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Psychosocial Risk Factors within the Essential Hypertension Development

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Abstract

Introduction: Psychosocial factors can be seen as the interaction of environmental stressors and individual responses to stress. This indicates a relationship between psychosocial factors and cardiovascular diseases or arterial hypertension. To some extent, it is clear that a positive family history, excessive and unhealthy diet, alcohol consumption and stress at work influence the development of essential hypertension. The goal of our study was to prove the connection between stress at work, family relationships and psychological disbalance with the occurrence of essential hypertension.

Methods: This cross-sectional study included 42 patients from the Primary Health Care Center of Sarajevo Canton diagnosed with essential arterial hypertension and excluded patients with secondary hypertension. The collected data consist of two parts, the first of which consists of data on participants' gender, age, marital status, employment, diagnosis of hypertension and its degree, family history, smoking, body mass index, physical activity, alcohol consumption and laboratory values of total cholesterol and triglycerides. The second part is related to data collected by application of the standardized test for assessing quality of life MANSA (Manchester Short Assessment of Quality of Life).

Results: The regression model was created in PASW Statistics software.

Specifically, the enter method for linear regression has been used. The dependent variable (mean arterial pressure) and 7 potential predictors were entered into the model. The obtained model proved to be highly statistically significant ($F(7)=7.77$, $p<0.001$). Significance of standardized regression coefficients has been obtained for the variables: family history ($\beta=0.54$, $p<0.001$), smoking ($\beta=-0.47$, $p<0.001$) and alcohol ($\beta=0.37$, $p<0.01$). When it comes to individual MANSA questions, answers on question 2 ($\beta=-0.37$, $p<0.05$), as well as the interaction of answers to question 7 and question 14 ($\beta=-0.66$, $p<0.001$) proved to be statistically significant predictors of mean arterial pressure.

Conclusions: According to the results of our study hypertension is mainly associated with family history, smoking, alcohol consumption and poor family atmosphere. Dealing with activities that do not include "family gatherings" result in an increase in blood pressure values.

Key words: psychosocial stress, quality of life, hypertension

Introduction

Experimental and epidemiological studies demonstrated a link between psychological stress and cardiovascular diseases, especially high blood pressure. The sign by which we recognize the exposure to stress are individual triggers of sympathetic nerve fibers that are repeated within a single cardiac cycle (1,2). It has been proven that people who are vulnerable at socioeconomic level and those who are discriminated have significant risk for essential arterial hypertension in the manner that pressure increase is higher for systolic than diastolic blood pressure (3). For long is known that the sympathetic nervous system plays an important role in the acute reaction to stress, however, the mechanisms that contribute to the continuous increase in blood pressure over a long period are still not fully understood. In response to stress small doses of angiotensin II are secreted, which

increases blood pressure, vascular T cell inflammation and gene expression for corticotrophin-releasing hormone in the paraventricular nuclei (4).

Therefore, the focus is placed on psychosocial factors that are manifested at the individual and population level, in order to achieve complete understanding of the disease etiopathogenesis (5). It is believed that there are multiple unknown mechanisms. It seems that organs and somatic disposition try to meet the psyche demands. It looks like the psyche "select" organs through which it will announce the specific disorder or function in which implementation brings discord. Hypertension is the presence of increased blood pressure, at the level where the patient is exposed to an increased risk of target organ damage in several vascular fields, including the retina, brain, heart, kidneys and large blood vessels. More specifically, arterial hypertension is defined as the change in blood pressure greater than 140/90 mm Hg.

Psychosocial factors can be viewed in dual manner, as environmental stress and as an individual characteristic or psychological reaction to stress. Stress is a subjective experience prompted by events that cannot be controlled or are threatening. Stress is not only a situation but also human reactions to a certain situation (6). Exposure to stress include acute life situations, chronic exposure to stress at work and other life circumstances. Stress is a common at the workplace, which are characterized by high demands, time pressure and low levels of control or decision-making limitations. For example, reactions to stressful situations include aggression, hostility and depression, which is reason enough for many to adopt bad habits such as smoking, unhealthy diet, physical inactivity, alcohol consumption and similar (1).

All these points to the fact that psycho-social factors are the strongest argument in explaining the importance of the connection between socioeconomic status and the emergence of cardiovascular disease. Severe physical exertion, the inability to control the situation at work, lack of support in the performance of tasks and the lack of psychological capacities that a person successfully copes with stressful situations in life, often resulting in the inability of the body to maintain homeostasis of the cardiovascular system, especially in the form of hypertension (7).

It is necessary to take care of sufficient consumption of potassium, calcium and magnesium, increase consumption of fruits, vegetables (at least 4 times a day), dairy product with low-fat content, with reduced saturated and total fat (adoption of so called DASH - Dietary Approaches to Stop Hypertension). The objective of all non-pharmacological measures is to reduce: blood pressure, total cardiovascular risk and the number of antihypertensive drugs used. Non-pharmacological measures should not be an unnecessary cause the delay the application of antihypertensive therapy, particularly in patients at an increased risk (8).

The exact cause and development of essential arterial hypertension are not yet fully understood. However, to some extent, it is clear that a positive family history, excessive and unhealthy diet, alcohol consumption, and particularly stress at work affect the occurrence and development of essential arterial hypertension.

The quality of life is greatly affected by the feeling of satisfaction with various aspects of life, for example: friendship, business, financial situation, housing, family, physical and mental health. Previous studies (9,10) have shown a positive correlation between the mentioned psychosocial factors with the occurrence and development of essential hypertension. Due to the fact that the psychosocial aspects of etiopathogenesis of arterial hypertension are insufficiently clarified reveals a legitimate interest for their additional analysis. The goal of our study was to prove the connection between stress at work, family relationships and psychological disbalance with the occurrence of essential hypertension.

Methods

This cross-sectional study included 42 patients diagnosed with essential arterial hypertension who have voluntarily agreed to participate in the study. Data were collected in the period April - May 2013, in the Public Institution Primary Health Care Center of Sarajevo Canton, at organizational unit of Old Town, Department of family health.

Inclusion criteria were essential arterial hypertension, and exclusion criteria were proven secondary hypertension (renal - renal artery stenosis or kidney parenchyma disease; endocrine - diabetes mellitus, pheochromocytoma, Cushing's syn-

drome, Conn's syndrome, thyroid dysfunction, parathyroid and pituitary gland, hormonal contraceptives, replacement estrogen therapy, pregnancy, epoetin alfa therapy, cardiovascular - coarctation of the aorta; neurological - brain tumors, quadriplegia, head injury, cocaine use, sympathetic stimulants).

The collected data consist of two parts, the first one included general information and second one standardized test for assessing quality of life MANSA (11). The first part of data consisted of basic information about the person such as gender, age, marital status, employment, diagnosis of hypertension and its degree, family history, smoking, body mass index, physical activity, alcohol consumption and laboratory values of total cholesterol and triglycerides. MANSA consist of 16 questions drawn from the Lancashire Quality of Life Profile (12). MANSA questionnaire include four objective questions to be answered "yes" or "no" and 12 subjective questions that aim to evaluate the feeling of satisfaction with certain areas of life. Estimated is satisfaction with life as a whole, employment/ retirement, financial situation, number and quality of friendships, leisure activities, accommodation, personal security, family members or the fact that person lives alone, sexual life, relationships with family, physical health and mental health. Each answer of the test is graded on a scale of satisfaction from 1 to 7 where 1 means "Could not be worse", 2 means "Very dissatisfied", 3 means "Mostly dissatisfied ", 4 means "Neither satisfied nor dissatisfied ", 5 means "Mostly satisfied ", 6 means "Very satisfied" and 7 means "Could not be better" (13).

For purposes of identifying the combination of factors (variables) which is associated with higher level of stress, as measured by the mean arterial pressure, we decided to create a regression model. The regression model was created in PASW Statistics software. Specifically, the enter method for linear regression has been used. The dependent variable (mean arterial pressure) and 7 potential predictors were entered into the model. The obtained model proved to be highly statistically significant (Table 1).

Results

Our sample consisted of 42 respondents - 18 men (43%) and 24 women (57%).

Regarding age, the respondents were divided into three groups: a group of 48 to 60 years of age with 20 respondents (48%), a group of 61-70 years of age with 14 respondents (33%) and group 71-83 age with 8 respondents (19%). Out of 42 respondents 25 of them were married (59%), 2 were single (5%) and 15 of them were widowed/separated (36%). Elementary school was completed by 4 respondents (10%), secondary school by 22 respondents (52%), college by 7 patients (17%), faculty by 8 patients (19%). One respondent was without formal education (2%). 12 respondents were employed (29%), 10 respondents were unemployed(24%) and 20 respondents were retired (47%). Out of the 42 respondents, 14 (33%) had grade I hypertension, 19 respondents (46%) had grade II hypertension and 9 respondents (21%) grade III hypertension.

