Postoperatively, the injured leg was immobilised and the patients were given analgesics, antibiotics and tromboprophylaxis. A blood test analysis was made on the first postoperative day so as to evaluate any significant blood loss. On the second postoperative day, a control x-ray was made. The surgical sutures were removed around 10 to 14 days following the surgery.

All of the patients were evaluated on the sixth month following the surgical intervention according to the Tegner / Lysholm and the Rasmussen functional score [1,2,3]. The total number of points that could be awarded according to the Tegner / Lysholm functional scale is 100; using the eight criteria given, the best possible score is 100 points which in turn means that there are no problems with the knee joint. The criteria used in evaluating the function of the knee joint are as follows: Limping, Support, Locking, Instability, Pain, Swelling, Climbing Steps, and Squatting. According to the Rasmussen functional score, the maximum points that could be awarded are 30 using the five criteria given. And they are as follows: pain, ability to walk, extension, range of movements, and stability. These two scores are compatible and complement each other. In combination, they give a complete picture of the function of the knee joint.

STATISTICAL ANALYSIS

For the analysis of data, the following software was used:

-Statistica 7.1 for Windows

The following methods were applied:

1. For the series containing numerical symbols – Limping; Support; Locking; Instability; Pain; Swelling; Climbing Steps; Squatting; Walking; Extension; Movement; Stability; Overall Score – a Descriptive Statistics (containing Mean; Std. Deviation; $\pm 95.00\%$ CI; Minimum; and Maximum) was made;

1.1 The distribution of data testing was done using the following tests: Kolmogorov–Smirnov test; Lilliefors test; Shapiro–Wilks test (p);

1.2 The differences between the two groups were tested using the Mann–Whitney U test (Z/p); The significance was determined to be if the value of $p > 0.05$. Tables and charts were used to present the data.

RESULTS

1. Fixation with contralateral elevation and percutaneous fixation with screws / Group A1

All of the patients were treated at the Clinic of Traumatology. The treatment of a total of 12 patients consisted of fixation with contralateral elevation and percutaneous fixation with screws. Table 1 and Fig 1 contain the descriptive statistics of parameters analysed. The analysed parameters vary in the following intervals: Limping 3.64 ± 1.57 points; Support 4.27 ± 1.68 points; Locking 11.45 ± 3.05 points; Instability 20.91 ± 7.01 points; Pain 21.82 ± 2.52 points; Swelling 9.64 ± 1.21 points; Climbing Steps 9.09 ± 3.02 points; Squatting 4.18 ± 1.66 points; Overall Score 79.83 ± 16.82 points.

Table 1. Descriptive statistics / Group A1

Parameters	Number	Average	Confidence -95,00%	Confidence +95.00%	Minimum	Maximum	Std. Dev.
Limping	12	3.50	2.30	4.70	0	5	1.88
Support	12	5.17	4.06	6.28	2	10	1.75
Locking	12	9.67	6.59	12.75	2	15	4.85
Instability	12	22.92	20.06	25.78	10	25	4.50
Pain	12	17.92	13.14	22.70	0	25	7.53
Swelling	12	8.08	6.05	10.12	0	10	3.20
Climbing Steps	12	8.33	6.63	10.03	2	10	2.67
Squatting	12	4.25	3.70	4.80	2	5	0.87
Overall Score	12	79.83	69.14	90.52	46	95	16.82

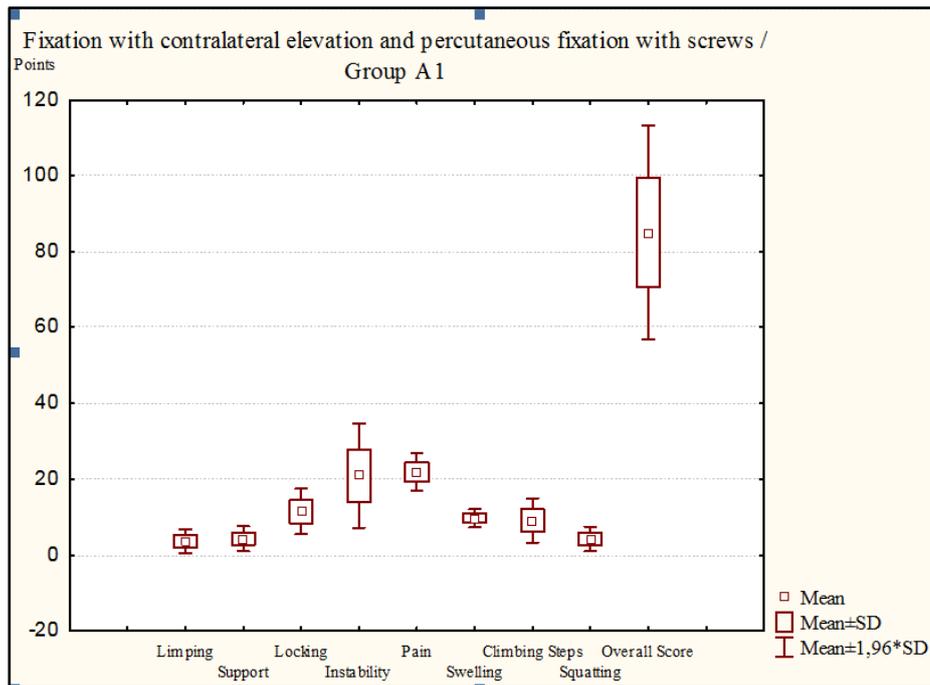


Fig. 1. Descriptive statistics / Group A1

2. Standard surgical technique and open approach / Group B1

A total of 11 patients were treated with a standard surgical technique and open approach. Table 2 and Fig 2 contain the descriptive statistics of parameters analysed. The analysed parameters vary in the following intervals: Limping 3.50 ± 1.88 points; Support 5.17 ± 1.75 points; Locking 9.67 ± 4.85 points; Instability 22.92 ± 4.50 points; Pain 17.92 ± 7.53 points; Swelling 8.08 ± 3.20 points; Climbing Steps 8.33 ± 2.67 points; Squatting 4.25 ± 0.87 points; Overall Score 85.00 ± 14.42 points

Table 2. Descriptive statistics / Group B1

Parameters	Number	Average	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std. Dev.
Limping	11	3.64	2.58	4.69	0	5	1.57
Support	11	4.27	3.14	5.40	0	5	1.68
Locking	11	11.45	9.41	13.50	6	15	3.05
Instability	11	20.91	16.20	25.62	5	25	7.01
Pain	11	21.82	20.12	23.51	20	25	2.52
Swelling	11	9.64	8.83	10.45	6	10	1.21
Climbing Steps	11	9.09	7.07	11.12	0	10	3.02
Squatting	11	4.18	3.06	5.30	0	5	1.66
Overall Score	11	85.00	75.31	94.69	50	100	14.42

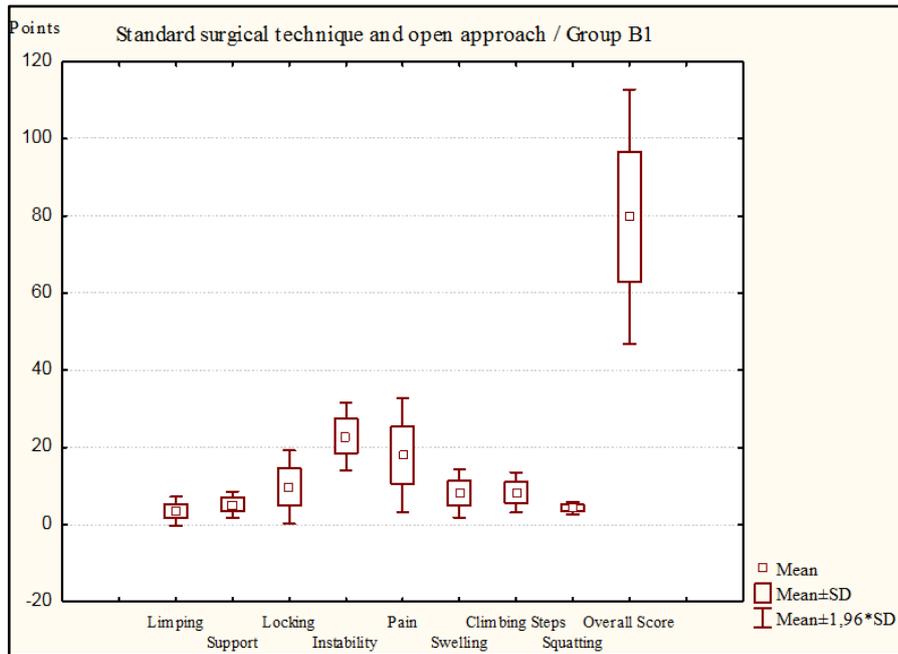


Fig.2. Descriptive statistics / Group B1

3. Difference: Fixation with contralateral elevation and percutaneous fixation with screws (Group A1) & Standard surgical technique and open approach (Group B1)

The differences between the two groups of patients in the parameters analysed are shown in Table 3. With $Z = 0.00$ and $p > 0.05$ ($p = 1.00$), there is no significant difference in the parameter Limping between the two groups of patients.

The parameter Support shows a greater score in patients treated with the standard surgical technique and open approach (Group B1), but the difference with respect to the score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), with $Z = -0.71$ and $p > 0.05$ ($p = 0.48$), is not a significant one.

The parameter Locking shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B1), with $Z = 0.80$ and $p > 0.05$ ($p = 0.42$), is not a significant one.

The parameter Instability shows a greater score in patients treated with the standard surgical technique and open approach (Group B1), but the difference with respect to the score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), with $Z = -0.55$ and $p > 0.05$ ($p = 0.58$), is not a significant one.

The parameter Pain shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B1), with $Z = 1.23$ and $p > 0.05$ ($p = 0.22$), is not a significant one.

The parameter Swelling shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B1), with $Z = 1.05$ and $p > 0.05$ ($p = 0.30$), is not a significant one.

The parameter Climbing Steps shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B1), with $Z = 0.86$ and $p > 0.05$ ($p = 0.39$), is not a significant one.

The parameter Squatting shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B1), with $Z = 0.89$ and $p > 0.05$ ($p = 0.37$), is not a significant one.

The Overall Score is greater in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A1), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B1), with $Z = 0.80$ and $p > 0.05$ ($p = 0.42$), is not a significant one.

Table 3. Difference: Fixation with contralateral elevation and percutaneous fixation with screws (Group A1) & Standard surgical technique and open approach (Group B1)

Parameters	Rank Sum Group A1	Rank Sum Group B1	U	Z	p-level	Valid N Group A1	Valid N Group B1
Limping	132.00	144.00	66.00	0.00	1.00	11	12
Support	120.50	155.50	54.50	-0.71	0.48	11	12
Locking	145.00	131.00	53.00	0.80	0.42	11	12
Instability	123.00	153.00	57.00	-0.55	0.58	11	12
Pain	152.00	124.00	46.00	1.23	0.22	11	12
Swelling	149.00	127.00	49.00	1.05	0.30	11	12
Climbing Steps	146.00	130.00	52.00	0.86	0.39	11	12
Squatting	146.50	129.50	51.50	0.89	0.37	11	12
Overall Score	145.00	131.00	53.00	0.80	0.42	11	12

4. Fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen)

A total of 12 patients were treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen). Table 4 and Fig 3 contain the descriptive statistics of parameters analysed. The analysed parameters vary in the following intervals: Pain 5.18 ± 0.60 points; Walking 5.18 ± 1.83 points; Movement 5.64 ± 0.67 points; Stability 5.45 ± 1.81 points; Overall Score 27.45 ± 3.27 points.

Table 4. Fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen)

	Number	Average	Confidence -95.00%	Confidence +95.00%	Minimum	Maximum	Std. Dev.
Pain	11	5.18	4.78	5.59	4	6	0.60
Walking	11	5.18	3.95	6.41	1	6	1.83
Extension	11	6.00			6	6	
Movement	11	5.64	5.18	6.09	4	6	0.67
Stability	11	5.45	4.24	6.67	0	6	1.81
Overall Score	11	27.45	25.26	29.65	19	30	3.27

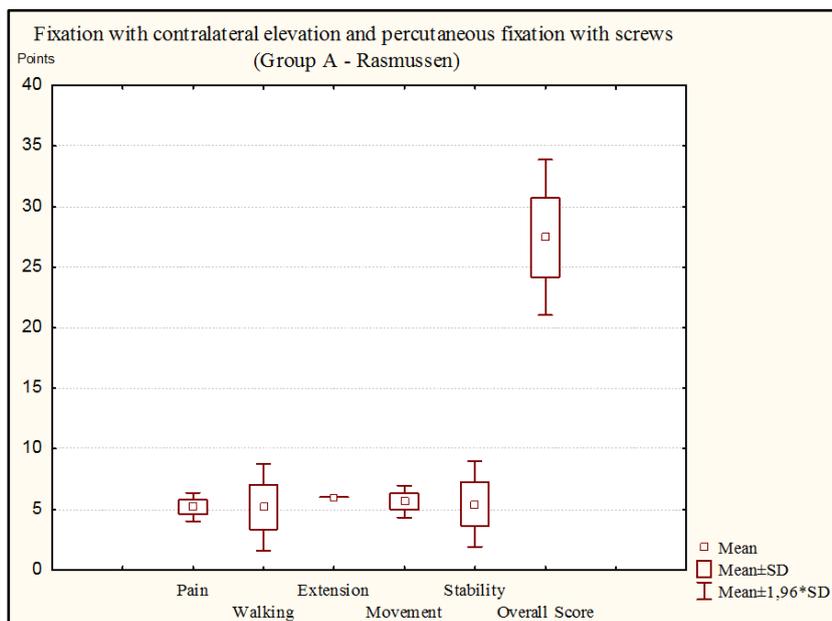


Fig. 3. Fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen)

5. Standard surgical technique and open approach (Group B – Rasmussen)

A total of 12 patients were treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group B – Rasmussen). Table 5 and Fig 4 contain the descriptive statistics of parameters analysed. The analysed parameters vary in the following intervals: Pain 4.25 ± 1.60 points; Walking 4.42 ± 2.07 points; Movement 5.17 ± 1.19 points; Stability 5.67 ± 0.78 points; Overall Score 25.50 ± 4.06 points.