Positive family history in terms of hypertension has been identified for 32 respondents (76%) and a negative family history has been identified for 10 respondents (24%). From the baseline 15 (36%) were smokers, and 27 respondents (64%) were

Table 1. Regression model characteristics

	B (SE)	Standardized coefficient
Constant	121.99 (3.08)	
Family history/genetics***	1.41 (0.32)	0.54
Smoking***	-8.26 (2.21)	-0.47
Alcohol**	8.33 (2.95)	0.37
Question 2 (Mansa)*	-1.79 (0.71)	-0.37
Question 7 (Mansa)	0.64 (0.70)	0.11
Question 14 (Mansa)	0.29 (1.06)	0.03
Questions 7 & 14 (Mansa)***	-3.87 (0.67)	-0.66

*Comment - Model: $F(7)=7.77$, $p<0.001$; $R^2=0.62$. Regression coefficients: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.*

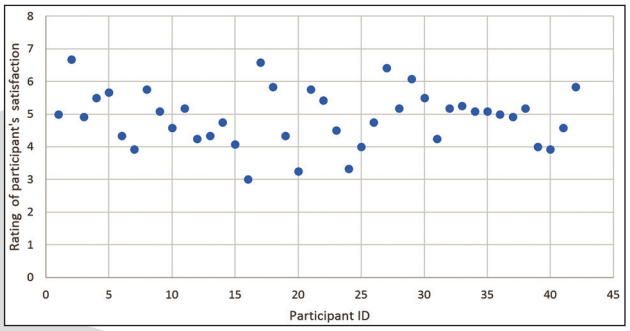
nonsmokers or had stopped smoking. Body mass index (BMI) in 9 respondents (21%) was normal with values ranging from 18.4 to 24.9; 22 respondents (53%) was overweight with BMI values ranging from 25 to 29.9 and 11 respondents (26%) were obese with a BMI over 30. Daily physical activity lasting more than 60 minutes had 32 respondents (76%), daily physical activity for 30 - 60 minutes had 3 patients (7%) and daily physical activity lasting less than 30 minutes had 7 patients (17%). Of the 42 respondent's alcohol consumed 7 of them (17%) while 35 respondents (83%) did not consumed alcohol.

In 38 cases (90%) members of the household had consumed alcohol, and in 4 cases (10%) members of the household did not consumed alcohol. Laboratory findings of respondents included the level of total blood cholesterol and triglyceride levels in the blood. Normal findings of cholesterol and triglycerides in the blood were found in 12 respondents (29%), abnormal findings of cholesterol and triglyceride had 19 respondents (45%), while in 11 cases (26%) there was no information about the analysis of the total cholesterol and triglyceride in blood.

On the second question of MANSA questionnaire that reads "How satisfied are you with your job (or education) as the main occupation? Or, if you are unemployed or retired: How satisfied are you as a non-employed/retired" from 42 respondents 2 (5%) responded that they could not be worse, 9 respondents (21%) were very dissatisfied, 5 respondents (12%) mostly dissatisfied, 7 respondents (17%) neither satisfied nor dissatisfied, 5 respondents (12%) mostly satisfied, 12 respondents (28%) very satisfied, and 2 patients (5%) answered that it cannot be better.

On the 7 question of MANSA questionnaire that reads "How satisfied are you with the activities in the leisure time?" from 42 respondents 2 (5%) said that they could not be worse, 2 respondents (5%) very dissatisfied, 4 respondents (10%) are mostly dissatisfied, 9 respondents (21%) that they are neither satisfied nor dissatisfied, 13 respondents (30%) are mostly satisfied, 8 patients (19%) are very satisfied and 4 respondents (10%) responded that it could not be better.

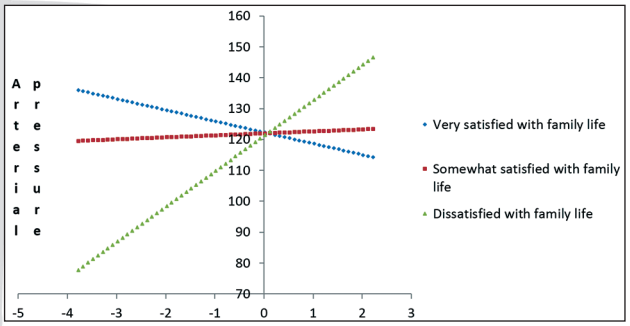
On the question 14 of MANSA questionnaire that reads "How satisfied are you with your family?" from 42 respondents, 1 respondent (2%) replied mostly dissatisfied, 5 respondents (12%) that are neither satisfied nor dissatisfied, 4 respondents (10%) are mostly satisfied, 24 respondents (57%) are very satisfied, and 8 patients (19%) that it could not be better.



Graph 1. General MANSA rating

A general assessment of satisfaction according to MANSA is calculated in the manner that is calculated the mean of the 12 subjective questions. The median was 4.95 and the standard deviation 0.81 on a scale from 1 to 7 (Graph 1).

The analysis of participants' answers to questions 7 and 14 proved to be particularly important for drawing conclusions about participants' level of stress. Within questions 7 (MANSA) of respondents were required to provide information on how they are satisfied "with their free time activities", while within question 14 respondents had to rate how much they are satisfied with "relationship with their family."



Graph 2. Satisfaction with free time activities

Neither of these two questions alone was not a statistically significant predictor of high blood pressure. However, the interaction of these two questions proved to be a highly significant predictor. Interpretation of the significance of this interaction can be carried out by following interactive chart (Graph 2).

Discussion

Based on the fact that for the obtained model $F(7)=7.77$ ($p<0.001$), we can conclude that the our regression model allows significantly better prediction of blood pressure in patients, compared to the situation when that prediction was attempted using empirically obtained average value of the mean arterial pressure, only. Predictors of the obtained model allow us to explain 62% of variance in the arterial pressure of the respondents.

It should be noted that two of the seven predictors from the regression model proved to be not statistically significant, but in line with the recommendation by Howell (2013) they are retained in the model, because their interaction proved to be statistically significant.

Below, interpretations of the individual predictors are provided.

Genetic factor significantly affects the level of arterial blood pressure. When the score on the scale of family history increases by one unit, mean arterial pressure increases by 1.41 units, provided that other predictors in the final model are kept constant. Also, we can say that when there is an increase in the score on the scale of family history by one standard deviation, blood pressure increases by 0.54 standard deviations. Generally, based on the size of standardized regression coefficients, we can conclude that family history, together with interaction of questions 7 and 14, proved to be the most important predictor of hypertension.

It is possible to change the sensitivity of the baroreceptors, which is genetically conditioned (14) and/or an inherited mutation in the gene coding for angiotensinogen (15) influence the development of hypertension in relatives. Looking at psychosocial aspects of the impact of positive family history, we can say that just knowing that patients diagnosed with hypertension in many cases has a negative impact on quality of life (16), and their presence and conversations convey a portion of the negative energy to family members. If the family member who does not have arterial hypertension is constantly exposed to it, and cannot cope with the negative energy to which it is exposed, there is the risk of developing hypertension.

Smoking significantly affects the mean arterial blood pressure as a measure of hypertension. The mean arterial pressure of smokers is lower by 8.26 units than in non-smokers, if other characteristics expressed through predictors from the model at are kept constant. This result does not agree with the results reported in other studies (17).

Alcohol consumption significantly affects the degree of hypertension. In people who do not drink alcohol, mean arterial pressure is on average for 8.33 units lower than in those who consume it, if other predictors in the model are kept constant. Certain alcohol drinks have a protective effect on blood vessels, but the damage caused by alcohol observed with psychosocial aspects exceeds the benefit. Alcohol has anxiolytic activity, but the effect lasts while maintaining a sufficient concentration of alcohol in blood. After that alcohol only encourages depression and further undermines the quality of life (7). Alcohol consumption affects not just the individual who consume it, but also its surroundings, its immediate environment. Discord in the family further undermines the quality of life, as the relations with the family is one of the most important predictors of the specified parameter.

In the question 2 (MANSA) the respondents were asked to answer whether they are satisfied with their job (or education) as their main occupation, or if they are unemployed or retired, their level of satisfaction as non-employed/retiree. It turned out that the increase of satisfaction on the scale of question 2 is statistically significantly associated with a lowering of the degree of hypertension. In particular, when the answer on question 2 (MANSA) increases by one, the mean arterial pressure decreases by an average of 1.79 units, if at the same time all the other predictors in the model are kept constant. It is possible that a person is exposed to stress at work, if the jobless person or without regular and dignified retirement, responding with constant tension which increases sympathetic tone and adrenal function. Due to the stress of this type are often time consuming, the body begins to dissipate physiological stocks in order to maintain homeostasis, which requires a lot of effort and energy. If the stress is still present, there is exhaustion of the body and the person can succumb to various diseases. According to the aforementioned results, we can conclude that stress from work affects the development of hypertension, which is consistent with the published literature (18).

Within question 7 (MANSA) the respondents were required to provide information on how satisfied they are "with their activities in the leisure time", while in question 14 respondents had to rate how much they are satisfied with "relationship within family." Neither of these two issues alone proved to be a statistically significant predictor of blood pressure level. However, the interaction of these two factors proved to be highly significant predictor. Interpretation of the significance of this interaction is shown on interaction chart (Graph 2).

Based on that chart, we can conclude that in participants who are very satisfied with their family life, the increase in satisfaction with free time activities leads to a decrease in arterial pressure decreases. In patients who express average satisfaction with family life, the increase in pleasure with arterial pressure slightly leads to an only slight increase of arterial pressure. Finally, in respondents who are dissatisfied with their family life, an increase in satisfaction with free time activities results in a significant increase of arterial pressure.

In other words, it is possible that intensive engagement in activities that do not include "family gatherings" result in an increase in blood pressure. These attitudes can be summed up in the statement, that the key to lowering hypertension degree is largely contained in the capability of simultaneous realization of good relations with the family and development of quality leisure activities.

The importance of family unity in the maintenance of internal peace of each individual is justified by the fact that of the 15 respondents who have lost a close family member or were divorced, 6 of them (40%) developed hypertension within one year. Aware of this fact Holmes and Rahe ranked "death of a family member" among the major life events that significantly affect the quality of life of the individual (19). Through this study it has been shown that psychosocial risk factors influence the occurrence and development of arterial hypertension, which is in line with many other scientific articles (10, 20-22).

Conclusions

In conclusion, according to the results of our study hypertension is mainly associated with family history, smoking, alcohol consumption and poor family atmosphere. Dealing with activities that do not include "family gatherings" result in an increase in mean arterial blood pressure. The regulation of blood pressure is largely contained in the capability of simultaneous realization of good relations with the family and development of quality leisure activities.

References

1. *Gasperin D, Netuveli G, Dias-da-Costa JS, Pattussi MP. Effect of psychological stress on blood pressure increase: A meta-analysis of cohort studies. Cad Saude Publica 2009; 25(4): 715–26.*
2. *Esler M, Eikelis N, Schlaich M, Lambert G, Alvarenga M, Dawood T, et al. Chronicmental stress is a cause of essential hypertension: Pres-ence of biological markers of stress. Clin Exp Pharmacol Physio 2008; 35(4): 498–502.*
3. *Strogatz DS, Croft JB, James SA, Keenan NL, Browning SR, Garrett JM, et al. Social support, stress, and blood pressure in black adults. Epidemiology 1997; 8(5): 482–7*
4. *Marvar PJ, Vinh A, Thabet S, Lob HE, Geem D, Ressler KJ, Harrison DG. T lymphocytes and vascular inflammation contribute to stress-dependent hypertension. Biol Psychiatry. 2012; 71(9): 774-82.*
5. *Kaplan AG, Everson AS, Lynch WJ. The contribution of social and behavioral research to an understanding of the distribution of disease: a multilevel approach. Am J Public Health 2002; 92(4): 588–97*
6. *Larsen RJ, Buss DH. Personality Psychology. New York: McGraw-Hill Education; 2013.*
7. *Boden JM, Fergusson DM. Alcohol and depression. Addiction 2011; 106(5): 906–14.*
8. *Beilin LJ. Stress, coping, lifestyle and hypertension: a paradigm for research, prevention and non-pharmacological management of hypertension. Clin Exp Hypertens. 1997; 19(5-6): 739-52.*
9. *Ayalon L, Gross R, Tabenkin H, Porath A, Heymann A, Porter B. Correlates of quality of life in primary care patients with hypertension. Int J Psychiatry Med. 2006; 36(4): 483-97.*
10. *Sparrenberger F, Cichelero FT, Ascoli AM, Fonseca FP, Weiss G, Berwanger O, et al. Does psychosocial stress cause hypertension? A systematic review of observational studies. J Hum Hypertens. 2009; 23(1): 12-9.*

11. *Priebe S, Huxley P, Knight S, Evans S. Application and results of the Manchester Short Assessment Of Quality Of Life (MANSA). Int J Soc Psychiatry. 1999 Spring; 45(1): 7-12.*

12. *Oliver JP, Huxley PJ, Priebe S, Kaiser W. "Measuring the quality of life of severely mentally ill people using the Lancashire Quality of Life Profile. Psychiatry Psychiatr Epidemiol. 1997; 32(2): 76-83.*

13. *Slade M, Leese M, Cahill S, Thornicroft G, Kuipers E. Patient-rated mental health needs and quality of life improvement. Br J Psychiatry. 2005; 187: 256-61.*

14. *Parmer RJ, Cervenka JH, Stone RA. Baroreflex sensitivity and heredity in essential hypertension. Circulation 1992; 85(2): 497-503*

15. *Caulfield M. Lavender P, Farrall M, Munroe P, Lawson M, Turner P. Linkage of the Angiotensinogen Gene to Essential Hypertension. N Engl J Med 1994; 330: 1629-33*

16. *Ames SC, Jones GN, Howe JT, Brantley PJ. A prospective study of the impact of stress on quality of life: an investigation of low-income individuals with hypertension. Ann Behav Med. 2001; 23(2): 112-9.*

17. *Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Zampi I, Battistelli M. Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in essential hypertension. Hypertens. 1995; 13(10): 1209-15.*

18. *Vrijkotte TG, van Doornen LJ, de Geus EJ. Effects of Work Stress on Ambulatory Blood Pressure, Heart Rate, and Heart Rate Variability" Hypertension. 2000; 35(4): 880-6.*

19. *Holmes TH, Rahe RH. The social readjustment rating scale. J Psychosom Res. 1967; 11(2): 213-8.*

20. *Yasein NA, Shakhatreh FM, Suleiman AA, Barghouti FF, Halaseh LJ, Abdulbaqi NK. Knowledge, Attitudes and Practices on Hypertension in patients attending Family Practice Clinics. HealthMED. 2011; 5(6): 1404-14.*

21. *Baune BT, Aljeesh Y. The association of psychological stress and health related quality of life among patients with stroke and hypertension in Gaza Strip. Ann Gen Psychiatry. 2006; 19; 5: 6.*

22. *Roca-Cusachs A, Ametlla J, Calero S, Comas O, Fernández M, Lospaus R, et al. Quality of life in arterial hypertension. Med Clin (Barc). 1992; 98(13): 486-90.*

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Effects of clomiphene citrate and HFHS during controlled ovarian stimulation with IUI in subfertile couples with mild male, female, mixed factor and unexplained infertility: a randomized controled trial

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Abstract

Introduction: Controlled ovarian stimulation (COS) with intrauterine insemination (IUI) is an effective treatment for mild male factor, female factor, mixed factor and unexplained subfertility, but it is unclear which cure for ovarian stimulation is more effective. The aim of this study was to determine whether COS / IUI with a low dose of human menopausal gonadotropin (hFSH) significantly improves the clinical pregnancy rate compared to treatment with clomiphene citrate (CC).

Patients and methods: A prospective randomized controlled trial (RCT) examines 43 subfertile couples with infertility duration longer than 1 year. Group hFSH (n=21) was treated with low doses hFSH 37.5 - 75 IU daily subcutaneously to achieve the target size of the follicles (≥ 17 mm), and the groups treated with CC CC oral dosing (n=22) with 50 mg/ day from 3rd-7th day of the menstrual cycle. The primary outcome was the point of clinical pregnancy rate per patient / cycle.

Main results: Pregnancy rates per patient/cycle in hFSH group was significantly higher (RR=1.47, 95% CI: 1.26-1.78, p <0.01, RR = 1.34, 95% CI: 1.12 to 1.46, p <0.01) compared to the CC group. Live birth rate per patient / cycle was significantly higher in the group with hFSH (RR=1.53, 95% CI: 1.26-1.78, p<0.02, RR = 1.46, 95% CI: 1.12 to 1.46, p<0:03) compared to the CC group. A significantly greater number of follicles was preovulatory in hFSH group (hFSH 1,8 vs. CC 1.3, p <0.03) and the endometrial thickness (hFSH 8.6 mm vs. CC 7.5 mm, p<0.04) compared the CC group, whereas there were no significant difference in the rate of spontaneous abortion between groups (RR=1.04, 95% CI: 0.76-1.2 8, p<0.96).

Findings: Controlled ovarian stimulation/IUI with a low dose of hFSH was superior in comparison to CC in the rate of clinical pregnancy rate and live births.

Key words: controlled ovarian stimulation/ intrauterine insemination/ clomiphene citrate/ human menopausal gonadotrophin/ mild factor/ female factor/ mixed/ unexplained infertility.

Introduction

The World Health Organization (WHO) designated the infertility as a disease, and its treatment as one of the fundamental human rights. Infertility is defined as the inability to concieve after one year of unprotected intercourse in pair of childbearing potential (1). The diagnosis of male factor is based on the results of the analysis of semen. World Health Organization defined cut-off value for differentiating normal and abnormal semen (2). Sperm is normal if TMSC> 20×10^6/ejaculate, lower values are considered abnormal spermiogram and define male infertility factor. If all parameters are above the cut-off value, the seed is defined as normospermia and couples with diagnosis of unexplained female infertility factor. Mild factor includes anovulatory cycle, unilateral tubal factor, mild endometriosis, the age of women less than 35 years, FSH <12 IU, AMH> 0.6 ng/ml. In subfertile couples with unexplained infertility, mild male and female factor and mixed factor, IUI with controlled ovarian stimulation (COS) is the first therapeutic choice in assisted reproductive

technologies-ART (3)as well as an endometriosis self-help group representative. After reviewing existing evidence-based guidelines and systematic reviews, the expert panel met on three occasions for a day during which the guideline was developed and refined. Recommendations based solely on the clinical experience of the panel were avoided as much as possible. The entire ESHRE Special Interest Group for Endometriosis and Endometrium was given the opportunity to comment on the draft guideline, after which it was available for comment on the ESHRE website for 3 months. The working group then ratified the guideline by unanimous or near-unanimous voting; finally, it was approved by the ESHRE Executive Committee. The guideline will be updated regularly, and will be made available at http://www.endometriosis.org/guidelines.html with hyperlinks to the supporting evidence, and the relevant references and abstracts. For women presenting with symptoms suggestive of endometriosis, a definitive diagnosis of most forms of endometriosis requires visual inspection of the pelvis at laparoscopy as the \ u2018gold standard\u2019 investigation. However, pain symptoms suggestive of the disease can be treated without a definitive diagnosis using a therapeutic trial of a hormonal drug to reduce menstrual flow. In women with laparoscopically confirmed disease, suppression of ovarian function for 6 months reduces endometriosis-associated pain; all hormonal drugs studied are equally effective although their side-effects and cost profiles differ. Ablation of endometriotic lesions reduces endometriosis-associated pain and the smallest effect is seen in patients with minimal disease; there is no evidence that also performing laparoscopic uterine nerve ablation (LUNA,(4),(5). Literature indicates the significantly higher rate of pregnancy after IUI in infertile couples with unexplained infertility and endometriosis which includes ovulation induction (6)the effectiveness of IUI treatment is not consistent, and the role of IUI and in vitro fertilization (IVF. For mild COS, CC, TSH, FSH, and aromatase inhibitors are used. Clomiphene citrate, or anti-estrogens are the first choice in the induction of ovulation and they are cheaper than therapy with gonadotropins. Clomiphene citrate is often ineffective in women with hypogonadotropic hypogonadism (hypothalamic amenorrhea) in which the axis of the hypothalamic-pituitary-ovarian is seriously dysfunctional. Clomiphene citrate is ineffective in women with hypergonadotropic hypogonadism (7),(8). Gonadotropin glycoprotein hormones are derived from the urine of menopausal women, or obtained by recombinant techniques. They simulate the growth of follicles acting on FSH receptors and have antiestrogen efects. Pregnancy rate in previously published RCTs with mild COS was similar and was up to 4-14% for CC ovarian stimulation and 7-20% for gonadotropin ovarian stimulation in couples treated with IUI (9)unexplained subfertility and minimal-mild endometriosis, but it is unclear which medication for ovarian stimulation is more effective. STUDY DESIGN, SIZE, DURATION: A total of 330 women scheduled for IUI during 657 cycles (September 2004-December 2011,(8),(7).