Table 5. Standard surgical technique and open approach (Group B – Rasmussen)

	Number	Average	Confidence -95.00%	Confidence +95.00%	Minimum	Maximum	Std. Dev.
Pain	12	4.25	3.23	5.27	0	5	1.60
Walking	12	4.42	3.10	5.73	1	6	2.07
Extension	12	6.00			6	6	0.00
Movement	12	5.17	4.41	5.92	2	6	1.19
Stability	12	5.67	5.17	6.16	4	6	0.78
Overall Score	12	25.50	22.92	28.08	17	29	4.06

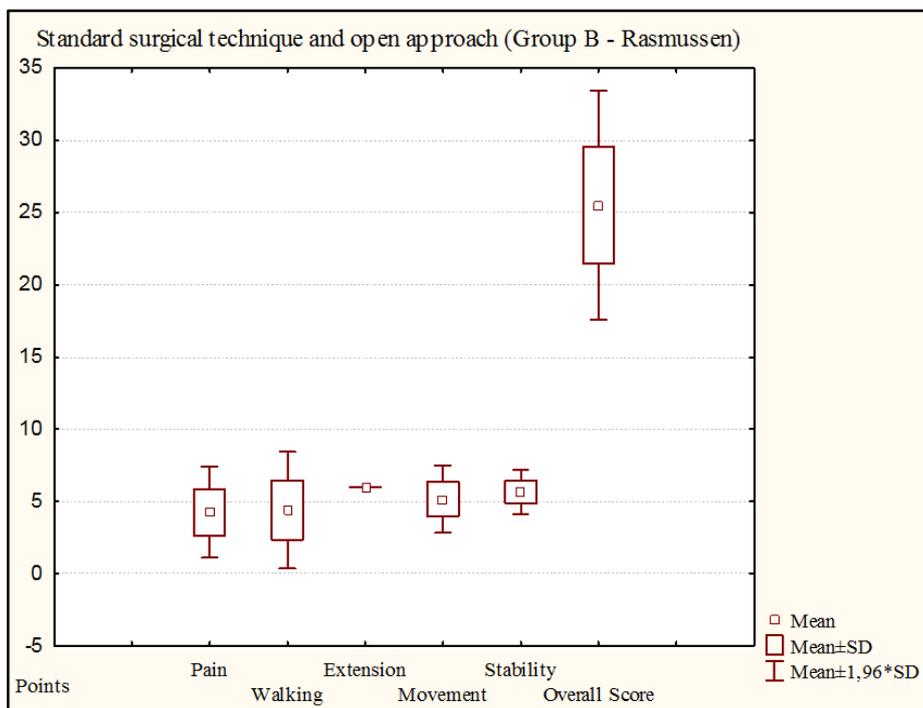


Fig. 4. Standard surgical technique and open approach (Group B – Rasmussen)

6. Difference: Fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen) & Standard surgical technique and open approach (Group B – Rasmussen)

The differences between the two groups of patients in the parameters analysed are shown in Table 6.

The parameter Pain shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B – Rasmussen), with $Z = 1.54$ and $p > 0.05$ ($p = 0.12$), is not a significant one.

The parameter Walking shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B – Rasmussen), with $Z = 0.83$ and $p > 0.05$ ($p = 0.41$), is not a significant one. With $Z = 0.00$ and $p > 0.05$ ($p = 1.00$) there is no significant difference in the parameter Extension between the two groups of patients.

The parameter Movement shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B – Rasmussen), with $Z = 0.95$ and $p > 0.05$ ($p = 0.34$), is not a significant one.

The parameter Stability shows a greater score in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B – Rasmussen), with $Z = 0.25$ and $p > 0.05$ ($p = 0.81$), is not a significant one.

The Overall Score is greater in patients treated with the fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen), but the difference with respect to the score in patients treated with the standard surgical technique and open approach (Group B – Rasmussen), with $Z = 1.23$ and $p > 0.05$ ($p = 0.22$), is not a significant one.

Table 6. Difference: Fixation with contralateral elevation and percutaneous fixation with screws (Group A – Rasmussen) & Standard surgical technique and open approach (Group B – Rasmussen)

	Rank Sum Group A	Rank Sum Group B	U	Z	p-level	Valid N Group A	Valid N Group B
Pain	157.00	119.00	41.00	1.54	0.12	11	12
Walking	145.50	130.50	52.50	0.83	0.41	11	12
Extension	132.00	144.00	66.00	0.00	1.00	11	12
Movement	147.50	128.50	50.50	0.95	0.34	11	12
Stability	136.00	140.00	62.00	0.25	0.81	11	12
Overall Score	152.00	124.00	46.00	1.23	0.22	11	12

DISCUSSION

Historically, the very complexity of the tibial plateau traumas made their treatment develop over a long period of time. At first, the tibial plateau fractures (Schatzker type I, II, III, and IV) were treated conservatively without taking into account the soft tissue trauma, depression of the plateau, residual instability, or the presence of varus or valgus angulation [4,5,6].

After the anatomy and function of the separate parts of the knee joint were examined in great detail, the opinion as regards the appropriate treatment changed. Thus, the treatment of tibial plateau fractures were primarily focussed on the depression of the fractured part, but the opinions regarding the extent of the depression differed [7,8,9]. The tibial plateau fractures were treated with the open approach with arthrotomy, and the fracture was fixated with plates and screws.

According to recent studies, a primary indication for the treatment of tibial plateau fractures is the residual instability and the presence of varus or valgus angulation [10,11]. Depending on the type of tibial plateau fracture, the treatments to be taken into consideration are: open reduction with arthrotomy; minimally invasive treatment with small incisions and specially shaped plates; minimally invasive treatment with traction and percutaneous fixation; and minimally invasive treatment with arthroscopy and percutaneous fixation. The open reduction with arthrotomy and fixation with plates is a method of choice used in comminuted and complex fractures. Because of this method's poor functional results (residual instability, very limited flexion, and high percent of infections), more and more schools promote the minimally invasive types of treatment.

The minimally invasive types of treatment are a method of choice in treating the tibial plateau fractures. Various schools promote different minimally invasive treatments. There are a number of studies which compare various minimally invasive treatments of tibial plateau fractures. Radheshyam Sament's study (Closed reduction and percutaneous screw fixation for tibial plateau fractures), examines parameters that are closest to the parameters examined in our study [12,13,14]. The results of the aforesaid study correspond to the results in our study. The results we have come to, support the above stated.

CONCLUSION

The contralateral minimally invasive approach of Schatzker classification I, II, III, and IV of tibial plateau fractures is a surgical treatment that results in a small number of complications and has its advantages over the open surgical approach used in patients with these types of injuries. The main benefit of this surgical treatment is preservation of the soft tissue which, of course, affects the end results as well. The minimally invasive surgical treatment allows for a shorter hospital stay of the patients, their quicker verticalization, and faster healing of the fracture, which in turn makes the effective return to everyday activities possible. On the other hand, the standard procedure of open surgical approach provides a direct visualization of the traumatised structures, making it easier to anatomically reconstruct the fractured bone fragments of the tibial plateau and to repair the soft tissue trauma.

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LIPOSUCTION - ASSISTED LIPECTOMYIgor Peev¹, Zhogovska-Mirchevska E¹, Spasevska L²¹University Clinic for Plastic and Reconstructive surgery, Medical Faculty, Skopje²Institute of Pathology, Medical Faculty, University St Cyril and Methodius, Skopje**ABSTRACT**

Background. Lipomas are the most common benign neoplasms originating from adipose tissue, usually subcutaneously located. Patients seek removal, mainly for aesthetic reasons as they often disfigure body contours mutilating natural appearance. Historically, surgical removal comprises the standard of treatment. Liposuction emerges as a new successful treating method in selected cases.

Objective. The primary objective is to evaluate the effectiveness of liposuction in removing lipomas in terms of success rate of total removal, risk of eventual recurrences and patients' satisfaction. Additionally, observation of postoperative events and their resolution is to be done.

Method. This is a retrospective – prospective study comprising 5 cases of liposuction - assisted lipectomies. Thorough analysis of the cases was conducted: preoperative assessment and diagnostics, operative technique and postoperative follow-up. Postoperative period was divided in short term (up to 4 weeks) when early postoperative complications were observed, and long term (up to 12 months) when remnants and eventual recurrences can be seen. Satisfaction was assessed as a questioned inquiry.

Results. Summarizing the results, descriptive statistic was used. In short term follow- up, self-resolving bruising, edema and mild pain were noted. There was no case of infection. In period of up to 12 months follow-up, total lipoma removal and 0% recurrence in all cases was pointed. Satisfaction rate of the patients was high.

Conclusion. Liposuction can be as effective as open surgical removal when treating conventional lipomas. High satisfaction rate, due to small incisional scars, can be achieved.

Key words: lipoma; liposuction; liposuction – assisted lipectomy

INTRODUCTION

Lipomas are the most common benign tumors of mesenchymal origin, with an incidence of 1-2.1 / 1000 [1]. Clinically, they represent mainly as well-defined, mobile, painless and slow-growing soft tissue masses that occur sporadically, but may be associated with hereditary syndromes as well. They can emerge anywhere in the body, but usually under the skin, on the trunk or extremities. [2]

Discussing about lipomas, we refer to the so-called conventional or common lipomas which are composed of pathologically mature adipocytes, without atypia, grouped into lobules by trabecules and fibrous septa. [3,4] In addition to endothelial and immune competent cells, in the fibro-vascular stroma located in the trabecules, there are also CD29 + / CD44 + cells, very similar to fibroblasts. These are stem cells originating from adipose tissue, which are thought to be probable cause of relapse in an incomplete removal of lipomas as they are the main precursors of adipocytes. [5]

Reasons for lipoma removal are an aesthetic nuisance, discomfort, functionally disrupting or cancer phobia. Clinical diagnosis is usually easily set up, but in unclear cases, imaging techniques complemented by thin - needle aspiration / core biopsy can help. Although much less common, it should be mentioned that there are malignant varieties originating from adipose tissue or that secondary malignant alteration is possible. [6,7]

Traditionally, open surgical extirpation is a widely accepted method for the treatment of lipomas. However, in recent decades new treatment modalities appear [8-13]. Liposuction, due to the simplicity and high security, is the most commonly used alternative with rapid growth in utilization. The main advantages of liposuction are effectiveness, small scars and better aesthetic results, shorter operative time, lower risk of hematoma and seroma, and high compliance of patients [8,9]. Despite expanding number of published scientific papers on its success in lipoma treatment, liposuction is still not widely accepted. Main drawbacks are limited visualization during removal, tissue sample fragmentation for histological analysis and possibility of recurrence due to incomplete removal of lipomatous or capsular/hard residual tissue.[14] However, in properly selected cases with good preoperative evaluation, with clear diagnosis and appropriate operative technique used, liposuction - assisted lipectomy may have an advantage over the classical operating technique.

This paper publishes the results of the treatment of lipomas with liposuction in a study of 5 cases. The primary objective is to assess the effectiveness of liposuction in lipoma removal, taking into account the degree of success, the risk of any recurrence and patient satisfaction. In addition, postoperative events will be observed, their progress and the need for any further interventions. Finally, the operative technique will be discussed and its applicability.

MATERIAL AND METHODS

This study included 5 patients with subcutaneous corporal lipomas which have been removed by liposuction. Patients were treated at the University Clinic for Plastic and Reconstructive Surgery in Skopje, where the standard treatment for lipomas is an open surgical extirpation. Patients were offered the new method and after the discussion about the benefits, limitations and risks of both methods, patients have embraced the alternative. The cases were followed prospectively and are still subject of monitoring. Lipomas that are moderately large or large, with a diameter equal to or greater than 5 cm were included. Lipomas smaller than 5cm were not taken under consideration. Ultrasonographic examination and fine-needle aspiration biopsy were made in each case preoperatively. Magnetic Resonance Imaging was used where ultrasonography was not conclusive. Clinical investigation concluded conventional subcutaneous lipomas in all patients.

Operative technique: Surgery is performed in local anesthesia solely or in combination with intravenous sedation. Single shot of broad spectrum antibiotic was given i.v. or i.m. 30-60min. before operation. Marking the outer margins of the skin lipomas follows. After administration of 2 ml local anesthetic (1% lidocaine + 0.01% adrenaline) on the sidelines of a lipoma or about 2 cm laterally (usually where most cosmetically desirable), a sharp 0.5cm incision is made with a scalpel No.15 . Through this port, using a ϕ 1mm/ ϕ 3mm blunt infiltration cannula, the tumor is infiltrated with modified Klein solution (0.1% lidocaine + 1: 1m adrenaline in 1000ml 0.9% NaCl solution) by means of tumescent "superwet" technique of infiltration. The endpoint of infiltration is an orange peel like pale skin. After a period of 15min. while gently massaging, the liposuction is conducted with a blunt Mercedes ϕ 3mm/ ϕ 5mm cannula (Byron®) using manually created vacuum with 60ml. Toomey syringe. End point of liposuction is receiving skin smoothing and predomination of a bloody aspirate in the syringe. (Figure 1) The aspirate is decanted and filtered on a gauze. The hard part is sent for pathohistological analysis. Through the same incision, any residues present in the cavity as hard residual tissue are removed with long paeen. It is grasped and pull out easily from the internal walls and then sent for pathohistological analysis. The incision is closed with resorptive subcuticular suture followed by a compressive dressing. Patient is discharged home few hours later same day. Check-ups are scheduled on the third and seventh postoperative day and their dynamics depends on further requirements. The patient is given advice to wear a compression garment or bandage for 3 weeks without limiting usual activities. During this period up to one month, we follow early postoperative complications and control the wound / scar. In the late follow-up period of one year, we follow and control the quality of the scar and the liposuctioned surface. At the end of the 12th month or later, overall patient satisfaction of the treatment is questioned. Special attention in this period is paid to the eventual development of recurrence.

Patients' satisfaction rate from operation and final aesthetics was evaluated by using 1 to 5 rating scale questioners.

RESULTS

All cases were operated on between the year of 2013 and of 2015. In all cases, the indications for surgery were solitary, suprafascial lipomatous lesions. Three of them are women and two men, aged 19 to 57 years (average 38 years). All lipomatous changes were at least a diameter greater than or equal to 5 cm (average size 7.6 x 10,4cm). In terms of location, 2 cases were located on the lateral chest wall, one on the upper dorsal region, one in front of the lower-lateral abdominal wall and one on the frontal shoulder. In all cases, the result of the patohistological analysis of the aspirate, with or without the capsule was an ordinary, conventional lipoma.

A common postoperative finding in all was swelling and soft tissue ecchymosis. They resolved spontaneously in the early follow-up period. Pain was moderate. In none of the cases, there was need for aspiration of collected seroma, nor was the case of infection or problematic healing of the wound. Complete removal of lipomas was achieved in all cases. In the late control for at least 12 months or later, there was not even one case with a relapse. There was no case of bad scar or indentation and the unevenness of the liposucted surface. When asked if they were satisfied with the treatment, all patients showed a high degree of satisfaction in terms of operation and in terms of early and late postoperative period. Summarized results are shown in Table 1. Photographed progress of a case shown in Figure 2.