The objective of this RCT was to determine the effectiveness of CC and hFSH in COS/IUI in couples with mild, male, female, mixed factor and unexplained infertility.

Material and Methods

Study design

A prospective randomized controlled trial (RCT) examines 43 subfertile couples with infertility duration longer than 1 year. Research was conducted from January 2014 to December 2015 in PHI of Human Reproduction "Dr Hajder" Tuzla. Analysis of infertility is conducted in accordance with the guidelines for infertility and consists of views of both partners (5). All the couples underwent following tests: spermiogram, analysis of sex hormones in the early follicular phase of the cycle, Anti-Müllerian hormone (AMH), ultrasound monitoring cycle (folliculometry), measuring of midlluteal progesterone, microbiological and immunological treatment of the infection, hysterosonosalpingographia, diagnostic laparoscopy in indicated cases.

Study population

The study included couples with unexplained infertility, mild male, female and mixed-factor infertility. The studies excluded couples with male factor with TMSC<$5x10^6$/ejaculate, mutual tubal factor, severe endometriosis, patients over 35 years

of age, FSH>12 IU, AMH<0.6 ng/ml and patients with ovarian cysts present (>19 mm >1 month).

Definition

Infertility is defined as the failure of conception, despite 12 months of unprotected intercourse (10). TMSCl is calculated by multiplying the concentration of sperm/milliliter (SC) x volume (ml) x motylity (A+B) divided by the 100. Spermiogram is normal if TMSCl>20×10^6/ejaculate, lower values are considered abnormal and spermiogram define male infertility factor. Infertile couples with normospermia and normal female factor were considered unexplained infertility. The normal menstrual cycle is between 25 and 35 days, the level of progesterone in the luteal phase of the medium>27 mmol/ l ,the duration of the luteal phase of >11 days. Multifollicular growth is defined if two dominant follicles have a minimum of 17 mm in diameter.

Treatments

Couples were randomized into two groups and treated till aim was acomplished. Group CC was (n = 22) treated with clomiphene citrate (Clomid, Sanofi, Belgium) at a dose of 50 to 100 mg of 3rd to 7th days of the menstrual cycle to achieve the goal. HFSH group (n=21) was treated with hFSH (Menopur, 75 IU Fering, Aalst, Belgium), the starting dose was 75 IU/day for women with a BMI <25 kg/m^2 and 100 IU/day of a woman with a BMI > 25 kg/m^2. The beginning of treatment is the second to fourth day cycle subcutaneously once a day to achieve the size of follicles 18 mm (4). In both groups where the size of the follicles was 17-18 mm hCG was given (Pregnyl, Schering-Plougk, Istanbul, Turkey) 5000 IU. On the day of administration of hCG endometrial thickness (mm) were measured and the size of the follicles and recorded multifollicular growth. The injection of hCG was not given if there were more than 3 follicles larger than 17 mm or >5 follicles >14 mm because of the risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). IUI was performed 36 hours after hCG administration. Women lay on their back for 15 to 20 min after IUI (11).

Semen analysis

The men made the spermiogram on arrival at the Institute. In the case of abnormal spermiogram, a second sample is analyzed 10 weeks later. Male partners gave a semen sample after 2-3 days of sexual abstinence. The seeds were stored at the Institute in sterile plastic container, or at home, as well as delivered to the laboratory of the Institute within 1 hour. During the analysis volume is measured by a numbered syringes. The sperm was read in megler th chamber, with an increase of 200 times MAKLER COUNTING CHAMBER for rapid sperm analysis (12). Mobility was expressed as a percentage of: (A) fast forward progressive sperm, (B) slowly forward progressive, (C) and non-progressive (D) immovable sperm to 200 as the total number of sperm in at least five fields, according to WHO guidelines (2). Sperm morphology was scored by Tygerberg criteria (13), analyzing 200 sperms. This study used a floating processing techniques of seed that is simple and cheap. Processed seed is then inseminated using soft catheter (MedGyn intrauterine insemination catheter, MedGyn Products, Inc., USA).

Outcome measures

The primary objective was to determine the rate of spontaneous pregnancies per cycle/patient in group CC vs. hFSH group. The secondary objective was to determine the number of live births, multiple pregnancy, ovarian hyperstimulation syndrome, multifollicular growth and spontaneous abortions. Pregnancy is defined when positive beta hCG> 25 IU/l after 12 to 14 days after IUI, ultrasound confirmation of beating fetal heart after 6-8 weeks of last menstrual period (14). Spontaneous abortion is defined by the loss of pregnancy less than 24 weeks of pregnancy, weight <500 g and delivery gestational age 24 weeks of pregnancy (15).

Statistics

The data were entered into the created database. Statistic processing was done by application software called SPSS for Windows version 16.0 (Statistical Package for Social Sciences, SPSS, Chicago, IL, USA) was used for this analysis.

Numerical data are presented as mean ±SD, range, the absolute number is expressed in %, 95% confidence interval (CI). To test the signifi-

cance between groups independent Student t-test or Mann-Whitney U-test and Fisher's exact test (univariate analysis) were used, level of significance of p <0.05. Binar logistic regression was performed for the dependent variable (type of pregnancy), with two outcome measures, ie pregnancy after 2 treatments in the COS/IUI. Relative risk ratio (RR) and their 95% confidence interval (CI) was calculated for the pregnancy rate and the rate of live births.

Results

During January 2014 and December 2015 the study included a total of 43 pairs/106 cycles with unexplained infertility, mild male and female factor and mixed factor. Randomized 43 pairs/106 cycles: 22 were in the group CC (52 cycles) and 21 pairs in the group hFSH (54 cycles). The demographic data are shown in Table 1. There were no significant differences between groups in age, BMI, smoking and TMSCl. There was also no significant difference in duration of infertility, the representation of primary and secondary infertility. The distribution of patients in groups with men's, women factor and unexplained infertility was the same without statistical significance.

Cycle characteristics are presented in Table 2. The duration of ovarian stimulation cycles in the CC group was 12 days, the group hFSH for 11 days, and there was no significant difference (CC 11 vs. hFSH12, p > 0.9). The average level of hormones on the third day of follicular phase of the cycle: FSH, LH, estradiol, AMH were the benchmarks and there were no significant differences among groups. The CC group had significantly lower endometrial thickness (CC 7.5 vs hFSH 8.6, p<0.04) compared to group hFSH on the day of hCG administration. On the day of hCG injection number of dominant follicles (≥17 mm) was significantly lower in this group than in the CC group hFSH (CC 1.3 vs. hFSH 1.8, p = 0.03).

The outcomes of treatment in both groups are shown in Table 3. The rate of pregnancy per patient / cycle in hFSH group was significantly higher (RR=1.47, 95% CI: 1.26-1.78, p<0.01; RR=1.34, 95% CI: 1.12-1.46, p<0.01) in relation to the CC group. The rate of live births per patient/cycle was significantly higher in the group of hFSH (RR=1.53, 95% CI: 1.26-1.78, p<0.02,

Table 1. Baseline characteristics of couples in the randomized clinical trial of ovarian stimulation and intrauterine insemination

Variable	Group CC Patient (n=22) Cycles (n=52)	Group hFSH Patient (n=21) Cycles (n=54)	P-value
Mean age of female (range)	31.2 (23.5-35.4)	30.1 (22.1-36.3)	0.9
Mean age of male (range)	33.4 (24.6-46.2)	34.1 (25.2-45.6)	0.7
Smoking (female) %	24	23	0.9
BMI kg/m^2 (range)	23.6 (19-35)	22.9 (20-34)	0.8
TMSC in millione (range)	26.2 (5-50.2)	27.1 (5.1-48.2)	0.8
Type of infertillity No %			
Primary	64	67	0.9
Secondary	36	33	0.9
Duration of infertillity in months (±SD)			
Primary	24±16	28±12.3	0.7
Secondary	21.5±13.2	22±13.1	0.9
Male factor (%)	24	23	0.9
Female factor (%)	30	32	0.8
Mixed (Male+Female) (%)	18	19	0.9
Unexplaned (%)	28	26	0.8

Note: Values are the mean ± SD,namber %, range, P<0.05 for Group CC vs. Group hFSH: Univariante analysis (t-test or x^2 test with p<0.05, Man Witney test for Group CC vs. Group uFSH).BMI- body mass index, TMSC-Total motile sperm count, CC- clomiphene citrate, hFSH-urinare FSH.

Table 2. IUI cycle characteristics

Variable	Group CC Patient (n=22) Cycles (n=52)	Group hFSH Patient (n=21) Cycles (n=54)	P-value
FSH on day of the cycle (mIU/mL)	6.1 ±1.2	6.3 ±1.1	0.9
E_2 on day 3 of the cycle (pg/mL)	46.2 ±18.6	49.1 ±17.3	0.8
LH on day of the cycle (mIU/mL)	7.1 ±1.3	7.6 ±1.2	0.5
AMH (mg/mL)	3.6 ±1.4	3.5 ±1.6	0.5
AFC	8 ±2	7.7 ±1.2	0.08
Duration of cycle (day)	12.0 ±1.3	11.0 ±1.4	0.09
N of ≥17 mm follicle	1.3 ±0.7	1.8 ±0.6	0.03
Endometrial thickness of day of hCG (mm)	7.5 ±1.4	8.6 ±1.2	0.04
N of cycle with multifollicular Growth (%)	36.2%	56.4%	0.01

Note: Values are the mean ± SD,namber %, P<0.05 for Group CC vs.Group hFSH: Univariante analysis (t-test or x^2 test with p<0.05, for Group CC vs. Group hFSH. BMI- body mass index, TMSC-Total motile sperm count, CC- clomiphene citrate, uFSH-urinare FSH.

Table 3. Pregnancy outcomes of the study groups

Outcome	Group CC Patient (n=22) Cycles (n=52)	Group hFSH Patient (n=21) Cycles (n=54)	Relative risk 95% CI	P-value
Pregnancy rate/patient	5/22 (22.7%)	7/21(33.3%)	1.47	0.01
Pregnancy rate/cycle	5/52 (9.6%)	7/54 (12.9%)	1.34	0.01
Live –birth rate/patient	4/22 (18.6%)	6/21 (28.5%)	1.53	0.02
Live –birth rate/cycle	4/52 (7.6%)	6/54 (11.1%)	1.46	0.03
Multiple pregnancy rate/patient	0 (0 %)	1/21 (4.7%)	-	0.56
Miscarriage rate/patient	1/22 (4.5%)	1/21 (4.7%)	1.04	0.96
Pregnancy rate /cycle with multifollicular growth (%)	5/36 (13.8%)	7/46 (15.2%)	1.12	0.28
OHSS rate (%)	0	1/21 (4.7%)	-	0.90

Note: Values are expressed as a percentage of the number with 95% CI. Binary logistic regression analysis, (RR, 95% CI, p<0.05). BMI- body mass index, CC- clomiphene citrate, uFSH-urinare FSH.

RR=1.46, 95% CI: 1.26-1.78, p <0.03) in relation to the group CC. The rate of multiple pregnancy is not recorded in the CC group, whereas in the group hFSH was 4.3%, but there were no significant differences (CC 0 vs hFSH 4.7, p <0.56). Spontaneous abortion rate was 4.5% in the CC group, in hFSH 4.7% with no significant difference (RR=1.04, 95% CI: 0.76-1.28, p <0.96). The rate of OHSS is not recorded in the CC group, while the group has seen a 4.7% hFSH, and there was no significant difference between the groups (CC 1 vs. hFSH 2, p<0.90). Amongst the group there was no significant difference in the rate of pregnancies with multifollicle growth (RR=1.12, 95% CI: 0.96-1.54, p<0:28).

Discussion

In subfertile couples with unexplained infertility, mild male and female factor and mixed factor COS/IUI is the first therapeutic procedure in ART (3)as well as an endometriosis self-help group representative. After reviewing existing evidence-based guidelines and systematic reviews, the expert panel met on three occasions for a day during which the guideline was developed and refined. Recommendations based solely on the clinical experience of the panel were avoided as much as possible. The entire ESHRE Special Interest Group for Endometriosis and Endometrium was given the opportunity to comment on the draft guideline, after which it was available for comment on the ESHRE website for 3 months. The working group

then ratified the guideline by unanimous or near-unanimous voting; finally, it was approved by the ESHRE Executive Committee. The guideline will be updated regularly, and will be made available at http://www.endometriosis.org/guidelines.html with hyperlinks to the supporting evidence, and the relevant references and abstracts. For women presenting with symptoms suggestive of endometriosis, a definitive diagnosis of most forms of endometriosis requires visual inspection of the pelvis at laparoscopy as the \u2018gold standard\ u2019 investigation. However, pain symptoms suggestive of the disease can be treated without a definitive diagnosis using a therapeutic trial of a hormonal drug to reduce menstrual flow. In women with laparoscopically confirmed disease, suppression of ovarian function for 6 months reduces endometriosis-associated pain; all hormonal drugs studied are equally effective although their side-effects and cost profiles differ. Ablation of endometriotic lesions reduces endometriosis-associated pain and the smallest effect is seen in patients with minimal disease; there is no evidence that also performing laparoscopic uterine nerve ablation (LUNA,(4). Despite wide use, role and type COS/IUI combined is controversial. Verhulst et al., in a meta analysis indicated that COS/IUI in combination is superior to the rate of clinical pregnancies than natural cycle controlled for unexplained fertility (16). Clomiphene citrate, or the anti-estrogens are the first choice in the induction of ovulation, and are less expensive than treatment with gonadotropins (8).

Data from the literature suggest a significantly higher rate of pregnancy after IUI in infertile couples with unexplained infertility and endometriosis which includes ovulation induction (17)(6)the effectiveness of IUI treatment is not consistent, and the role of IUI and in vitro fertilization (IVF. IUI shows the analysis of 3,662 cycles significantly increase pregnancy rates compared to the planned time sexual intercourse in natural cycles, regardless of the type of infertility (OR=2.43). It is also proven that in cycles with COS/IUI shown a higher rate of pregnancy (OR=2.2) compared to the time planned relations in the natural cycle (18).

The results of this randomized, controlled studies have shown that COS/IUI with low doses of gonadotropins (hFSH) was superior to stimulation with CC in the rate of clinical pregnancy rate and live births, without higher rates of multiple pregnancies in couples with female, male, mixed factor and unexplained infertility.

Results of this study are consistent with the results of other randomized controlled trials (RCTs). Pregnancy rates in earlier published studies were similar and were 4-14% for CC ovarian stimulation and 7-20% for gonadotropin ovarian stimulation in couples treated with IUI. In some studies, the advantage was with gonadotropin ovarian stimulation and in other studies, there was no significant difference, and it would be necessary to conduct a meta-analysis of previously published studies. Results are somewhat different, probably due to the selection of infertile couples (9)unexplained subfertility and minimal-mild endometriosis, but it is unclear which medication for ovarian stimulation is more effective. STUDY DESIGN, SIZE, DURATION: A total of 330 women scheduled for IUI during 657 cycles (September 2004-December 2011,(8),(7). Peeraer et al. have shown that the results of the RCT COS/IUI with a low dose of hFSH was superior to the stimulation of the CC for the rate of clinical pregnancy was significantly higher (RR=1.6), significantly higher rates of live births (RR=1.6, $p<0.03$) lower number preovulatory follicles ($p<0.001$), and no significant difference in the rate of multiple pregnancies between groups in couples with male, female, mixed factor and unexplained infertility (9)unexplained subfertility and minimal-mild endometriosis, but it is unclear which medication for ovarian stimulation is more effective. STUDY DESIGN, SIZE, DURATION: A total of 330 women scheduled for IUI during 657 cycles (September 2004-December 2011.

Berker et al. pointed out the results of RCTs that COS/IUI with rFSH had the advantage at the rate of live births compared to CC, but the advantage of rFSH was superior to the number preovulatory follicles (>17 mm) on the day of hCG and higher multifollicular increase ($p<0.1$) in couples with unexplained infertility and male subfertility (8).

Dankert et al. have pointed out in RTC that COS/IUI with low doses of rFSH had the advantage at the rate of live births compared to a CC stimulation (RR=1.11) in couples with unexplained infertility and male subfertility. Results of this study showed that the thickness of the endo-

metrium at the day of hCG, and the number of follicles preovulatory cycle with multifollicle growth was significantly higher in hFSH group in comparison to the CC group (7).

Results of this study are consistent with other studies (9)unexplained subfertility and minimal-mild endometriosis, but it is unclear which medication for ovarian stimulation is more effective. STUDY DESIGN, SIZE, DURATION: A total of 330 women scheduled for IUI during 657 cycles (September 2004-December 2011,(8). Endometrial thickness on hCG day was significantly higher (hFSH=8.5 vs. CC=7.5, p<0.001), the number of dominant follicles (> 14 mm) on the day of hCG was significantly lower (hMG=1.2 vs. CC=1.5, p<0.001) compared to CC stimulation (9)unexplained subfertility and minimal-mild endometriosis, but it is unclear which medication for ovarian stimulation is more effective. STUDY DESIGN, SIZE, DURATION: A total of 330 women scheduled for IUI during 657 cycles (September 2004-December 2011. Berker et al. presented the results of studies that indicate that the number of preovulatory follicles on day of hCG (>17mm) was significantly higher in the rFSH group (1.7 vs. 1.4, p<0.01), whereas no significant difference in the thickness of the endometrium on the day of hCG (9.3 vs. 9.6, p <0.12) (8). Number of cycles with multifollicle growth was significantly higher in the group with rFSH (54.8% vs. 35.1%, p <0.01).

Conclusion

In conclusion, hFSH is superior to CC in COS/IUI on pregnancy rates, the rate of live births, a small number of dominant follicles (>14mm), the greater the number of cycles with multifollicle growth and thicker endometrium on the day of hCG in couples with unexplained infertility, woman, man and mixed factor.