Table 1. Summarized results

Patient/gender	Age	Size(cm)	Location	Relapse	Contentment
M.Jb. ♀	19	5x6	Thorax	-	+++++
J.A. ♀	32	3x6	Thorax	-	+++++
M.M. ♀	42	7x10	Omaris	-	+++++
Г.И. ♂	41	13x20	Abdomen	-	+++++
J.JI. ♂	57	10x10	Dorsi	-	+++++

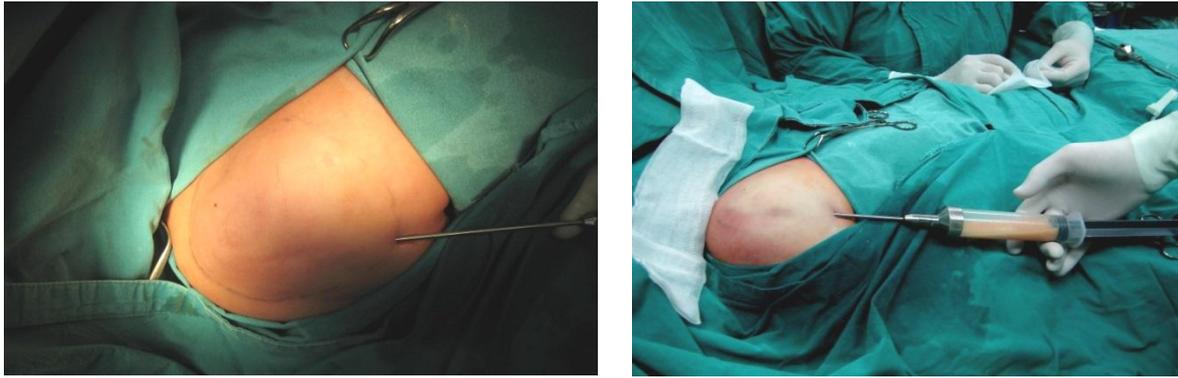


Fig. 1. Liposuction - assisted lipectomy (infiltration and liposuction)



Fig. 2. Preoperative diagnosis, early postoperative period, evaluation of late results.

DISCUSSION

Liposuction technique as a method of evacuation of the adipose tissue was introduced in the mid-70s of the last century with the work of Fischer brothers, primarily for aesthetic purposes. With the introduction of wet technique of Illouz, and then the tumescent technique of Klein, safety in its use significantly improved, which expanded indications for its application. [15]. Its safety standards are well documented. [16,17] In 1985, Rubenstein et al. published the first liposuction - assisted lipectomy [18], which was an introduction to non-aesthetic applications of liposuction [19], and today, lipomas are the most common reason for that. There are numerous case reports and series of patients, both children and adults, which highlight its success in lipoma treatment. [8,9,18,20-30] It is appropriate in removal of moderately large (4-10cm) and large lipomas (over 10 cm), although there are reports of removal of small lipomas (less than 4cm). [21] Our observations suggest that subcutaneous lipomas with diameter more than 5cm can be safely, effectively and completely removed with liposuction. The outcome may vary for lipomas with intramuscular propagation. The main advantages of liposuction stand out: a good aesthetic result, safety, lower risk of seroma, hematoma and complications in general, inconspicuous incisional scar, less pain, a good cost / benefit ratio, the possibility of removing more lipomas with fewer scars, the opportunity to remove lipoma through remote incision acceptable cosmetically etc [19]. The main concern comes from the possibility in overlooking malignancy and a higher risk of recurrence observed in some series. [14]

In order to exclude malignancy, before using this technique, an exact preoperative diagnosis is an imperative, which in most cases clinically is not difficult. Additional information may be obtained by linear ultrasonography and thin - needle aspiration biopsy/nuclear core biopsy. These should be a minimum of preoperative tests, as in our series. One should always take into consideration the atypical lipomas and liposarcoma that can mimic same clinical presentation. Every lipoma with atypical clinical features should be further examined before undergoing liposuction. [6,31] Doubt should arouse abrupt and painful growth of the tumor sizes over 10cm and locations that are uncharacteristic and deeper, especially in patients over 5th decade of life. In that case an MRI in the hands of an experienced radiologist can determine the diagnosis because it is highly sensitive and specific for soft tissue tumors [31,32]. Finally, in such cases, before any decision for surgery it should be preceded by an open biopsy. Although liposarcoma accounts for almost 20% of all soft tissue sarcomas [31], their incidence is very low ($2.5 / 10^9$ per year), and most of them are well - differentiated. [3,7]. However, the standard of their treatment is an open and radical surgical excision. Error as liposuction of misdiagnosed liposarcoma is an extremely undesirable scenario [33].

Additionally, the hard decanted liposuctional aspirate should be sent to pathohistological verification. Several studies demonstrate the integrity of the cell and stem cells in liposuction aspirate [34, 35], meaning that their reliable microscopic examination is possible. In this regard, the correct preoperative and postoperative diagnosis, the mistakes for misdiagnose are annulated.

The second concern relates to possible higher rate of recidivism, a statement that seems to be extracted prematurely as an observational conclusion from studies with small numbers of patients. The reason stated is the difficulty in removing the fibrous capsule and hard residual tissue with liposuction. [18] The late contains adipose derivate stem precursor cells. [5]. Recurrence risk in open classical lipectomy is about 2%. [31] All studies published in the literature on liposuction - assisted lipectomy are with limited number of participants to identify lower risk of recurrence or about 2%. [30] The only comparative study conducted by Raemdonck et al. which includes 30 cases, shows unacceptably high risk of recurrence in liposuction method compared to an open excision. [14] In a prospective study of Wilhelmi et al., in follow-up period to 10 years, no recurrence was observed in any of all 5 patients. [21]

Liposuction lipectomy in giant lipomas cases report an absence of recurrence in the follow-up period of 2 years. [25,26] In order to reduce the risk of recurrence, Al-Basty et al., recommended after completed wet liposuction, excision of the fibrous capsule with paeen (forceps) through the same or through counter-incision for larger lipomas. With this modification, in the follow-up period of 6 years no recurrence was observed in any of the 16 patients. Additionally, the extracted hard tissue can be sent for pathohistological analysis. [23] Choi et al. applied the proposed modification, but by using tumescent infiltration to the lipomas prior to liposuction. In the period of 2 years follow-up, no relapse was noted in 12 patients; still, in the early postoperative period 3 lipomatous remnants were found in dorsally located lipomas. [27] The author believes that due to stiffness/hardness of the dorsally-located lipomas, complete removal was not possible. The difference between these two studies is the infiltration technique, in the second being tumescent. It can have an impact as within this technique endpoint of liposuction is less obvious. Latest and largest study published comprises 44 lipomas in 23 patients where no recurrence is evidenced within a mean follow-up period of 6 years. Author used same modification i.e. combination of liposuction with extirpation of hard residual tissue using wet infiltration technique. [30] It seems that capsulectomy (hard residual tissue removal) should be included as a supplement to liposuction in order to achieve radicalism thus avoiding recurrence. Probably hard residual tissue bears the highest concentration of stem cells and they cannot be always mechanically destroyed only by means of liposuction. This might be an object of further examination. In our series a tumescent infiltration technique is used as it has advantages in terms of reduced bleeding risk. Whether capsule extraction follows, depends on the case. In fact, our objection is that in some cases suction is possible for the capsule as well, particularly in cases with a shorter medical history. Here, it is not very adherent to the surrounding tissue contrary to cases with longer history.

Postoperative period is usually accompanied by swellings, mild pain and moderate ecchymosis that are self- retreated. If hematoma and seroma occurs, punctional aspiration is needed and they resolve residue less. Infections are not common. [23,27,30] For these reasons, and due to effectiveness and safety, liposuction - assisted lipectomy is followed by high satisfaction and compliance of the patients. In our series, we found no complications outside the usual and all patients were satisfied with the final result.

CONCLUSION

Despite the rise of liposuction as a minimally invasive method for lipoma removal, with all its advantages, it is still not widely accepted among surgeons. It can be effectively and safely used in the treatment of subcutaneously located, moderately large and large, ordinary lipoma with clear preoperative diagnosis. In such cases, it might be superior alternative to classical open surgery with high satisfaction rate as an outcome. However, for such conclusions to be uniformed, larger randomized studies comparing the separate techniques, are required.

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GLUCOSE-INSULIN METABOLISM IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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ABSTRACT

There has been a great interest in the interaction between obstructive sleep apnea (OSA) and impaired glucose-insulin metabolism, but a shared intimate relationship with obesity makes discerning an independent link challenging. The aim of this study was to evaluate the prevalence of glucose abnormalities in patients suspected for OSA, referred to our Sleep laboratory. Two hundred patients with suspected OSA underwent standard polysomnography. Patients who had respiratory disturbance index (RDI) above 15 were diagnosed with OSA. In the morning after polysomnography, fasting blood levels of glucose, insulin and glycosylated hemoglobin (HbA1c) were determined, and homeostasis model assessment (HOMA) score was calculated. In the study, both OSA positive and OSA negative patients were divided according to the body mass index (BMI) in two groups: the first group with BMI ≤ 30 kg/m² and the second group with BMI > 30 kg/m². OSA positive patients with BMI ≤ 30 kg/m² had statistically significant higher blood level of insulin and HOMA index when compared to OSA negative patients with BMI ≤ 30 kg/m². There was no statistical difference in age, glucose and HbA1c level between these two groups of patients. OSA positive patients with BMI > 30 kg/m² had higher blood level of glucose, insulin and HbA1c and higher HOMA index versus OSA negative patients with BMI > 30 kg/m², but without statistically significant differences.

This study suggests that OSA could play a significant role in worsening of glucose metabolism in non-obese patients, but in obese patients, extra weight makes the impairment of glucose-insulin metabolism.

Keywords: obstructive sleep apnea, glucose, insulin

INTRODUCTION

Obstructive sleep apnea (OSA) is a common chronic disorder that is characterized by repetitive upper airway obstructions resulting in intermittent hypoxia and sleep fragmentation caused by arousals [1]. Among adults, 30–70 years of age, approximately 13% of men and 6% of women, have moderate to severe forms of OSA [2]. OSA is often closely associated with other conditions which are recognized causes of morbidity and mortality such as obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus, atherosclerosis and systemic inflammation [3, 4]. The pathophysiological mechanisms of alterations in glucose metabolism in OSA are incompletely understood. The process is likely multifactorial and our current concept involves sympathetic nervous system overactivity, systemic and adipose inflammation, oxidative stress and hormonal alterations among the most important pathways [5]. Although the evidence for a causal link remains limited, the major characteristics of OSA, namely sleep fragmentation/deprivation and intermittent hypoxemia likely play pivotal roles as triggering factors of the pathophysiology [6]. Obesity, type 2 diabetes mellitus (T2DM), glucose intolerance and insulin resistance (IR) are common in subjects with OSA, but a shared intimate relationship with obesity makes discerning an independent link challenging [7-9]. However, the available data are somewhat controversial, since the association of OSA and insulin resistance was mostly accounted for by obesity in other studies [10-13].

The aim of this study was to evaluate the prevalence of glucose-insulin abnormalities in patients suspected for OSA referred to our sleep laboratory for polysomnography.

MATERIALS AND METHODS

The study included 200 patients. It was conducted at the University Clinic of Pulmonology and Allergy in Skopje. Inclusion criteria were age from 35 to 60 years and persistence of minimum 2 of 3 clinical symptoms of OSA. The symptoms were snoring, witnessed apnea and daytime sleepiness. Exclusion criteria were previous history and treatment of diabetes and lipid abnormalities. Body mass index (BMI) was calculated and patients were divided into two groups according to the BMI. All patients underwent polysomnography (Respironix, model Alice 5). All results from polysomnography were scored manually according to standard criteria. Apnea, hypopnea and arousals were also identified according to the standard criteria and summarized in the form of a respiratory disturbance index (RDI). All patients with RDI above 15 were diagnosed with OSA. In the morning after polysomnography, fasting blood sample was collected from all patients. Blood levels of glucose (G), insulin (INS), glycosylated hemoglobin (HbA1c) were determined in all patients, and insulin resistance (IR) was calculated using the homeostasis model assessment (HOMA) score (fasting serum insulin (mIU/l) \ fasting plasma glucose mmol/l)/22.5) (14).

Biochemical measurements were conducted using a Hitachi auto analyzer. Serum insulin was determined with an enzyme immunoassay. Statistical analyses were performed using the Statistica software (Stat Soft). Comparisons between variables were made using the unpaired t-test for parametric data and the Mann Whitney U test (ANOVA) for non-parametric data. Statistical significance was considered at $p < 0.05$.

RESULTS

From all study patients, 51 were female with an average age of 49 ± 9 years and 149 were men with an average age of 47 ± 9 years. There was no significant difference in age, BMI and RDI between males and females. There was a significant difference in the occurrence of OSA in men versus women, 109 (73.2%) of males and 31 (62.8%) of females were OSA positive ($p < 0.03$). According to BMI, patients in the study were divided into 2 groups. There were 120 non-obese patients with $BMI \leq 30 \text{ kg/m}^2$, and 80 obese patients with $BMI > 30 \text{ kg/m}^2$. In non-obese group with $BMI \leq 30$, 62 patients were OSA negative and 58 patients were OSA positive. In obese group with $BMI > 30$, 14 patients were OSA negative, and 66 patients were OSA positive (Figure 1).

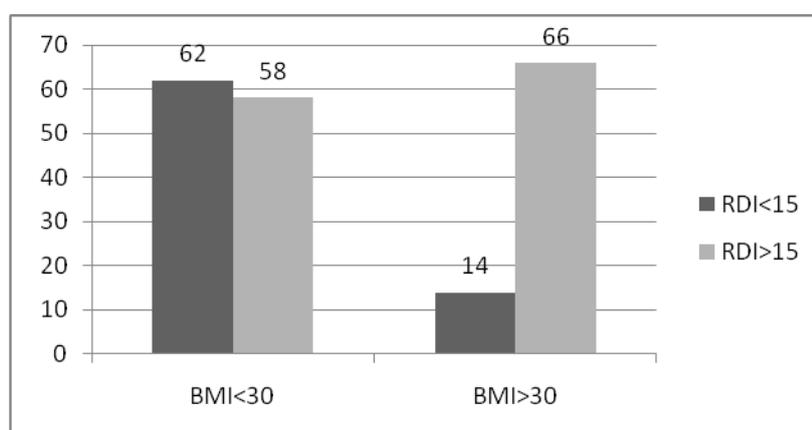


Fig. 1. Frequency of OSA in study patients divided according to BMI

In the study, both OSA positive and OSA negative patients were divided according to BMI in two groups: the first group with $BMI \leq 30 \text{ kg/m}^2$ and the second group with $BMI > 30 \text{ kg/m}^2$. OSA positive patients with $BMI \leq 30 \text{ kg/m}^2$ had statistically significant higher BMI, insulin blood level and HOMA index when compared to OSA negative patients with $BMI \leq 30 \text{ kg/m}^2$. There was no statistical difference in age, glucose and HbA1c level between these two groups of patients. (Table 1).

Table 1. Comparison between OSA positive and OSA negative patients with $BMI \leq 30$

	BMI ≤ 30				p
	RDI < 15 (62 pts)		RDI > 15 (58 pts)		
	X	\pm SD	X	\pm SD	
RDI	4.65	3.41	38.68	16.92	0.000
Age (years)	47.08	9.56	47.62	8.38	NS
BMI	26.55	2.40	27.38	1.80	0.035
G (mmol/L)	5.16	0.60	5.30	0.39	NS
INS (IU/ml)	5.25	1.61	6.47	2.05	0.000
HbA1c (%)	5.17	0.32	5.20	0.25	NS
HOMA	1.21	0.42	1.53	0.54	0.000

OSA positive patients with $BMI > 30 \text{ kg/m}^2$ had higher blood levels of glucose, insulin and HbA1c and higher HOMA index versus OSA negative patients with $BMI > 30 \text{ kg/m}^2$, but without statistical significant differences (Table 2).