Reference

1. *Hajder E, Hajder M. Evaluation of marital infertility. In: Hajder E, Et.al. Infertility and Reproductive Endocrinology. Tuzla: OFF SET Tuzla; 2011: 1–31.*
2. *Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HWG, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010; 16(3): 231–45.*
3. *Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005; 20(10): 2698–704.*
4. *Cohlen BJ. Should we continue performing intrauterine inseminations in the year 2004? Gynecol Obstet Invest. 2005; 59(1): 3–13.*
5. *National Institute for Health and Care Excellence N. Fertility: assessment and treatment for people with fertility problems. NICE CLincal Guidel. 2013; (May): 274 – .*
6. *Ospedale F, Policlinico M. Intrauterine insemination. Hum Reprod Update. 2009; 15(3): 265–77.*
7. *Dankert T, Kremer J a M, Cohlen BJ, Hamilton CJCM, Pasker-de Jong PCM, Straatman H, et al. A randomized clinical trial of clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimulation in intrauterine insemination cycles for unexplained and male subfertility. Hum Reprod. 2007; 22(3): 792–7.*
8. *Berker B, Kahraman K, Taskin S, Sukur YE, Sonmezer M, Atabekoglu CS. Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing intrauterine insemination: a randomized trial. Arch Gynecol Obstet. 2011; 284(6): 1561–6.*
9. *Peeraer K, Debrock S, De Loecker P, Tomassetti C, Laenen A, Welkenhuysen M, et al. Low-dose human menopausal gonadotrophin versus clomiphene citrate in subfertile couples treated with intrauterine insemination: a randomized controlled trial. Hum Reprod. 2015; 30(5): 1079–88.*
10. *Ciglar S. Marital Infertility. In: Šimunić V. et al. Gynecology. Zagreb: Ljevak 2001; 2001; 349–537.*
11. *Custers IM, Flierman PA, Maas P, Cox T, Van Dessel TJHM, Gerards MH, et al. Immobilisation versus immediate mobilisation after intrauterine insemination: randomised controlled trial. BMJ. 2009; 339: b4080.*

12. *Makler A. Biotechnology of human reproduction, 2003. In: Revelli A, Tur-Kaspa I, Holte JG, Massobrio M, editors. Biotechnology of Human Reproduction. New York: Parthenon Publishing Group; 2003; 115–30.*

13. *TF K, Van Waart J, Van der Merwe K. The Tygerberg strict criteria: what are the clinical thresholds for in vitro fertilization, intrauterine insemination, and in vivo fertilization? In: Atlas of Human Sperm Morphology Evaluation. London: Taylor and Francis; 1988; 13–8.*

14. *Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009*. Fertil Steril. 2009; 92(5): 1520–4.*

15. *WHO. WHO Regional Strategy on Sexual and Reproductive Health. Copenhagen, Denmark; 2001.*

16. *Verhulst SM, Cohlen BJ, Hughes E, Te Velde E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2006; 4: CD001838.*

17. *Abdelkader AM, Yeh J. The potential use of intrauterine insemination as a basic option for infertility: a review for technology-limited medical settings. Obstet Gynecol Int. 2009; 2009: 584837.*

18. *Cohlen BJ, Vandekerckhove P, te Velde ER, Habbema JD. Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men. Cochrane database Syst Rev. 2000; 2: CD000360.*

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The examination of (non) prophylaxis of blood exposure incidents related to hepatitis B risks among dental staff in Bosnia and Herzegovina

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Abstract

The relationship between exposure incidents, procedural reports of exposure incidents, and prompt pre-exposure and post-exposure prophylaxis among dental staff in the region of the Federation of Bosnia and Herzegovina in public institutions has not been analysed yet. The aim is to assess the correlational relationship between the rate of prevalence of exposure incidents and the reports of exposure incidents, the relationship between the rate of exposure incidents and the determination of the protective antibody titre against HBV, and also the relationship between exposure incidents and the vaccination status of participants. By the perspective study of a mean, a vulnerable group of dental staff (n=369 participants) is included, with the mean age of 45 years. The survey was conveyed using a standardized questionnaire about exposure incidents among healthcare workers. By analyzing data provided by participants, it has been found that only 22 % of participants have reported an exposure incident, while 64% of participants have never been involved in the determination of protective antibody titre against HBV hepatitis, being unaware of infectious status concerning HBV. This unawareness of the risk associated with exposure incidents might have been expected in the case of general population, but not in the case of dental population. The results indicate a serious public health problem that needs to be treated strategically.

Key words: reports of blood exposure incidents, pre-exposure prophylaxis, hepatitis B vaccine, post-exposure prophylaxis, dental staff

Introduction

In the European Union (the EU), in order to reduce the risk of blood-borne diseases among healthcare workers, universal prevention measures are conducted. Also, the level and quality of the use of personal protection resources has been raised. There is an implementation of routine hepatitis B vaccination (pre-exposure prophylaxis) and post-exposure prophylaxis. Furthermore, safety devices, register and monitor of incidents and injuries have been designed, and adequate laws and regulations have been passed (1-2). However, these interventions are rarely available to healthcare workers in countries in development, such as our country. Less attention has been paid to risks related to professional blood exposure, the level of infection control in practice is low, and the frequency of exposure incidents is greater (3). Dental staff are constantly subject to exposure incident during their dental interventions (4-5). They are, like other healthcare workers, obliged to obey pre-exposure and post-exposure prophylaxis measures aimed at preventing potential hepatitis B (HBV) infection (6-8). They are also obliged to report incidents to relevant institutions of Occupational Health and to address reports to the referent institution that has to file incidents, evaluate them, and plan strategies of prevention (7, 8). There are clear legal provisions of the Federation of Bosnia and Herzegovina related to reporting injuries at work, as well as for documenting and keeping statistics about injuries at work (8). Dental staff has to protect itself and its environment from expanding blood-borne diseases, but also help every patient who contacts them for help (6, 9). Employ-

ers are also responsible for safety at workplace related to exposure incidents. They have to monitor and optimize all aspects of pre- and post-exposure prophylaxis (1, 2 6, 9). Excessive fear can be dangerous to the same degree as negligence in protection and self-protection from expanding diseases. It is necessary to offer medical protection to every patient, including those infected with HBV, HCV and HIV (10). The introduction of rigorous protection measures in health institutions caused the decrease of the number of blood-borne viral infections in countries in development. Nevertheless, they are mostly a consequence of not enforcing adequate protection measures in health institutions in countries in development (10). The aim is to evaluate the correlational relationship between the rate of prevalence of needle stick and sharps injuries including exposure incidents and reports of exposure incidents, the relationship between the rate of exposure incidents and the determination of protective antibody titre against HBV, and the relationship between exposure incidents and the vaccinational status of participants.

Materials and methods

A prospective cross-sectional study was conducted in dental departments of the primary public health sector in the Federation of Bosnia and Herzegovina during 2014. The research comprised n=369 participants, dental office workers: 166 (45%) dentists, 129 (35%) dental nurses, 48 (13%) dental technicians including 11 (3%) cleaners. The mean age of participants was 45.30±9.003 years, and the mean exposure (working hours) was 18.627 ±10.283 years. The sample consisted of 80% of female participants and 20% of male participants. The examined group consisted of 288 participants that experienced exposure incidents. The research was conducted by an anonymous survey using "The questionnaire about blood exposure incidents and infections among dental staff". The questionnaire is standardized, translated into many languages, including ours, and it is used in numerous studies in the region of the South East Europe. (2, 7 9, 11) The questionnaire was distributed to participants through authorized executives of dental departments who controlled the survey together with the researcher. Before accessing the survey, the approval from the Ethic Committee of Dental Chamber of the Federation of Bosnia and Herzegovina had been requested. The questions from the questionnaire include general, demographic data, as well as the question whether and how many times participants experienced exposure incidents in the previous year, meaning 2014, (an annual rate) and during their whole life, questions about pre-exposure prophylaxis (the vaccination status against HBV, characteristics of the determination of the protective antibody titre against hepatitis B, titre anti-HBs), conditions (risks) under which exposure incidents occur, questions about reporting incidents (to whom, and if they do not report them, what is the reason). Responses are designed according to a Likert scale.

An exposure incident (a percutaneous contact or injury) is defined as a contact with blood, other body fluids or tissues of an infected person which is manifested through punctures with sharp objects (endodontic instruments, hollow needles, injection needles, dental probes, levers, pincers, scalpels, scissors, drills and other sharp objects).

The information gathered is shown in graphs and tables. Also, the normal distribution analysis was used (Smirnov-Kolmogorov test). In accordance with the obtained results, the further statistical analysis was carried out using parametric tests. Multiple analyses of variance (ANOVA) were used in the analysis of the differences in the average annual number of blood exposure in groups of healthcare workers. The differences in qualitative data were analysed using nonparametric Mann-Whitney test. The values $p < 0.05$ are a significant difference. During the statistical analysis, the computer programs Microsoft Office Excel 2003 (Microsoft), Med Calc v.10.2 (MedCalcSoftWare) and the Statistical Package SPSS v.17.01 (Chicago Inc.) were used.

Results

The relationship between exposure incidents and their reports and prophylaxis is easily noticeable from the presented figures. The prevalence of exposure incidents is 78% (288 of the total of 369 participants). 280 out of 288 participants experienced exposure incidents which have characteristics of needle stick and sharps injuries during the

whole exposure period (of work time) (97%: 86% experienced exposure incidents more than once, 11% experienced it once) (figure 1).

216 (75%) of the total of 369 participants have never reported an exposure incident, 61 (21%) sometimes reported it, and 11 (4%) participants said that they reported an exposure incident every time it occurred (figure 2). The relationship between the rate of the prevalence of exposure incidents and the reports of the same depicts the flippancy and irresponsibility of dental workers to themselves and to their patients. Even though the problem is not noticeable, it is very serious- due to not reporting it, the rate of the prevalence of exposure incidents has been reduced by 19.5 times (78%:4%; figure 1 and 2).

The reasons for not reporting exposure incidents are shown in Figure 3. Dental workers most frequently do not report exposure incidents (n=269) because: the patient did not seem risky (24%), they were unaware of the infection risk (21%), they did not know that there is a protocol to report incidents (18%), they did not know to whom to report them (13%), they did not know that they need to report an incident (8%), 6% of participants were not familiar with the safety procedure and 10% due to other reasons.

Only 96 out of 369 (26%) participants have properly implemented pre-exposure protection by prophylaxis and received 3 doses of vaccine against HBV and checked protective antibody titre (titre HBS). The rate of the prevalence of participants that have received 3 doses and have not checked the determination of the protective antibody titre is 20%. 159 (41%) participants were not vaccinated. The results shown in Table 1 reveal that there are statistically significant differences between the quality group of the vaccination status and exposure incidents (P=0.006). In fact, the rate of those facing exposure incidents and the risk of HBV infection (unprotected dental workers) who have not implemented pre-exposure prophylaxis is high: 82% participants who have received 3 doses of vaccine and have not checked HBs antibody titre, 89% participants who have received less than 3 doses of vaccine, and 79% of those who have not been vaccinated at all (Table 1). There is not a statistically significant correlation between the vaccination status and exposure incidents in the case of our patients (Spearman's factor of correlation= 0.061, P=0.246). These are two dependant variables, and if there is not adequate prophylaxis against HBV, the factor of correlation is certainly statistically significant. We are speaking about bad or non-existent prophylaxis.

217 (59%) out of 369 dental employees have never tested their blood nor have they determined HBs antibody titre. They do not even know their infection status, so our epidemiological information about HBV infections is irrelevant. Only 27 (7%) out of 369 have adequately taken blood tests after three doses of vaccine. The results presented in Table 2 show that there are no statistically significant differences between groups that determined HBs antibody titre and exposure incidents (P=0.127). However, there is a statistically significant correlation blood test for protective antibody and exposure incidents in the case of our participants (Spearman's factor of correlation= -0.118, P=0.030).

Discussion

Hepatitis B virus (HBV) is one of the most common infections in the world. According to the information from the World Health Organization (WHO), one third of the world population is infected with HBV, and approximately 5% have chronic infection (12). Around 80% of chronic HBV infections cause liver cirrhosis and development of primary hepatocellular cancer (13). HBV poses the main professional risk to healthcare workers. In developing parts of the world 40%-65% HBV infections among healthcare workers occur due to percutaneous exposure to the virus. In developing countries, the ratio of HBV among healthcare workers is less than 10%, mostly due to pre-exposure vaccination and post-exposure protection (14). The risk factors for the occurrence of HBV are primarily connected to the frequency of blood contacts in the workplace, and also to the number of contacts with the persons who are HBeAg positive (11, 13, 15-19).

Quite concerning is the fact that only 4% of dental workers report an exposure incident and that there are 19.5 times less reports compared to the real rate of prevalence of injuries caused by needle sticks, sharp objects and instruments in stomatol-

ogy. 59% of dental workers have never been tested for hepatitis markers and the determination of HBs antibody titre. Only 26% have been properly vaccinated against HBV in pre-exposure prophylaxis. The majority (24%) do not report exposure incidents because their patients do not seem risky or because 21% of them are unaware of the risk of HBV infection. The research has shown that there is not a statistically significant relationship between the vaccination status and exposure incidents in the case of our participants (Spearman's factor of correlation P= 0.061, P=0.246).

The results of our research show the need for education in the field of KPI prevention among dental staff. Of significant importance is vaccination of dental workers and the rest of the staff working in dental departments against HBV. It is also important to monitor immunity after vaccination. Furthermore, by continuous education it is necessary to raise awareness about the danger of KPI and the necessity to regularly report all exposure incidents with the aim of self-protection and protection of patients against infection. Health is the primary driving force for the development of life, and at the same time our most valuable gift which we need to protect unconditionally. Bad life decisions, carelessness or accidental puncture and the transfer of blood-borne infections must not serve as a stigma in the society, because every individual might experience the same situation. Education and familiarity of citizens about the prevention, protection and treatment of the viral disease that is already present are of the extreme importance not only for the health of an infected person, but also for the health of healthcare workers. It can be concluded that there should not be a health problem which would make us feel ashamed or which we have to hide in order to protect ourselves from the intolerance of individuals. Let's be ambassadors of our own health and let's protect healthcare workers because they serve our health every day and always!

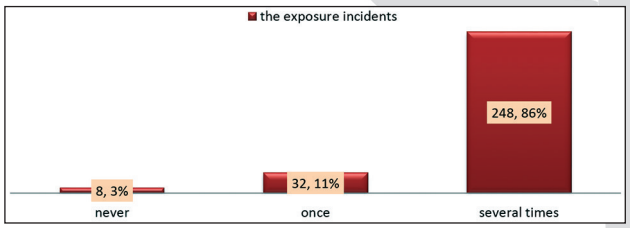
The researches of other authors in the health sector reveal three main reasons for not reporting the exposure: they did not know the procedure of reporting, some of them believed that the exposure was not risky, and some of them thought that it was not important to report an incident (2,7,11). As reasons for not reporting an incident the following have been included: the lack of time (overwork), the lack of staff, the low level of education, the underestimation of the infection risk, unfamiliarity with the procedure of reporting exposure incidents, not knowing to whom to report and how to report. Some believe that the procedure is too complicated (19-20).

Pre-exposure prophylaxis measures are activities which are implemented before a possible exposure incident and potential dangers of an exposure incident among groups at risk (12). Those measures also include standard protection measures such as protective means (gloves, coats, glasses, masks) and activities for protection (hand washing, adequate infectious waste disposal). Technical protection measures are also important: needle sticks that have protection mechanism, waterproof containers for infective waste. As a specific measure for protection, infection prophylaxis with HBV vaccine has the most significant importance (21-22). WHO suggested implementing HBV vaccine in the national calendar of vaccination (12). In order to enhance efficiency and expediency of vaccine, healthcare workers should get vaccinated as soon as possible in their career. It is even recommended to get vaccinated while studying at medical school (12). If vaccination and pre-exposure protection were implemented, then post-exposure prophylaxis of HBV infection would rarely be necessary (12, 23, and 24). Post-exposure preventive measures are applied after exposure and they include the evaluation of exposure risk, and, if necessary, the implementation of post-exposure prophylaxis (PEP) (9, 10, 12).

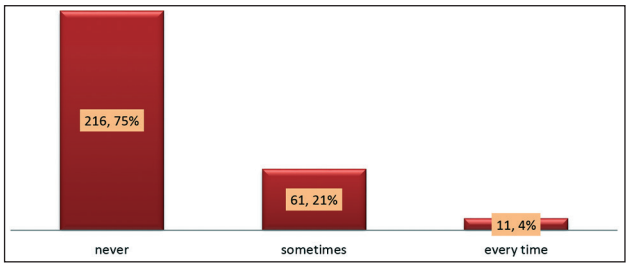
In order for an employee to get an adequate post-exposure protection, it is important to report every exposure incident, and the evaluation of exposure incidents and results should be implemented by well-educated healthcare workers (2, 7, 11, 12, 24). The overall post-exposure procedure and its efficiency depend on the confirmation and exclusion of infection found in the source patient. For that reason, it is important to promptly implement the clinical and epidemic evaluation of the infection risk, and the serological testing of the source patient and the exposed healthcare workers (2, 7). Post-exposure prophylaxis of HBV infection involves implementing combined active-passive prophylaxis that consists of HVB vaccination and the implementation of specific hepatitis B immunoglobulin.

Conclusion

There is an urgent demand for educating dental staff about effects of blood exposure incidents, especially about those related to needle stick and sharps injuries in the field of dentistry, and also basics of pre- and post-exposure prophylaxis in the Federation of Bosnia and Herzegovina. The advantages of hepatitis B vaccination including availability and effectiveness, characteristics of the vaccination status but adequate procedure of vaccination need to be stressed. It is important to introduce them with safety procedures and regulations in this field, as well as with the importance of monitoring HBs antibody titre. With strategic approach and regulations, there has been a reduction in injuries and sharps incidents in the case of 3, 5 millions of healthcare workers in the EU (24).

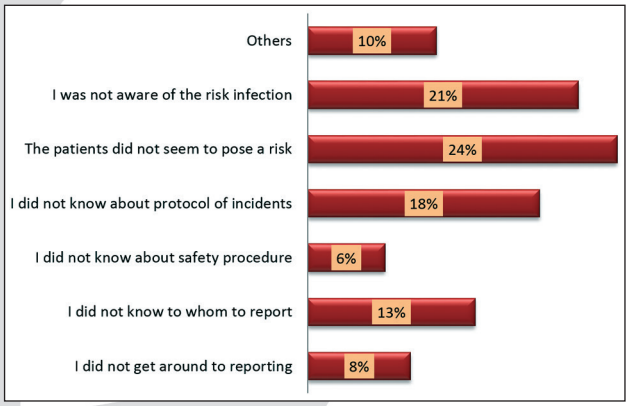


Picture 1. Prevalence rate of exposure incidents during the career (n=288)



Picture 2. Prevalence rate of report of exposure incidents

Only 11 (24) of the total of 288 who experienced exposure incidents have reported them by procedure and protocol.