Table 2. Comparison between OSA positive and negative patients with BMI>30

BMI >30					
	RDI < 15 (14 pts)		RDI > 15 (66 pts)		
	X	±SD	X	±SD	p
RDI	6.81	5.01	48.26	19.17	0.000
Age	48.21	10.76	48.74	8.62	NS
BMI	32.14	1.59	34.38	3.11	0.011
G (mmol/L)	5.63	0.50	5.68	0.61	NS
INS (IU/ml)	7.29	5.07	8.17	5.04	NS
HbA1c (%)	5.44	0.41	5.48	0.37	NS
HOMA	1.82	1.20	1.98	1.33	NS

(OSA)-Obstructive sleep apnea, (RDI)-Respiratory disturbance index, (BMI)-Body mass index, (G)-glucose, (INS)-insulin, (HbA1c)-glycosylated hemoglobin, (HOMA)-homeostasis model assessment.

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DOES INTRA-ABDOMINAL PRESSURE MEASUREMENT INCREASE THE RISK OF URINARY TRACT INFECTION IN CRITICALLY ILL PATIENTS?

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ABSTRACT

Introduction. Intra-abdominal hypertension and abdominal compartment syndrome have been shown to contribute to organ dysfunction and mortality in critically ill patients. The diagnosis relies on intra-abdominal pressure measurement.

Aim. To determine whether intra-abdominal pressure monitoring using the Foley catheters and bladder pressure measurements increases the risk of urinary tract infection.

Material and methods. Retrospective chart and database review of 130 critically ill patients who underwent intravesical pressure monitoring was done in the Intensive Care Unit at the University Clinic for Anesthesia, Reanimation and Intensive Care, Skopje-Macedonia. For the measurements of intra-abdominal pressure a standard sterile procedure was used. A system was used in which a three-way stopcock was inserted for measuring the intra-abdominal pressure after instillation of 25 mL of saline into the bladder. Analysis and urine cultures of patients that developed fever of > 38.5°C were obtained. Urinary tract infection was defined by microbiological culture documentation of more than 100,000 colony-forming units per high power field of either a specific bacterium or fungus together with significant pyuria.

Results. In a total of 130 patients intra-abdominal pressure measurements were made via the bladder. Patients had 520 intravesical pressure measurements performed. In total 4.6% of the patients who required intravesical pressure monitoring developed a urinary tract infection.

Conclusion. Intravesical pressure monitoring does not have an influence on the risk of urinary tract infection in critically ill patients.

Keywords: intra-abdominal pressure; intra-abdominal pressure monitoring; urinary tract infection

INTRODUCTION

Intra-abdominal pressure (IAP) has gained interest in a wide variety of patient populations since intra-abdominal hypertension (IAH) and abdominal-compartment syndrome (ACS) have been recognized as a major cause of potentially life-threatening end-organ dysfunction. As IAP increases, the physiology of multiple organ systems is affected leading to inadequate organ perfusion and tissue oxygenation, multiple organ failure, and death [1].

Recent studies have shown that clinical judgment or physical examination is far from accurate in predicting a patient's IAP. Diagnosis relies on IAP measurement [2-4].

Different techniques have been developed, either measuring IAP directly or indirectly (via stomach, bladder, rectum, or inferior vena cava) [4,5]. The Abdominal Compartment Society (WSACS, www.wsacs.org), founded in 2004, outlined definitions and recommendations referring to the measurement of IAP in 2006/2007 [6, 7], which were subsequently updated in 2013 [8]. These documents include an underlying and fundamental message that we need to measure IAP.

The referred standard for intermittent IAP measurement is via the urinary bladder [7, 9]. Intravesical pressure (IVP) monitoring is considered the method of choice for indirect IAP measurement due to its accuracy and relative ease of implementation [10-13].

Although the benefits of IVP monitoring in the diagnosis, prevention, and management of IAH/ACS have been demonstrated [14], some clinicians remain reluctant to institute this monitoring technique out of concern for increasing the patient's risk of device-related nosocomial urinary tract infection (UTI) [15]. In addition, nosocomial infections are associated with substantial increases in morbidity and mortality rates, particularly in critically ill patients [16]. Many studies have demonstrated prolonged hospital stays and higher cost secondary to device-related blood stream infections (BSI), ventilator-associated pneumonia (VAP), and UTI [17,18].

The aim of the study was to determine whether intra-abdominal pressure monitoring using the Foley catheters and bladder pressure measurements increases the risk of urinary tract infection.

MATERIAL AND METHODS

Patients

This is a retrospective cohort study conducted in the 18 bed Intensive Care Unit (ICU) of the tertiary hospital - University Clinic for Anesthesia, Reanimation and Intensive Care, University Clinical Center "Mother Theresa" Skopje - Macedonia. Using patient database, patient demographics, patients who required IVP measurements, number of IVP measurements, number of patients with urinary tract infection and urine culture samples taken were collected.

In all patients admitted to ICU, according to the standard sterile procedure a urinary Foley catheter was placed. In patients who had more than two risk factors (obesity, sepsis, abdominal surgery, ileus development, fluid resuscitation) for developing IAH, IAP was measured. All patients were cultured according to the standing ICU protocol on admission (nose and throat swab culture test and additionally investigations according to patient medical history, clinical symptoms and underlying disease). Patient data were accessed and exported to an Excel worksheet (Microsoft). For this study there was no need for an informed consent due to the retrospective nature of the analysis.

Method of intravesical pressure measurements

According to WSACS, IAP was measured via urinary Foley catheter, an indirect, simple, minimally invasive, closed system procedure. IAP was expressed in mmHg, measured at the end of expiration, in the supine position. The transducer was zeroed at the level of the mid-axillary line, with an instillation volume of no greater than 25 ml of saline, and measured after 30-60 seconds to allow bladder detrusor muscle relaxation and measured in the absence of active abdominal muscle contractions. If the patient was awake, we explained the procedure to him/her; if the patient was sedated, then we ensured a good sedation (8,9). Measuring technique is demonstrated in Figure 1.

Figure 1.

Patients were divided in three groups according to the level of IAP, proposed by the WSACS. Group I patients with IAP of 12-15mmHg, Group II patients with IAP 16-20mmHg and Group III patients with IAP 21-25mmHg.

APP was calculated as mean arterial pressure minus intra-abdominal pressure.

$$APP = MAP - IAP$$

Method for detection of urinary tract infection

Urine analysis and urine cultures were obtained from any patient that developed a fever of $> 38.5^{\circ}\text{C}$ or had macroscopically grossly purulent urine.

Definitions

Urinary tract infection was defined by microbiological culture documentation of more than 100,000 colony-forming units per high power field of either a specific bacterium or fungus together with significant pyuria.

Statistical analysis

Descriptive statistics are presented as mean \pm standard deviation. The data are analyzed using Difference test.

RESULTS

In a total of 130 patients admitted in the ICU urinary Foley catheter was placed and IAP measurements were performed. IAP measurements were obtained via the bladder.

Demographic data of the patients were similar, with respect to sex, age, weight, height and BMI (Table 1). There was variety of clinical diagnosis. As a value of IAP, APP, MAP and peripheral saturation with oxygen (Sat%), we used the mean value from all measurements. The results obtained are presented in Table 2.

Patients underwent a total of 520 intravesicular pressure measurements.

The total number of urine cultures was 34. Six patients who required intravesicular pressure monitoring developed a urinary tract infection, 6 of the samples were positive for more than 100,000 colony-forming units per high power field, and none of the samples taken was positive for specific bacterium or fungus.

Overall, 4.6% of the patients who required intravesicular pressure monitoring developed a urinary tract infection.

Data regarding the crude and adjusted rate of UTI are shown in Table 3.

Table 1. Patients characteristic

Patients characteristic	
Sex M/F	78/52
Age/year	54±14
BMI, kg/m ²	27±4
Height, cm	169±9
Weight, kg	74±7

BM I= body max index; F = female; M=male. Data are presented as mean ± standard deviation.

Table 2. Values of IAP; MAP; APP; Sat%

Parameters	Group I	Group II	Group III
IAP	13.22±0.93	17.76±1.35	22.35±1.13
MAP	88.74±13.55	90.84±15.39	78.89±14.46
APP	75.28±13.30	72.56±16.59	56.74±14.99
Sat%	99±1	98±1	96±1

IAP= intra-abdominal pressure; MAP= mean arterial pressure; APP=abdominal perfusion pressure; Sat%= peripheral saturation with oxygen. Data are presented as mean ± standard deviation

Table 3. Risk and rate of urinary tract infections

	Patients	UC	UC/ patients	>100,000 CFU	specific bacterium / fungus	UC POS	UC POS/ UC sample	UTI	UTI risc (CR)%	UTI risc (ADJ)%
Group I	61	13	0.2	2	/	2	0.15	2	0.02	0.15
GroupII	42	9	0.2	1	/	1	0.11	1	0.007	0.1
Group III	27	12	0.4	3	/	3	0.25	3	0.02	0.25
Total	130	34	0.3	6	/	6	0.17	6	0.04	0.17

IAP= intra-abdominal pressure; CFU= colony-forming units per high power field; UC= urine culture, POS= positive (bacteriuria); UTI= urinary tract infection; UTI risk (CR)= the number of UTI divided by the total number of patients; UTI risk (ADJ)= the number of UTI divided by the number of UC taken.

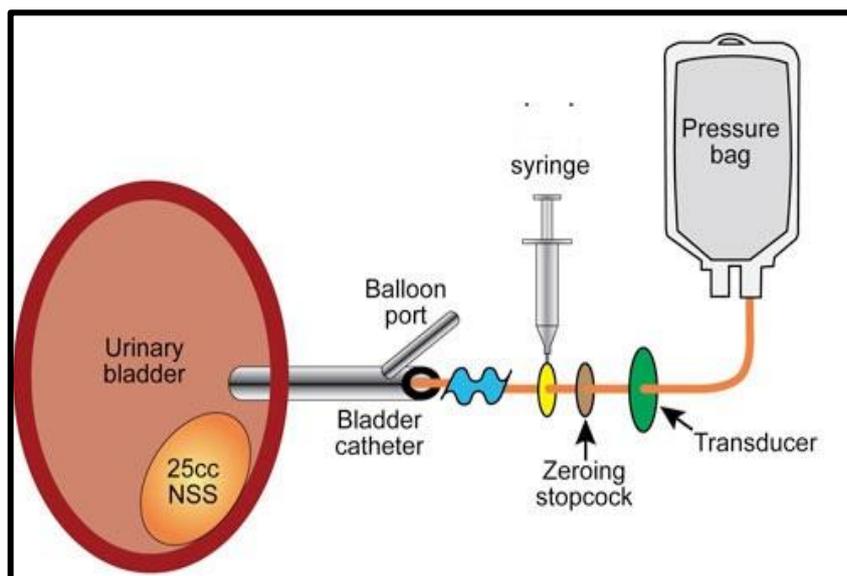


Fig. 1. Intravesicular manometry device. Intravesicular pressure monitoring involves measuring bladder pressure after infusing 25 mL of 0.9% normal saline.

DISCUSSION

Many factors contribute to the development of UTI, particularly in the critically ill patient. These usually are associated with manipulation of the genitourinary tract by catheters. The catheter acts as a conduit for introduction of bacteria into the normally sterile bladder. This foreign body in the presence of a compromised host allows bacterial overgrowth and subsequent infection [19,20]. Given the epidemiology of UTI, we hypothesized that greater manipulation of these catheters, such as by pressure measurements, would result in more infections.

The approach in our institution during this study was a closed technique in which the catheter was not compromised. In this study, patients who had IAP measurements were not at an increased risk of developing UTI, and IAP measurements were not an independent predictor of infection.

The original method for IVP monitoring was described by Kron and co-workers and required the patient's urinary catheter to be disconnected [21]. This leads to justified fears for device-related UTI. The modified technique proposed by Cheatham still used sterile saline instillation into the bladder but maintained the patient's urinary catheter as a closed system, which put to rest some of the concerns relating to UTI [22].

Duane *et al.* demonstrated a greater risk of UTI with bladder pressure measurements using an open technique in which the Foley catheter was compromised through insertion of an 18-gauge needle and disconnection of the Foley catheter to allow instillation of 50 ml of saline into the bladder [23]. This differs from our study since we did not disconnect the catheter to insert saline, but we used stopcock instead. In the study of Duane *et al.* trauma patients were investigated, while in our study we examined critically ill patients. On the other hand, in our study for measuring IAP we used installation of 25ml saline according to the WSACS) [9]. More than a decade ago Wallace *et al.* [24] observed that trauma patients were at a higher risk of nosocomial infections than other surgical patients. Since then, more emphasis has been placed on infection control measures, including minimization of device use. Miller *et al.* [25] significantly decreased the rates of BSI and UTI and reduced the occurrence of VAP with initiation of evidence-based plans, staff education, and commitment to protocol compliance.

Cheatham *et al.* have published a study on UTI risk in relation to IBP monitoring using other devices [15]. They found that IBP monitoring using a closed transducer technique with sterile saline instillations is safe and does not increase the risk of UTI. Ejike *et al.* presented similar results in a prospective observational study conducted in critically ill children, also using a closed technique with sterile saline installations [26].

The study of Desie N compared IAP measurements with three different intravesical methods: a modified homemade technique, a Foley Manometer with 35 ml reservoir, and a Foley Manometer low volume with less than 10 ml priming volume. They found that intravesical pressure monitoring as estimate for IAP either via a closed transducer technique or the closed Foley Manometer technique seems safe and does not alter the risk of UTI in critically ill patients [1].

There are some important and obvious limitations of our study. First of all, it is the retrospective design of the study that did not include data on antibiotic use. The second limitation is small sample size included. Furthermore, no interventions were evaluated to identify ways to improve the UTI rate and reduce the mortality rate.

In summary, intravesicular pressure monitoring does not have an influence on the risk of urinary tract infection in critically ill patients.

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MATERIAL AND NON-MATERIAL GIFTS FROM GENERAL PRACTITIONERS TO THEIR PATIENTS

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ABSTRACT

The topic of “gift giving” from doctors to patients is more than scarcely covered in the literature.

This paper presents results of a study on doctors’ material and non-material gifts to their patients, and the physician-patient relationship (PPR), where gifts are seen as agents of relation. This is a part of a large study about gifts from and to patients. It was conducted through an open-ended questionnaire, on a representative sample of Croatian general practitioners (GPs), N=265, from 2358 in total.

GPs give a lot of gifts to their patients, free examination being the most frequent one. Only two participants said they had never given anything to their patients. Money as a gift was explicitly declared by 39 participants (15%) and explicitly denied by only one.

To estimate the PPR, we compared the total number of gifts given from with those given to GPs, noticing a significant correlation. Regardless of the number of gifts, GPs' high level of humanity is positively correlated with received “gifts with no-expected-benefit”, i.e. gifts from former patients, from those who are already deceased, gifts brought without asking any examination or prescription. GPs’ humanity score is calculated as the sum of positively coded free-entry answers as: devotion, emotionally giving gifts, individual approach, gifts more appropriate to family members than to patients, GPs' composure or cheerful mood, gestures beyond the call of duty.

GPs who give a lot to their patients also receive a lot, but only those who express a high level of humanity receive the deep gratitude and appreciation in the form of “gifts with no-expected-benefit”, and this is considered a very good PPR.

Key words: Gift Giving, Family Medicine, Physician-Patient Relation, gifts from doctors to patients, Ethics, Altruism, Croatia

INTRODUCTION

Little is known about gifts given from doctors to patients. It is illustrative that there are only few orientational recommendations [1,2], much less then regarding patients’ gifts [3-6].

The articles on this topic are mostly based on single or hypothetical examples [7-10] and authors mainly speak about ethical aspects of these gifts. Some of them are stating it is not ethical at all [8,11,12,13], especially when money is in question [8,13], others are conflicted [7], and some accept positive therapeutic experience resulting from giving gifts to patients [2,7,9]. Special dilemmas are: the danger of becoming too close to patients [8,13], which might compromise therapeutic effects; the problem of negative legislative implications [1,7,8,10,12,11], which sometimes seems absurd even to the authors [7].

The very old basic hypothesis is that gifts are a kind of a materialized expression of emotions and gratitude [1]. H. Stein spoke about „love embodied in the gifts” already in 1966 [14]. If we consider gifts non-verbalized vectors of communication, than the logical question would be: how does this type of communication influence the physician-patient relationship (PPR)? Some patients’ gifts have positive and emotionally warm effects on physicians, such as letters and children drawings (9,15,16). A late non-material gift from a former patient could improve doctor’s mood for the whole day [17]. Some physicians could also experience discomfort in situations related to gift giving (18,19). Yet, doctor’s gifts can have a positive impact on patient’s illness [1,7,9,20,21,22] since the patient is no more “an object of treatment”, but a human being and a “friend” [7,21,23]. Nevertheless, authors caution physicians not to obligate patient with their gifts [1,12,13]. Only one study systematically explores therapeutic effects of doctors’ gifts [22]. Most importantly, PPR is a consequential element in treating patients [5,14,18,21,23,24,25].

The study in question aims at describing what doctors, general practitioners (GPs) in particular, actually give to their patients, meaning material and non-material gifts, what the elements of this interactive process are, and finally to explore the elements influencing PPR.

METHODS AND RESPONDENTS

The survey on gifts giving was conducted in 2006 and approved by the Ethical Committee of the Medical School of the University in Zagreb. The target population were Croatian active GPs, N=2358. The sample was collected randomly as proportionally stratified, with the following stratum criteria: region (21 counties), gender, the number of patients in care; all visible from the List of Family Medicine Teams (26). The GPs with less than two years of practice were excluded before approaching the survey. Final N=265, response rate 95.7%.

The survey was originally designed in the form of a large questionnaire, to explore GPs' experiences concerning gifts, both those given to and those received from patients. Gifts were defined as material and non-material.

To describe gifts given to their patients, GPs answered the question: "Have you, as a doctor, given a patient a gift?" They were asked to rate the following 11 types using the Likert scale from 0-10, with 0 meaning "never" and 10 meaning "every time in such an occasion":

1. Examination (for an uninsured person)
2. A box of medicine
3. Clothing or school supplies for poor families/children
4. A job offer or help in finding a job or income
5. Gifts you received yourself, but don't need
6. Asking a colleague for a favor for patient
7. Personal expert engagement, beyond the call of duty (personal phone number, home visits after working hours or during vacations)
8. A personal, professional favor that goes beyond official boundaries. Do you try to accommodate patients even if that might be against the rules? (unjustified sick leave so the patient has time to finish his/her house or make some extra money on the side, work in the field, nurse a sick parent, false sick leave codes so others do not find out about an abortion, hepatitis C, AIDS, false doctor's notes when a child admits he/she is not really ill)
9. Information on books or patient's interests
10. Unusual and specifically targeted gifts ("a loan" for cigarettes, some money to buy laxatives, items of a religious nature)
11. Other

There was also a free-entry question: "Describe impressive, common or typical gifts you give your patients." Spontaneous comments were also allowed, considered, and with all free-entry answers coded in 7 categories concerning different types of expressed humanity. The obtained result was simply the sum of all such attributes identified for each GP.

Several questions were taken from other parts of the study in order to estimate the influence of doctors' gifts on the physician-patient relationship (PPR):

1. "Have you had a patient (or a family member) come to your surgery just to bring you a gift, without needing any medication or examination?", with 7 available answers:
 - For Christmas, feasts
 - For your birthday
 - For some other reason (wedding, graduation, 'to share their joy with you')
 - As a sign of appreciation or gratitude for a past medical service
 - Other reasons
 - Have you received a gift from your former patients, after they went on to another GP's care?
 - Have you ever been left a gift by a patient who has been deceased, but designated a gift for you before he/she died?

The answers were simply Yes or No, with a possibility to add a comment. The method of counting these 7 questions was simply the sum of Yes answers for each GP.

2. A Likert question 0-10: "How many gifts do you receive in general?"
3. "How many days in the last 180 working days have passed without you receiving any gifts?" Write a number:

The survey was conducted as an open-ended, led questionnaire, under supervision and with the presence of the same researcher. Questions were allowed during the survey, but the respondents were not permitted to consult with each other about their responses, and no discussion with the researcher was allowed. Oral and written instructions were clearly presented beforehand and given right before the questionnaire was filled in. The respondents were informed about the topic beforehand, but without any details about the content.

Statistics

Descriptive statistics were used to describe GPs' gifts, Pearson and t-tests to analyze the correlation between gifts to and from patients, and ANOVA to determine the difference in gifts in relation to age and years of practice.

RESULTS AND DISCUSSION

DESCRIPTIVE PART

Description and level of GPs' gifts, self-assessed on Ls 0-10

Average Likert 0-10 values for gifts given from GPs to patients, sorted by questions:

1. A free examination	8.31
2. A free box of medicine	8.52
3. Clothing or school supplies for poor families/child	6.34
4. A job offer or help in finding a job or income	4.30
5. Gifts you received yourself, but don't need	4.35
6. Asking a colleague for a favor for patient	7.15
7. Personal expert engagement, beyond the call of duty	5.94
8. A personal, professional favor that goes beyond official boundaries. Do you try to accommodate patients even if that might be against the rules?	6.93
9. Information on books or patient's interests	5.92
10. Unusual and specifically targeted gifts	5.24
11. Other	5.01
12. TOTAL	6.31
13. All non-material gifts	6.15
14. All material gifts	6.42
15. Gifts indicating devotion (questions 7 and 8)	6.40

As seen above, GPs declared free examination and a box of medicine as the most often types of gifts to patients (average 8.31 and 8.52 out of 10).

The average is 6.31 for all gifts, 6.42 for material gifts and 6.15 for non-material gifts.

GPs' devotion

Answers to questions 7 and 8 were used to estimate GPs self-assessed willingness to be devoted, unselfish and altruistic.

There is an impression that GPs underestimate their efforts in helping their patients. An average value for the question 7 is quite low (5.94), while free-entry descriptions seem to indicate more devotion than the self-assessment part. The reason for that might be in GPs' perception of these gestures; they see them as "normal".

GPs' „risky gifts“ – breaking the rules in patient's interest

The most uncomfortable question for GPs was about "risky gifts", i.e. those that are breaking the rules: giving unjustified sick leave for social reasons, false absentee notes etc.; all in trying to accommodate patients' requests and needs. This question had the biggest number of spontaneous comments, dealing with ethical dilemmas GPs are worried about:

- The fear of penalty, which they consider unfair
- Guilt and regret for not making more of these forbidden acts in patients' interest (having fear of risk, but working against own conscience)

Doctors are in fact right about such forbidden acts, because the official recommendation is: "Physicians must base their counsel on the interests of the individual patient, regardless of the insurance or medical care delivery setting." (5). And: "worst professional/ethical violation is permitting current risk-management principles to take precedence over human interventions" (1).

Monetary gifts

There was no specific question about monetary gifts, but 39 participants (14.7%) spontaneously declared they give money to their patients, while only one explicitly denied this.

The amounts are mostly small (2-3 euro) for a bus ticket, or a „loan“ for cigarettes or some medicine. Some monetary gifts are obviously not small: paying examinations for patients, donations for a sick child surgery in a foreign country, regular financial support to a single mother...

Opinions on giving money to patients largely differ: while some are strictly against this (8.13), others see it as something positive (7.9).

Money is mostly given as a gift from heart and as charity. Only few participants resented patients' ingratitude. Some GPs give money and other gifts quite routinely, "almost to everyone who asks". Although often giving money, these few GPs might receive a small number of "gifts with no-expected-benefit" (see below).

GPs' humanity shown by coding their free-entry answers

Free-entry answers to: "Describe impressive, common or typical gifts you give your patients." were coded and sorted in 7 categories, each as a particular indicator of GP's humanity. Examples for each:

1. Individual approach (selectively aimed at poor patients, sick children, etc.)
2. GP's gifts and gestures that would be more appropriate to a family member than to a patient (buying a coat to a girl leaving to school in a big city, finding a job for an unemployed patient)
3. Personal engagement beyond official work (making oneself available 24/7, giving personal contacts, always having enough time for patients, staging an exhibition of patient's poetry in the surgery)
4. Expressed warm emotions by giving/receiving gifts
5. Good atmosphere while giving/accepting gifts to/from patients (GP's composure, GP openly cheerful when giving/receiving gifts; smiles, jokes)
6. Interactive relation (exchanging books or plants, patients regularly praying for the GP, GPs so good in patients' eyes that they try to find a specific gift they like)
7. Devotion and altruism (going to NGOs for a patient who deserves help, GP giving all received gifts to "those who need them more", buying food for a poor old lady on daily basis and delivering it to her home, GP carefully listening even working sick)

The reason for taking the indicators of GPs' humanity as an adequate measure of good PPR is given in the literature, through a description of a patient who deliberately refuses to give a gift despite a successful serious hospital surgery, because of "no nice and no human treatment" (25). It can thus be said that patients are thankful for the human way of treating them, not only for the treatment outcome. "Affective neutrality breaks the bond that holds people" (20). Additionally, the mutuality of friendships (21) and non-material gifts to patients are welcome in psychotherapy (1,2,22).

"Gifts with no-expected-benefit", as a measure of good PPR

Positive answers to the question:

"Have you had a patient (or a family member) come to your surgery just to bring you a gift, without needing any medication or examination?" are taken as experienced "gifts with no-expected-benefit", sorted in 7 types.

The main criterion for recognizing which gift is a sign of gratitude, without a hidden agenda for getting some benefits, is not the value of a gift, but the intention of the patient who does not expect anything in return (1,3,4,5,6). Such gifts are therefore taken as indicators of good PPR (1,4,9,15,16,17).

The results of positive answers to the questions about received "gifts with no-expected-benefit":

- For Christmas 235 GPs (89%)
- For birthday 132 GPs (50%)
- When patients "just wants to share their happiness" ... 179 GPs (68%)
- As a sign of gratitude and appreciation 213 GPs (81%)
- Other reasons 106 GPs (48%)
- From former patient, after having transferred to another GP 189 GPs (72%)
- From patients who have been deceased, but designated a gift for you before they died 126 GPs (48%)

Surprisingly, the percentages of "birthday gifts" and those for „other reasons" are almost the same: 50% vs. 48% (the percentage for "other" category was expected to be low). The reason is provided in some of GPs' comments: they hide their date of birth so that patients would not be encouraged to bring them gifts. Example:

„ They don't know my birthday. But they know my name day!" (The doctor's name is usually written on the surgery door).

It is hard to live in the same community for years and hide one's personal information. Yet, it seems GPs are doing just that, to avoid having their patients feel obligated to bring them gifts. This is the recommendation for all gifts from doctors (1,12,13) and from patients (18). However, in psychotherapy there is also a different approach, where anniversary gifts are sometimes intentionally used in therapy (22).

ANALYTIC PART – INFLUENCE ON PHYSICIAN-PATIENT RELATIONSHIP (PPR)

Gifts are considered non-verbal agents of relation. Therefore, an analysis of correlations between different gift types to and from patients is used to estimate their impact on PPR.

The correlation between the quantity of gifts received from patients and the quantity of gifts given to patients.

ANOVA is highly significant, $p < 0.01$, $F = 46.77$, 9 df.

Pearson test: significant positive correlation ($r=0.780$, $p<0.01$, df 263, 2-tailed) between the average number of gifts received from patients (shown on this question on a Likert scale 0-10) and the average number of gifts given from GPs to patients (calculated from GPs' answers on Likert scales 0-10, as average).

The correlation between the number of days without receiving gifts from patients in the last 180 days and the number of gifts given to patients

ANOVA has a significant level, $p<0.01$, $F=142.39$, 5 df .

Pearson test: significant negative correlation ($r=-0.866$, $p<0.01$, df 263, 2-tailed) between the number of days without receiving gifts from patients and the average number of GP's gifts to patients (the average is calculated from GPs' answers on Likert scales 0-10).

The average of gifts given proportionally rises as the number of days without receiving patients' gifts decreases.

The explanation of the two analyses above: The number of received gifts rises proportionally to the number of gifts given to patients.

The correlation between received patients' "gifts with no-expected-benefit" with GPs' gifts/gestures coded as "humanity"

Compared the number of received "gifts with no-expected-benefit" with GPs' "very human" gifts/gestures, coded as described above, show an almost linear positive correlation, regardless of total number of gifts given or received. ANOVA is highly positively significant, $p<0.001$, $F=92.2$, with 6 df . The Pearson correlation test is shown below.

Table 1. Correlation between received patients' "gifts with no-expected-benefit" and GPs' gifts and gestures coded as "high humanity" in 7 categories

		Patients' "gifts with no-expected-benefit"	GPs' gifts coded as "humanity"
Patients' "gifts with no-expected-benefit"	Pearson Correlation	1	.854**
	Sig. (2-tailed)		.000
	N	216	205
GPs' gifts coded as "humanity"	Pearson Correlation	.854**	1
	Sig. (2-tailed)	.000	
	N	205	248

** . Correlation is significant at the 0.01 level (2-tailed).

The level of correlation between experienced patients' "gifts with no-expected-benefit" and GPs' very human gifts is very firm, almost linear, $r=0.854$, with a 99% reliability rate. Explanation: GPs who give their patients very human gifts/gestures receive significantly more "gifts with no-expected-benefit". This type of gifts from patients should be considered signs of a very good PPR (gifts from former patients, gifts brought without asking any examination or prescription...).

Age, years of practice, and gender comparison

ANOVA, used to analyze the relation between the age and any type of gift giving, from and to patients, does not show any significant differences. It is no different in the comparison with the years of practice, even with a tendency that GPs with only 2-6 years of practice receive less "gifts with no-expected-benefit", where level of significance is little bit above the standard, $p<0.078$. Presumably, GPs with only a few years of practice, did not have enough time to build such good relations with their patients.

On the other hand, the t-test proves that gender does matter. Female GPs give more gifts of all types to their patients (GPs' gifts in total, or those indicating GP's high humanity) and receive more gifts of all types from patients (in total number, or from the category "gifts with no-expected-benefit"). The significance of t-tests for all combinations is from $p<0.001$ to $p<0.02$ for female GPs. From an unknown and inexplicable reason, female GPs give and receive more gifts than their male colleagues.

In general, Croatian GPs give a lot of gifts to their patients, and show a high level of humanity. In return they also receive more gifts from patients. However, simply receiving a lot of gifts does not necessarily produce a good PPR. A very good PPR, seen through the quality of gift giving, and receiving patients' "gifts with no-expected-benefit", is observed in those GPs who either give very humane gifts or give them in a highly humane manner.

It could thus be said that gifts from doctors to patients are not "forbidden and non-ethical", as some authors are stating [8,11,12]. Some think the opposite [1,20,21], adding by that some cautions [1,2,22]. Authors assert that an emotionally warm treatment, considered as a kind of gift [2,22], is the most important for the patient [2,20,21,22].

Consequently, a patient's gratitude and mutual satisfaction expressed with gifts [25,21] is a sign of good PPR, i.e. PPR is improved with material and non-material gifts considered the means of expressing (patients') gratitude, and nice gestures and warm emotions (from both sides).

These results are not simply applicable on hospital doctors or specialists, because their situation and position is very different.

CONCLUSION

DESCRIPTION of GPs' gifts to their patients

GPs in Croatia give many material and non-material gifts to their patients. GPs' answers on the Likert scale about all types of gifts make an average of 6.31 (out of 10). The gift of free examination is dominant; only 4 out of 265 respondents never provide free-of-charge examinations to their uninsured patients, with the average answer on the Likert scale 0-10 being 8.31.

The average value on the Likert scale from 0-10 is 6.15 and 6.42 for all non-material and material gifts respectively. Out of 265 respondents, 39 GPs explicitly mentioned "money" as gift to patients (15%). Only one GP explicitly said she never gives money. The amounts are mostly small (2-3 euro), but some monetary GPs' gifts are real donations.

In giving gifts, GPs express a high degree of sensibility for their poor or seriously ill patients. In general, GPs are inclined towards patient-specific gifts and often give from the heart. GPs' devotion is higher than expected. Their self-assessed answers on such a type of Likert questions seem lower than their free-entry descriptions would indicate. The descriptions and optional comments paint a picture of a GP who is involved in a family and goes out of their way to do the work that should in fact be done either by the family or the social service.

IMPACT ON THE PHYSICIAN-PATIENT RELATION

The correlation of the gifts to and from patients shows that those GPs who give a lot are also the ones who receive a lot of gifts. However, regardless of the quantity of gifts, only those GPs whose answers reveal a high level of humanity receive patients' "gifts with no-expected-benefit", which are nice and warm signs of appreciation and deep gratitude.

The results are not to be simply applied on doctors other than GPs, because hospital doctors and specialists are in a very different position.

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DUPUYTREN'S CONTRACTURE - RECIDIVATE OR NOT?Mancev Lejla¹, Gecevska D², Koevska V², Dimovska A², Dodevski A³¹Private ambulance specialized in physiotherapy and rehabilitation "Matar Medika", ²Institute for physical medicine and rehabilitation, Skopje, Macedonia, ³ Institute of Anatomy, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, Macedonia**ABSTRACT**

Background: The rehabilitation process of Dupuytren's contracture is complex and depends on the outcome of the surgical technique which has been chosen for treating a patient. There are numerous options based on individual hand assessment results and cost benefit for the patient regarding possible complications. Corrective procedures range from extensive surgery to less invasive procedure. Following any hand procedure, the function of the hand will be compromised, and there is a need of rehabilitation. Although lots of debates regarding surgery treatment techniques are presented throughout the reported literature, but still the recidivism of the condition remains unclear.

Case report: In this report a patient who has rehabilitated for two times at our clinic for both hands with a 3 years' interval between the rehabilitation following a surgical procedure for Dupuytren's contracture for each hand is presented.

Conclusion: Surgery can help the improvement of the hand function with people affected by contractures, but it doesn't stop the process that causes the development of contracture on first place. Therefore, there's a chance the condition to be returned in the same place, or it may reappear somewhere else after the treatment. Physiotherapy procedures and rehabilitation program have got significant role in the postsurgical treatment of Dupuytren's contracture, in terms of improving the function of the fingers and palm but not preventing the recidivism of the condition.

Key words: Dupuytren's contracture, recidivism, fasciectomy (aponeurectomy), kinesitherapy.

INTRODUCTION

Dupuytren's contracture (Dupuytren's disease) is a condition that affects the hands and fingers. It develops as a result of palmar fibromatosis and causes one or more fingers to flex into the palm of the hand with restricted maximal finger extension. It can affect one or both hands, very often fourth and fifth fingers are affected and sometimes the thumb [1, 2, 3].

Dupuytren's contracture occurs when the connective tissue in the palm thickens. Often the tissue thickens in one small area first, and a "nodule" is formed (a small, hard lump about 0.5-1cm) under the skin of the palm. The nodule sometimes is felt tenderly to begin with, but this usually passes. More nodules might develop then. Over time, the nodules can extend and form cords of tissue. These cords can be shortened (contract), and if the cords run along a finger or thumb they can pull it, so it becomes bent towards the palm. These contractures are often mild and painless, but they can get steadily worse over time [1, 2, 4].

The nodules are non-cancerous (benign) and the condition isn't life-threatening for those who develop it, although it can be a nuisance to live with as it affects the daily living activities.

Although Dupuytren's contracture aetiology is unknown, it's thought to be genetic, as it often runs in families. Genetic predisposition and presence of some factors such as diabetes, smoking and certain medications (for example, medication for epilepsy) might activate the condition. However, it's not clear how significant these factors can be [1, 2, 4].

It can affect both sexes, but it affects men more than women. The condition usually occurs during later life, although some cases have been reported in children. Most cases occur in men over 50 and women over 60. Usually it is bilateral and in 20% recurrence occurs [2, 4, 5].

The condition seems to be more common in people of North European descent. It's thought the gene associated with the condition was brought to the UK by the Vikings. This condition is named by the baron Guillaume Dupuytren, a surgeon who first described the corrective surgery procedure in Lancet 1831[4].

In 2011 Dibenedetti et al, reported a large population-based study (23,103 individuals) conducted to estimate the prevalence of Dupuytren's disease in US adults and describe associated treatment patterns. The results from this study indicate a number of unmet medical needs, so strategies to raise physician awareness of disease symptoms and effective treatment options might be helpful, as the authors concluded [6].

The objective of the case report presented in this paper is the recidivism of the Dupuytren's contracture.

CASE REPORT

A patient with initials SB, male, 68 years old, smoker, a servicer for kitchen equipment (fridges) by occupation, came to our clinic on 09.04.2014 for physiotherapy and rehabilitation. The patient reported for physiotherapy 3 weeks after he was made a partial excision of the palmar fascia due to Dupuytren's contracture of the left hand forth finger (Fig.1). On clinical examination the patient restricted flexion and extension on the forth finger with difficulties in performing everyday activities, even shaking hand.

This was his second time at our clinic as in 2011 he went through a rehab process after surgical partial excision of the palmar fascia due to the Dupuytren's contracture of the right hand fourth and fifth finger (Fig.4).

The rehabilitation after a palmar fasciectomy is extensive. Although the required time for recovery varies, as a guideline, physiotherapy sessions should be expected for up to six weeks. Heat treatments, soft tissue massage, and a program of vigorous stretching can be applied. A personalized patient program is usually provided to speed the recovery and the goals of the physiotherapy are individually set (Fig. 2).

In this case laser therapy was applied for the scar of the surgical section. Also electrotherapy and soft tissue massage were applied for preventing the return of the contractures. The kinesitherapy started with gentle stretching and gradually increases more vigorously in order the patient to be able to put the hand in use and to be able to straighten all joints within four to six weeks. An occupational therapy was also administered to provide the patient with practical support for fulfilling the everyday tasks and activities (either at work or home) easier.

The goal of the physiotherapy is to speed the recovery so that the patient can return quicker to the everyday activities. Although the sessions ended after 3 weeks, the patient was taught for a home exercise regime as part of an ongoing program for preventing recurrence that would be done by himself (Fig 3).

In this patient fully recovery occurred and he was able to return to his work after 5 weeks as he closely followed our advice.

DISCUSSION

Many cases of Dupuytren's contracture are mild and don't need a treatment. The treatment might be helpful if the condition interferes with the normal functioning of the hand [7,8,9]. In the article treatment options for Dupuytren's contracture were systematically reviewed, and the conclusion was that there is a little evidence on the effectiveness of many treatment modalities for Dupuytren's disease other than expert's opinions (level 4) [10].

Non-surgical treatments include radiation therapy and collagenase clostridium histolyticum (CCH) injection. These are generally the most effective ones if are used before the condition becomes severe [11, 12]. According to the review by Rijssen et Werker, the radiotherapy and the use of collagenase are promising, but their role in treating Dupuytren's disease is still unclear. In 2010, the National Institute for Health and Care Excellence (NICE) issued guidance about the use of radiation therapy for treating the Dupuytren's contracture. Radiation therapy aims to prevent or delay the need for surgery [12].

In The Journal of Hand Surgery, Peimer et al reported that the overall recurrence rate of 47% was comparable to the published recurrence rates after surgical treatments with one reported long-term treatment-related adverse event, five years after the successful CCH treatment. Collagenase clostridium histolyticum injection proved to be an effective and safe treatment for Dupuytren contracture [13].

The Law on Health Protection prescribes mandatory use of professional guidance for practicing [14]. According to the Guidance for practicing evidence based on medicine for Dupuytren contracture in physical medicine and plastic and reconstructive surgery, flexor contracture (which exceeds 30 degrees in the metacarpophalangeal joint) is considered as an indication for a surgical intervention. Surgery is indicated only if the patient has got a functional damage of the hand or if the contracture affects the everyday activities [15].

In the clinical trial of 140 patients with an MCP contracture of 20° or more with a single finger in Dupuytren disease were enrolled, and 69 patients of them were randomized to collagenase treatment and 71 patients to needle fasciotomy. The results showed that there was no significant difference between the treatment outcomes after collagenase and needle fasciotomy treatment after 1 year [16].

Most hand surgeons perform selective fasciectomy for Dupuytren's disease. Because of its lower recurrence rate, dermofasciectomy is increasingly being performed to treat recurrences. Percutaneous needle fasciotomy is a minimally invasive treatment with good short-term results in patients with mild to moderate contractures, but it has got a high recurrence rate [17,18].

A fasciectomy is a more extensive operation than a fasciotomy, so the risk of complications is slightly higher, at around 5%. However, the results are longer-lasting. For example, the rate of recurrence of Dupuytren's contracture following dermofasciectomy might be as low as 8% [8, 9,17].

The surgery for Dupuytren's contracture can't always fully straighten the affected finger or thumb, and the contracture can recur after surgery. If a contracture does recur, further surgery might be possible. Having surgery to remove the first nodule that appears, it doesn't mean it won't stop the condition from progressing, as this won't stop the condition occurring elsewhere in the palm. It's usually best to avoid surgery until a contracture develops as it interferes the use of the hand [8, 9, 18].

In the review by Hakstian, after careful evaluation of the many factors involved, one or other procedure cannot be routinely applied to all cases and there are appearance of definite indications for extensive fasciectomy and for fasciotomy as well as for partial fasciectomy. While 51% of hands redeveloped disease, only 25 % required secondary surgery for functional disturbance or severe deformity[19].

In an article by Bulstrode et al, a recurrence of Dupuytren's disease occurred in 23 of 75 patients after a mean follow-up period of 9.4 years. The complication rate increased with the severity of disease particularly if the proximal inter-phalangeal joint contracture was 60 degrees or more. There was no difference in the complication rate for patients who had surgery for primary or recurrent disease [20].

Nerve injury is most common surgical complication. Also a complex regional pain, syndrome splitting the skin with the needle during a needle fasciotomy and joint stiffness are some of the surgery risks that can be developed. The outcome of the surgery won't be fruitful if a contracture of the joint capsule has been developed before. Sometimes for severe contractures and complicated cases, the best option can be finger amputation or hand surgery[18, 21].The hand therapist has got a vital role in the early detection and treatment of many of these complications [22].

Sometimes after the surgery, wearing a splint is recommended during night for keeping the joints straight and preventing new contractures from forming [7,8, 17].

The selection of a method for dealing with the disability and deformity produced by diseased palmer aponeurosis has been one of the most difficult decisions that have been made for the Dupuytren's disease management

The treatment plan has to be flexible, more than in most areas of hand surgery. The most important points in hand therapy after surgery for Dupuytren's disease include: 1) early detection of potential postoperative complications--including disturbances in wound healing; 2) oedema control; 3) scar management; 4) maintenance of surgical correction; 5) restoration of finger flexion to the degree of preoperative range of motion. The postoperative program of hand rehabilitation depends on type of surgery, and therapist's education [23].

Ongoing researches suggest some other treatment options for Dupuytren's contracture, but there's currently not enough medical evidence to support their use. Dupuytren's contracture often runs in families and so the genetic researchers hope to identify the genes responsible for the condition. This could lead to the development of treatments that prevent contractures occurring in the first place.

CONCLUSION

Surgery can help to improve the hand function with people affected by contractures, but it doesn't stop the process that caused the contracture to develop in the first place and it might reappear the same place or somewhere else after the treatment. The chances of the condition returning after the surgery also depend on the specific performed procedure. Dupuytren's contracture recurs in more than half of the people who have got a type of minor procedure called a needle fasciotomy, but only one in three people who have got a fasciectomy. A dermofasciectomy is associated with the lowest risk of recurrence, with the condition reappearing in less than 1 in 10 people after the procedure. Physiotherapy procedures and rehabilitation program have got significant role in the postsurgical treatment of Dupuytren's contracture, in terms of improving the function of the fingers and palm, but not preventing the recidivism of the condition.



Fig. 1. Three weeks after a partial excision of the palmar fascia on the left hand (in 2014) before starting physiotherapy



Fig. 2. One week after starting physiotherapy



Fig. 3. Three weeks after starting physiotherapy

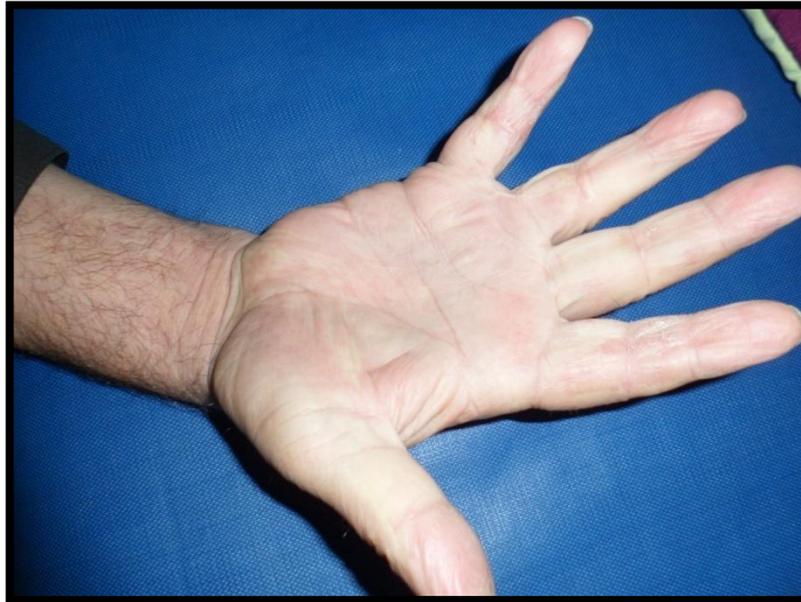


Fig. 4. Right hand in 2014 after partial excision of the palmer fascia and physiotherapy performed in 2011

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OCT ET PATIENTS WITH MYOPIA, WITH AND WITHOUT DIAGNOSED GLAUCOMA NABOLICS ABUSE AND CARDIOMYOPATHY IN A BODYBUILDER: A CASE REPORT

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ABSTRACT

Introduction. Eyes with high myopia are less tolerant of fluctuation in IOP, from other eyes. Among them, eye is larger, lamina cribrosa is thinner and the scleral wall is thinner with a different elasticity. Even the smallest increase of IOP, can cause damage to the back wall, because myopia eye has an elongated elliptical shape and the back wall is stretched more. Death of ganglion cells, which occurs in glaucoma, is detected by measuring RNFL, using OCT (optical coherence tomography).

Objectives. The primary objective is to define the similarities and differences of the thickness of retina nerve fibers in patients who have myopia, compared to patients who have myopia and glaucoma. Other objectives are to evaluate the changes that we diagnosed at these two groups of patients, and to determine whether myopia is a risk factor for the occurrence of glaucoma in patients

Methods. The study included 20 patients with Myopia refractive anomaly, 8 patients diagnosed with glaucoma and 12 patients without diagnosed glaucoma. On every patient has been made OCT of PNO (papilla nervi optici) and OCT of RNFL (retinal nerve fibres layer).

Results. More than half of patients with myopia without diagnosed glaucoma have thinning of RNFL, which is one of the primary findings to diagnose glaucoma.

Conclusion: All patients, diagnosed with nearsightedness, myopia, to conduct investigations for the detection of glaucoma, for timely prevention of damage to the nerve and vision.

Keywords: myopia, glaucoma, OCT, layer of retinal nerve fibres

INTRODUCTION

Glaucoma, a leading cause of irreversible blindness in the elderly population worldwide, represents a progressive optic neuropathy [1]. Primary open angle glaucoma (PGOA) is the most common type of glaucoma among the population, according to recent studies. Glaucoma is characterized by loss of retinal nerve fibers, which is clinically recognized as defects in the visual field, and the loss of coating of the optic nerve, called glaucomatous optic neuropathy (GON) [2]. The global prevalence of glaucoma is expected to be 80 million in 2020 [3].

Myopia or nearsightedness is a refractive anomaly in which the parallel light beams coming from distance, after refraction through the cornea and lens, focus in front of retina and vitreous, and in a state of divergence, create retinal circles.

For high myopia, especially are characteristic changes in the fundus. During the development of myopia, stretch the back half of the eye. The sclera easily adapts to change. Ability of chorioidea to be stretched is less, and the retina, which has high differential structure, is the least. By increasing the eye, first changes were observed peripapilar. Modified arrangement of nerve fibers of papilla, leads to a different response of the tissue, of some pathological changes. Deformed and partially atrophic papilla with high myopia, doesn't develop classical excavation if occur glaucoma [4].

One theory for the occurrence and development of myopia, refers to the effect of increased IOP, and insufficient resistance of the sclera in a number of young people. In their eyes, sclera under the influence of a slightly increased IOP, is stretching, and the eye on the whole becomes bigger. This mechanism called "minihydroftalmus", is not proven, in most myopes, yet [4].

Eyes with high myopia are less tolerant of fluctuation in IOP from other eyes. Among them, eye is larger, lamina cribrosa is thinner and the scleral wall is thinner with a different elasticity. Even a smallest increase in IOP can cause damage to the posterior pole, because myopia eye has an elongated elliptical shape, the back wall is stretched more [4]. There are several theories to explain the link between myopia and primary open-angle glaucoma. One of the main theories is the death of ganglion cells, which occurs in glaucoma, which is detected by measuring RNFL, using OCT (optical coherence tomography). This in turn is correlated with the excesses of visual field defects that appear. Therefore measuring RNFL and macular ganglion cell complex are good techniques for the detection and clinical evaluation of patients with glaucoma and myopia [5].

MATERIALS AND METHODS

This study represents a case-control study involving patients aged 25 to 70 years, with a refractive anomaly myopia. The study is done at the University Clinic for Eye Diseases in Skopje, in the cabinet for glaucoma. In the study are included 20 patients with myopia refractive anomaly, 8 patients diagnosed with glaucoma and 12 patients without diagnosed glaucoma. On every patient has been made OCT of PNO (papilla nervi optici) and OCT of RNFL (retinal nerve fibres layer). The results are shown tabelar.

RESULTS

Table 1. Size of excavation of papilla - Normal time 0.4

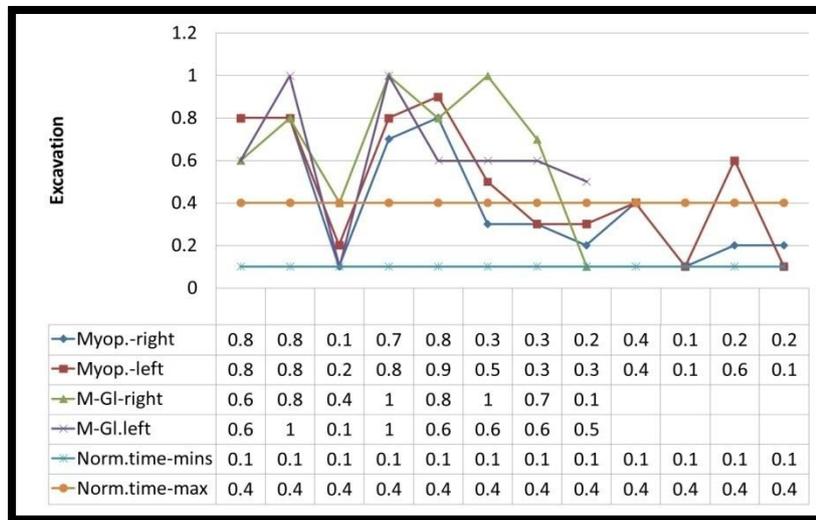
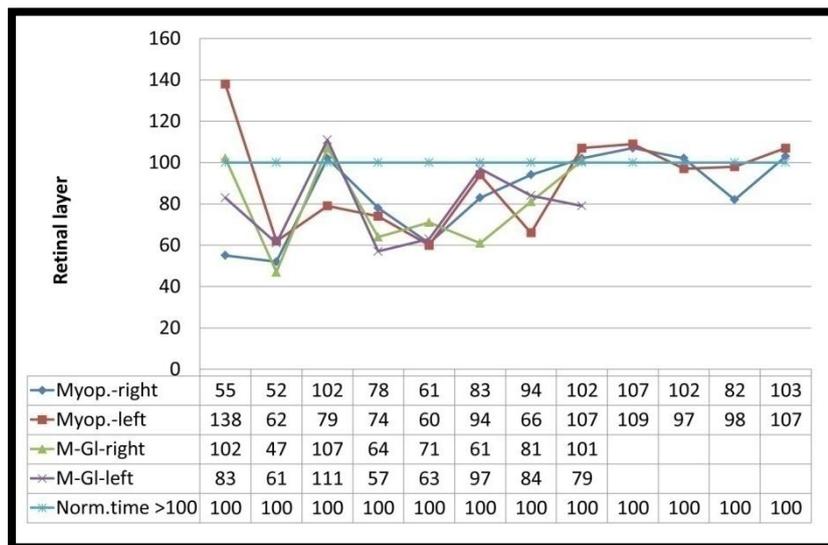


Table 2. Thickness of retinal nerve fiber layer - Normal time 100



The results can be found as follows: there is no significant difference among the excavation of the papilla between the two groups of patients. In both groups are found values that are above the normal limit. Typical results from a survey, examinations of the thickness of the layer of retinal nerve fibers. This thinning is notes in both groups of patients. More than half of patients with myopia without diagnosed glaucoma have thinning, which is one of the primary findings to diagnose glaucoma.

DISCUSSION

Ophthalmologists, during the examinations of patients with high myopia, often faced with a diagnostic dilemma. "High myopes may not have glaucoma, but the situation looks like glaucoma. Or maybe they have glaucoma, but not sure "(Simon K. Law).

The link between myopia and glaucoma has been researched many years. A big number of studies, including the "Blue Mountains Eye" study, and "Beijing Eye" study showed that the risk for glaucoma is increased in patients with high myopia (-6D or more).

Among recent studies, is the study of Kuldev Singh and Shan C. Lin, which published a similar association among the population of the United States.

Simon K. Law, on one occasion, said that, the difficulty in diagnosis is that, papilla of optical nerve (PNO) in myopia usually looks abnormal, and that changes are also one of the parameters for diagnosis in glaucoma. And the eye pressure may not be very high. Even there may be defects in the visual field who are not progressing or have a different progress. It gives a diagnostic problem and problems ahead.

One of the largest studies done is screening for myopia and glaucoma made of 32,918 respondents in Sweden, aged 57 to 79, where it is observed prevalence of newly glaucoma, whose numbers grow with the growth of myopia ($p < 0,0001$).

CONCLUSION

The extent of damage that glaucoma may causes depends on the time of its detection. Later diagnosed glaucoma will cause major damage. That's the reason, this paper to light the need, all patients diagnosed with myopia, to conduct investigations for the detection of glaucoma, for timely prevention of damage to the nerve and vision.

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OVERVIEW OF THE TREATMENT OF EPILEPSY: ADVANCES AND FUTURE PROSPECTS

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ABSTRACT

Epilepsy is a common neurological disorder and affects about 1% of the population. Many new antiepileptic drugs have been discovered, and a greater proportion of the patients suffering from epilepsy will achieve seizure stability with an appropriately chosen AED regime. However, treatment of patients suffering from refractory epilepsy caused by drugs still represents a challenge. Many surgical procedures which resect the epileptic hotspots are available (focii), especially of temporal lobe epilepsy. Nowadays, available treatment options of patients with refractory epilepsy, who are not good candidates for surgical treatment, include: vagal nerve stimulation, electric stimulation of the brain nuclei (direct and indirect), which are believed to be included in epilepsy formation, as well as the ketogenic diet. Hormone therapy and immunological therapy can be useful in some epileptic syndromes.

Key words: epilepsy, treatment, antiepileptic drugs, alternatives

INTRODUCTION

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the resulting neurobiologic, cognitive, psychological, and social consequences of the condition [1]. The occurrence of 2 or more unprovoked seizures is classified as epilepsy. Epilepsy afflicts approximately 0.5% to 1% of the population [2] which makes it one of the most common neurological disorders. There are different epileptic syndromes, which differ in terms of the age of onset and the dominant type of seizures. The type of seizures depends on the location of the epileptic discharges in the cerebral cortex and the extent and pattern of their propagation in the brain. The type of seizures is determined by their clinical and electroencephalographic appearance. In general, we recognize two patterns of seizures: 1) *Focal (partial) seizures*, which in turn can be simple focal, complex focal, or secondarily generalized. 2) *Generalized seizures*, which can be either tonic, atonic, absences, myoclonic or tonic-clonic seizures. *Status epilepticus* is the condition where seizures (either focal or generalized) occur continuously or repetitively for more than 30 minutes with no recovery in between. Determining the type of seizure is important as different epileptic syndromes respond to different types of treatment. There are many available antiepileptic drugs (AED) and new ones are continuously being researched and placed on the market. A significant proportion of patients will remain seizure-free for longer periods of time with a single AED or a combination of AEDs, however, some will continue to suffer from uncontrolled seizures despite maximally dosed medications and some will have unacceptable medication-related side effects. Alternative treatment options are available for patients with refractory seizures. Surgery for epilepsy leads to long-term freedom from seizures in more than half of suitable surgery candidates. For the remainder, neurostimulation or a ketogenic diet may provide an alternative treatment.

Overview of Antiepileptic Drugs

The mainstay therapy for treatment of the chronic recurrent seizures that are the signature of epilepsy are drugs that manipulate levels of neuronal excitability in the brain. Selection of an anticonvulsant medication depends on an accurate diagnosis of the epileptic syndrome. The goal of treatment is to achieve a reduction of seizure frequency or a seizure-free status without adverse effects. Monotherapy decreases the likelihood of adverse effects and avoids drug interactions. Carbamazepine, ethosuximide, and valproate were the mainstays of epilepsy treatment until the 1990s. Since then, newer, efficacious, better tolerable and less toxic agents have been developed.

Many brain structures are involved in the development of a seizure, including neurons, ion channels, receptors, glia, and inhibitory and excitatory synapses. The AED are designed to modify these processes so as to favor inhibition over excitation and thereby stop or prevent seizure activity. The AED can be grouped according to their main mechanism of action, although many of them have several actions and others have unknown mechanisms of action. The main groups include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, and drugs with unknown mechanisms of action.

Sodium channel blockers

AED that target the sodium channels prevent the return of these channels to the active state by stabilizing them in the inactive state. In doing so, they prevent repetitive firing of the axons. *Carbamazepine* is a major first-line AED for partial seizures and generalized tonic-clonic seizures. It is one of the most widely used AED in the world. The drug is highly effective and well tolerated. However, drug-interactions with other AED and other medications are common. *Phenytoin* is a first-line or adjunctive treatment for partial and generalized seizures, Lennox-Gastaut syndrome, status epilepticus, and childhood epileptic syndromes.

One disadvantage is that it causes central nervous system (CNS) adverse effects. However, the once-daily dosing, the good efficacy, the possibility of monitoring the plasma levels, and the availability of a parenteral preparation make it suitable for use.

Oxcarbazepine is a newer analogue of carbamazepine, developed with the attempt to avoid the adverse effects and drug interaction properties of carbamazepine. It is used as a first-line therapy in some countries for the treatment of partial and secondary generalized seizures. *Lamotrigine* is chemically unrelated to the other AED and is used as adjunctive therapy for partial and generalized seizures. Unlike other AED, it causes few CNS side effects. It is one of the preferred monotherapies during pregnancy, as it has a low reported incidence of congenital malformations. *Zonisamide* is approved as adjunctive therapy for patients with partial seizures above the age of 12. It is very effective for absence and juvenile myoclonic epilepsy. *Lacosamide* is a newer AED which does not have significant interactions with other AED and is effective as adjunctive therapy, currently approved for the treatment of partial-onset seizures in patients aged 17 years or older. Its safety and efficacy are being evaluated in children with refractory epilepsy of different etiologies.

Calcium channel blockers

Calcium channels function as the "pacemakers" of normal rhythmic brain activity. This is particularly true of the thalamus. T-calcium channels have been known to play a role in the 3 per second spike-and-wave discharges of absence seizures. AED that inhibit these T-calcium channels are particularly useful for controlling absence seizures. *Ethosuximide* is used since the 1960s as a first-choice drug for absence seizures without generalized tonic-clonic seizures

GABA enhancers

GABA-A receptors have multiple binding sites for benzodiazepines, barbiturates and other substances. The benzodiazepines most commonly used for treatment of epilepsy are: *Diazepam* and *Lorazepam* (mainly for emergency treatment of seizures, while long-term use is limited by the development of tolerance). *Clonazepam* is one of the first benzodiazepines used for epilepsy and is the drug of choice for myoclonic seizures. To a lesser extent, it is effective in other types of seizures and is very effective in the treatment of status epilepticus. *Clobazam* is a benzodiazepine that also affects sodium and calcium channels and is a potent anticonvulsant for partial epilepsy, but may be effective in a wider range of epilepsies. Tolerance is also common. Of the barbiturates, *Phenobarbital* was the most commonly prescribed AED in the 20th century, but is now being avoided because of its adverse effects. It is effective in a wide variety of seizures and is a first-line drug in the treatment of status epilepticus. Because of its low cost, it is still widely used in developing countries. *Tigabine* is a GABA reuptake inhibitor used for the treatment of partial or secondarily generalized seizures that are refractory to treatment. *Vigabatrine* is a GABA-transaminase inhibitor used for refractory partial seizures and is the drug of choice for infantile spasms outside the US (it is not FDA-approved due to its adverse effects). *Valproate* and *Gabapentin* have a certain stimulating effect on the enzyme glutamic acid decarboxylase, which converts glutamate into GABA, in addition to other potential mechanisms of action. Valproate is one of the most commonly used AED in the world. It is the drug of choice for primary generalized epilepsies and juvenile myoclonic epilepsy; it is a first-line treatment for Lennox-Gastaut syndrome and photosensitive epilepsy; it is a second choice for infantile spasms. It is also approved for the treatment of partial seizures. Newer extended-release preparations may decrease the dose-related adverse effects and toxicity. *Pregabalin* is a newer drug, which acts as a GABA analogue in an unknown manner and is proven to be efficacious as adjunctive therapy for partial epilepsy.

Glutamate blockers

Glutamate receptors bind glutamate, an excitatory amino acid neurotransmitter. AED that modify these receptors are antagonistic to glutamate. *Topiramate* is one of the new AED and is a very potent anticonvulsant drug with multiple mechanisms of action (it also has an inhibitory effect on sodium conductance and enhances GABA by unknown mechanisms and is also a weak inhibitor of carbonic anhydrase). It is effective in a wide variety of seizures, including partial and secondarily generalized tonic-clonic seizures, primary generalized tonic-clonic seizures and Lennox-Gastaut syndrome, as both monotherapy and adjunctive therapy. *Perampanel* is used as adjunctive treatment for partial onset or secondary generalized seizures refractory to other AED in adults and children aged 12 years or older. The use of *Felbamate* is restricted to severe refractory partial epilepsy or Lennox-Gastaut syndrome, because of the potentially fatal toxic effects.

Carbonic anhydrase inhibitors

Inhibition of the enzyme carbonic anhydrase increases the concentration of hydrogen ions intracellularly and decreases the pH. The potassium ions shift to the extracellular compartment. This event results in hyperpolarization and an increase in seizure threshold of the cells. Acetazolamide is used for the treatment of epilepsy in adults and children over the age of 12 as an adjunctive therapy in refractory seizures, especially with catamenial pattern.

AED with other mechanisms of action

Levetiracetam is a very well tolerated AED with a significant effect in generalized epilepsies. It is used as adjunctive treatment in primary generalized tonic-clonic seizures, partial-onset and myoclonic seizures. Because of its insignificant drug reactions, it is useful for patients on concomitant medications. The mechanism of action is possibly related to a brain-specific stereo-selective binding site, synaptic vesicle protein 2A (SV2A), which appears to be important for the availability of calcium-dependent neurotransmitter vesicles ready to release their content [3]. Ezogabine is a novel drug with a unique mechanism of action as a potassium channel opener. It may be a useful option for patients with epilepsy resistant to other AED.

Treatment alternatives for pharmacoresistent epilepsy

The International League Against Epilepsy (ILAE) has proposed defining drug-resistant epilepsy as the failure to achieve sustained seizure freedom despite adequate trials of 2 antiepileptic drugs, either as monotherapy or in combination.^[1] The drugs must have been appropriately chosen and used, and failure must have occurred because of lack of efficacy and not because of adverse effects. Approximately one-third of all epilepsy patients get little to no clinical relief from AED therapeutic regimens. Drug resistance in epilepsy is particularly common in individuals with focal seizures.

Surgery

Ever since the first half of the twentieth century, surgery which involves excision of the epileptogenic region of the brain has been a major treatment option for epilepsy. Most clinicians now endorse a neurosurgical consultation after approximately two failed regimens of AEDs.

Temporal lobe epilepsy (TLE) is the most common form of medically intractable epilepsy and comprises about 80% of epilepsy surgeries with the majority of patients gaining complete seizure-freedom. Temporal lobectomy is focused on resection of mesial structures such as the amygdala, hippocampus, and parahippocampal gyrus, while preserving as much of the neocortex as possible resulting in optimum seizure control with minimal neurological deficits. The use of temporal lobectomy for intractable TLE in adults has been proven to be effective, but fewer studies have examined seizure outcomes and predictors of seizure freedom after temporal lobectomy in pediatric patients. Englot et al performed a systematic review and meta-analysis of studies including 10 or more pediatric patients (age ≤ 19 years) published over the last 20 years examining seizure outcomes after temporal lobectomy for TLE. They included 36 studies and 1318 pediatric patients with a mean age of 10.7 ± 0.3 years. They found that seizure freedom was achieved in 1002 cases (76%), while 316 patients (24%) continued to have seizures. Statistically significant predictors of seizure freedom after surgery included lesional epilepsy etiology, abnormal findings on preoperative MRI, and lack of generalized seizures [4].

Though not as successful as TLE surgery because of their frequent proximity to eloquent brain structures and more diffuse pathology, epileptogenic foci located extratemporally also benefit from resection. Outcomes in extratemporal lobe resections are similar in children and adults. Outcomes are better with well-circumscribed lesions, such as developmental tumors and cavernous malformations and outcome correlates with completeness of lesion resection and unilobar localization [5]. In the UCLA series of pediatric cases, 56% of extratemporal unilobar epilepsy cases were seizure free at 2-5 years [6]. Prediction of seizure outcome in each of these procedures has heavily relied on pre-operative imaging. However, in the absence of visible lesions on MRI, recent improvements in secondary imaging modalities such as fluorodeoxyglucose positron emission computed tomography (FDG-PET) and single-photon emission computed tomography (SPECT) have led to progressively better long-term seizure outcomes. Additionally, hemispherectomy has been extensively used quite successfully for diffuse epilepsies often found in pediatric patients. Although total anatomic hemispherectomy is not utilized as commonly today, it has given rise to current disconnective techniques such as hemispherotomy [7].

Electrical neurostimulation

For many patients with epilepsy surgery is not an option, for example when the seizure onset zone co-localizes with eloquent brain function and cannot be resected, or the seizure onset zone is not well localized, or when seizures independently originate from both temporal lobes. For many of these patients, electrical stimulation is a viable treatment option. The use of electrical stimulation in many forms to treat drug-refractory epilepsy has grown markedly over the past few decades, with some devices and protocols being increasingly used as standard clinical treatment. Both extracranial (vagus nerve stimulation) and intracranial (deep brain stimulation and cortical stimulation) neurostimulation have been used as treatments for epilepsy.

Vagus nerve stimulation (VNS)

VNS has been in clinical use since 1996 and is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures which are refractory to antiepileptic medications. Its exact mechanism of action on seizures is still unknown. VNS used in the acute setting can both abort seizures and have an acute prophylactic effect.

This effect increases over time in chronic treatment to a maximum at around 18 months. A vagus nerve stimulator consists of two electrodes embedded in a helix that is wrapped around the left cervical vagus nerve. The electrodes are connected to an implantable pulse generator (IPG) which is positioned subcutaneously and is programmed by computer via a wand placed on the skin over it. In addition, extra pulses of stimulation triggered by a hand-held magnet may help to prevent or abort seizures. Vagus nerve stimulation is well tolerated and has few significant side effects, however, a significant reduction in the frequency and severity of seizures can be expected in only about one third of patients. VNS is essentially a palliative treatment and the number of patients who become seizure free is very small.

Deep brain stimulation (DBS)

Intracranial stimulation is the direct application of an electrical current to central nervous system structures by means of implanted (DBS) or subdural (cortical stimulation) electrodes connected to an implantable pulse generator. Stimulation of electrodes placed in the epileptic onset region (for example the hippocampus) may lead to 'local' inhibition of the hyperexcitable region and to seizure suppression. Stimulation of electrodes placed in key structures responsible for seizure propagation (for example the thalamus) may additionally lead to suppression of seizure spread, based on the connections between the area of stimulation and other parts of the central nervous system. DBS for seizures has been applied to the cerebellum, caudate, locus coeruleus, subthalamic nucleus, mammillary bodies, centromedian thalamus, anterior nucleus of thalamus, hippocampus and amygdala, hippocampal commissure, corpus callosum, neocortex, and occasionally to other sites. A wide variety of stimulation parameters have been employed in multiple different combinations of frequencies, amplitudes, and durations. However, we still do not know the mechanisms, the best stimulation parameters, the best patient population, or how to predict benefit in advance. With the advancement of technology, responsive cortical stimulation systems have been developed that are able to detect seizure activity in real time and deliver direct electrical stimulation to seizure foci in response. This is a field that provides future prospect in the treatment of drug-resistant epilepsy.

Sprengers et al have analyzed ten randomized control trials of DBS in different brain regions and have found a statistically significant reduction in seizure frequency for anterior thalamic DBS, responsive ictal onset zone stimulation and hippocampal DBS. Asymptomatic intracranial haemorrhage and soft tissue infections were the main reported adverse effects [8]. The Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial was the first large, multicenter, double-blind, randomized trial that examined the effects of DBS of the anterior nucleus of the thalamus in patients with intractable epilepsy. A total of 110 patients underwent bilateral electrode implantations. At the end of the 3-month blinded phase, there was a 40.4% decrease in median seizure frequency in the stimulated group compared with a 14.5% decrease in the control no-stimulation group. That the control group also had a decrease in seizure frequency is consistent with studies mentioned previously showing an implantation effect. During the long-term follow-up there was a 41% decrease in median seizure frequency at 13 months and 56% decrease at 25 months. The most common adverse event was paresthesias, occurring mostly during the first month of implantation. Fourteen patients were seizure-free for at least 6 months during the study period, indicating that some patients may benefit from DBS stimulation more than others. Further study of the optimal patient selection criteria for this promising procedure is indicated [9].

Responsive stimulation is an important recent development in treatments involving brain stimulation, which is based on 'open-loop' or responsive cortical stimulation. Whereas traditional DBS involves the use of chronic, continuous stimulation of a target tissue (so-called closed-loop stimulation), responsive stimulation involves the implantation of subdural or depth electrodes in the area of interest which beside the stimulation function, also have a detection function. The electrocorticographic activity of the target is continuously monitored and when abnormal activity is detected, electrical stimulation is delivered. This represents a promising potential approach for the treatment of epilepsy and potentially for other disorders. More studies are required to determine the full advantages and disadvantages of closed-loop and open-loop DBS.

Ketogenic diet

The ketogenic diet is a high-fat, low-carbohydrate, and restricted protein diet that is useful especially in pediatric patients with refractory epilepsy. The efficacy of the ketogenic diet is better than most of the new antiepileptic drugs. Other diet modifications may also be beneficial, such as the modified Atkins diet and the low glycemic index treatment. There is a lack of awareness of the ketogenic diet as a treatment modality for epilepsy amongst pediatricians and neurologists [10]. Levy et al reviewed four randomized studies of the ketogenic diet that suggest that in children, the ketogenic diet results in short to medium term benefits in seizure control, the effects of which are comparable to modern antiepileptic drugs [11].

However, one study of long term outcome reports that many children find the diet difficult to tolerate. The main reasons for drop-outs in the included studies included gastrointestinal side effects and dislike for the diet. Fewer studies have involved adults or other diets. The Atkins diet, which is a less restrictive diet, has shown similar benefits in some studies, but requires further investigation.

Immunotherapy

Immunotherapy may be a viable treatment strategy in a subset of epileptic patients whose poor seizure control may result from the presence of neural-specific antibodies, which has been referred to as 'autoimmune epilepsy'. Iorio et al found autoantibodies specific to neural antigen in 2 of 29 patients with epilepsy and other neurologic symptoms and/or autoimmune diseases (group 1) and in 9 of 30 patients with AED-resistant epilepsy (group 2). Of the patients in group 2 who received immunotherapy with 1) intravenous steroids and IV immunoglobulin for 6 months, (2) IV methylprednisolone, IV immunoglobulin, and rituximab, or (3) IV steroids, 5 cycles of plasmapheresis, and oral steroids, 75% had a reduction in seizure frequency of 50% or greater [12].

Hormonal therapy

A patient's hormonal milieu contributes to the timing of emergence of several epilepsy syndromes that are known to begin at puberty and recede with the end of reproductive potential [13]. Catamenial epilepsy refers to seizure clusters occurring in a cyclical pattern related to menses. Treatment of epilepsy using hormones such as progesterone complements standard antiepileptic therapy and has shown to have a significant effect in women with intractable catamenial epilepsy in decreasing the frequency of seizures.

CONCLUSION

Although approximately two thirds of patients with epilepsy will achieve seizure stability with one or a combination of two or three AED, the remaining third will have pharmacoresistant epilepsy for which several other treatment modalities exist. Surgery is the preferred treatment option for selected candidates with unilateral lesions visible on MRI. Deep brain stimulation has shown to be effective in certain patients and with certain brain localizations of the epileptogenic foci, but requires further investigation for improvement in the selection of patients, parameters and targets. Vagus nerve stimulation has not shown such promising results. For children in whom surgery is unsuitable, a ketogenic diet could improve seizure control, but tolerability is poor. Future advances in AED will involve agents that alter the natural history of epilepsy and modify disease as opposed to providing primarily symptomatic treatment. Responsive cortical stimulation is a field that provides future prospect in the treatment of drug-resistant epilepsy.

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G g	G g	P p	P p
D d	D d	R r	R r
\	G g	S s	S s
E e	E e	T t	T t
@ '	Zh zh] }	K k
Z z	Z z	U u	U u
Y y	Dz dz	F f	F f
I i	I I	H h	Kh kh
J j	J j	C c	Ts ts
K k	K k	^ ~	Ch ch
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