Picture 3. Prevalence rate of the reasons why dental staff do not report exposure incidents

Table 1. Relationship between vaccination HBV status and exposure incidents among all participants (n=369)

Vaccination status	Exposure incidents No (%)		P
	No exposure	Yes exposure	
All 3 doses, protection confirmed	30 (31)	66 (69)	$\chi 2=14.288$ P=0.006
All 3 doses , blood test not performed	13 (18)	59 (82)	
Less than 3 doses of vaccine	4 (11)	32 (89)	
Have not been vaccinated	34 (21)	125 (79)	

Spearman's factor of correlation= 0.061; P=0.246

Table 2. Relationship between protective antibody titer (HBS- titer) and exposure incidents among all participants (n=369)

HBS- titer (blood test)	Exposure incidents		P
	No exposure	Yes exposure	
Never	41	176	$\chi^{٥,٧١٢=٢}$ P=0.127
Once immediately after vaccination	7	20	
Once, >3 months vaccination	12	23	
More times in career	17	43	

Spearman's factor of correlation= -0.118; P=0.030

References

1. *Makary MA, Al-Attar A, Holzmueller CG, Sexton JB, Syin D, Gilson MM, Sulkowski MS, Pronovost PJ. Needlestick injuries among surgeons in training. New Engl J Med 2007; 356: 2693-9.*

2. *Bećirević S, Pranjić N, Sarajlić-Spahić S, Ahmetagić S, Huseinagić S. Assessment of Reporting, Attitudes and Knowledge About the Stab Incidents and Professional Risk of Viral Infection among Health Care Professionals in Primary Health Care. Mat SocMed Jun, 2013; 25(2): 113-117.*

3. *Gessessew A, Kahsu A. Occupational exposure of health workers to blood and body fluids in six hospitals of Tigray region (August 1-30, 2006): magnitude and management. Ethiop Med J 2009; 47: 213-9.*

4. *Gupta N, Tak J. Needlestick injuries in dentistry. Kathmandu Univ Med J 2011; 35(3): 208-12.*

5. *Martins A, Santos N, Lima M, Pereira R, Ferreira R. Needlestic and sharp instrument injuries among dentists in Montes Claros, Brasil. Arquivos em Odontologia. 2010; 46(3): 127-35.*

6. *Smith AJ, Cameron SO, Bagg J, Kennedy D. Management of needlestick injuries in general dental practice. British Dental Journal. Vol. 190: 645-650.*

7. *Pranjić N, Stojić V, Ahmetagić S. Profesionalno povređivanje oštrim predmetom i prenos krvlju prenosivih infekcija u bolničkih zdravstvenih radnika: puno pitanja i malo odgovora. Knjiga sažetaka – ICTIP, Zenica; 2012; septembar 87.*

8. *Anonymous. Law on Health Care in FB&H (Zakon o zdravstvenoj zaštiti FBiH). Official Gazette of 22 June, 2010. No46/10.*

9. *Cvejanov- Kezunović LJ, Mustajbegović J, Milošević M, Čivljak R. Occupational Exposure to Blood Among Hospital Workers in Montenegro. Arh Hig Rada Toksikol. 2014; 65: 273-80.*

10. *Nelson KE, Williams CM, Graham NMH. (2001) Infectious disease epidemiology. Gaithersburg: Aspen Publishers.*

11. *Čivljak R, Begovac J. Profesionalna ekspozicija zdravstvenih djelatnika infekcijama koje se prenose krvlju. Infektološki glasnik. 2003; 23: 183-8.*

12. *Anonymous (2002) WHO/CDS/CSR/LYO/2002.2: Hepatitis B. World Health Organization. URL:http://www.who.int/csr/disease/hepatitis/whocdscsr-lyo20022/en.*

13. *Yun-Fan L, Chia-Ming C. Hepatit virosa B infection. Lancet. 2009; 373(9663): 582-592.*

14. *Singhal V, Bora D, Singh S. Prevalence of Hepatitis B Virus Infection in Healthcare Workers of a Tertiary Care Centre in India and Their Vaccination Status. Journal of Vaccine & Vaccination, 2011; doi:10.4172/2157-7560.1000118.*

15. *Anonymous (1998) Recommendations for Prevention and Control of Hepatitis C virus (HCV) Infectious and HCV – Related Chronic Disease. CDC, MMWR 47/NO RR-19.*

16. *Anonymous (2002) WHO/CDS/CSR/LYO/2002.2: Hepatitis B. World Health Organization. URL:http://www.who.int/csr/disease/hepatitis/whocdscsr-lyo20022/en*

17. *Jagger J, Dc Carli G, Perry J, Puro V, Ippolito G (2003) Occupational exposure to blood borne pathogenes: epidemiology and prevention. U: Wenzel RP, ur. Prevention and control of nosocomial infections. 4. izd. New York: Lippincott, Williams & Wilkins.*

18. *Gerberding JL. Management of occupational exposures to blood-borne viruses. N Engl J Med. 1995; 332(7): 444-51.*

19. *Čivljak R, Begovac J. Profesionalna ekspozicija zdravstvenih djelatnika infekcijama koje se prenose krvlju. Infektološki glasnik. 2003; 23: 183-8.*

20. *Voide C, Darling KEA, Kenfak-Foguena A, Erard V, Cavassini M, Lazor-Blanchet C. Underreporting of needlestick and sharps injuries among healthcare workers in a Swiss University Hospital. Swiss Med Wkly; 142: w13523 stick injuries in the National Health Service: a culture of silence. J R Soc Med.; 2012; 97(7): 326-7.*

21. *Tetali S, Choudhury PL. Occupational exposure to sharps and splash: Risk among health care providers in three tertiary care hospitals in South India. Indian J Occup Environ Med. 2006; 10: 35-40.*

22. *Krišto D, Bogadi-Šare A, Knežević B. Zbornik radova 4. međunarodnog stručno-znanstvenog skupa Zaštita na radu i zaštita zdravlja / Vučinić, Jovan; Kirin, Snježana (ur.). - Karlovac: Veleučilište u Karlovcu, 2012.*

23. *Rapiti E, Pruss-Ustun A, Hutin Y. Sharps injuries: assessing the burden of disease from sharps injuries to health-care workers at national and local levels. Geneva, WHO (WHO Environmental burden of disease series, No.11) 2005.*

24. *Čivljak R, Begovac J, Puro V, Cicalini S, De Carli G. Ipoolito G. Europske preporuke za postekspozicijsku profilaksu HIV-infekcije u zdravstvenih djelatnika - Hrvatske smjernice. Infektološki glasnik. 2004; 24(3): 139-144.*

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Stressors' and Coping Strategies among Saudi Nursing Students' in their Clinical Practice Environment

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Abstract

Background: Stress among nursing undergraduate students has been extensively investigated by several researchers. According to the literature, many studies reported that, nursing students are facing stress when exposed to the clinical setting environment. Clinical practice placements' in all nursing specialties is considered stressful experience among nursing undergraduates students.

Objective: To identify the sources and types of stressors among undergraduate nursing students. Also to identify the coping strategies employed by nursing students'.

Methods: This is a Descriptive design study by means of validated questionnaires. The data collection took place in November and December 2015. Data collection was conducted at Princess Nourah Bint Abdulrahman University (PNU), the college of nursing in Riyadh, Saudi Arabia. PNU is the largest University campus in the world and is inclusive to females' students only. All participants' were in their final year 4th year.

Results: The most perceived stressors' among nursing students were from the assignments and workloads followed by stress from teachers and nursing staff and the clinical environment. Interestingly, the least three stressors' were related to peers and daily life, lack of professional knowledge and skills and taking care of patients. The most employed coping approach among nursing students during their clinical training setting was the stay optimistic approach followed by problem solving. The least coping approach was avoidance strategy of coping.

Conclusion: Stress is common among nursing undergraduates' students during their visit to clinical settings. As a result, it affects the quality of students' learning experience. Nursing students suffers high levels of stress during their studies. Stressors for undergraduate nurses' included; assignments, long hours of studying and pressure from teachers and nursing staff. Interestingly, nursing students' mostly apply the optimistic coping approach to deal with stress.

Key words: clinical practice, clinical placement, coping, nursing student, stress, Saudi Arabia

1. Introduction

The issue with undergraduate nursing student having stress in their clinical settings environment is an ancient dilemma (1).There are many definitions of stress and the most related definition to this research study was done by Furnham in 2005, were he described stress as a reaction to a situation which might have either positive or negative influence on human being (2) . For example, in nursing students, a positive stress which is also referred to eustress (3) can be done through providing support, guidance and empathy for nursing students in their clinical placements which will result in high achievement and positive coping mechanism (3, 4). While a negative stress, or sometimes referred to as "distress" (3), can be observed in many areas. For example; fear of failure, not coping with the clinical setting or even a complete drop out of the nursing program (4-8). Distress among nursing students is the most discussed factor of stressors in the literature and is the focus of this research study.

A recent systematic review (5) reported that there are many types of stressors which affect undergraduate nursing students during their exposure to hospitals. The authors critically reviewed thirteen papers related to nursing undergraduate stressor through searching four data bases namely; CINAHL, PubMed, PsycINFO and Medline. The searches took place between 2002 and 2013 (5). The researchers' summarise their results by cate-

gorising undergraduate nursing stressors' into four themes, which are; "initial clinical experience, comparison between different academic years, cross-cultural comparison, and eustress aspects of clinical experience" (5). Finally the systematic review highlights the need for more research to be done in this field and suggested that clinical placement should provide specialized workshops for nursing students on clinical practice guideline adherence and to provide nursing students with support and motivation (5). Moreover, Ismaile in 2015, stressed on the importance of the academic nursing faculty in preparing their students with the needed knowledge, skills and implementing new technologies in teaching and learning to adapt with the demanding clinical setting needs (5). The issue of the importance of guideline adherence in the clinical setting among nursing students and the gap between what is taught in the class and what students' actually deal with in the clinical setting is perceived as an important stressor facing students during their clinical practice placements (5).

Stress among medical and allied health undergraduate students' has been extensively investigated by several researchers (9-11). According to the literature; stress is not only common in nursing undergraduates but also in all medical and allied health undergraduates (9-11). Many studies reported that, medical students and allied health undergraduates including nursing are facing stress when exposed to the clinical setting environment (1, 7). A recent study, found that the first exposure to clinical practice in nursing undergraduates is considered as a highly-stressful experience (9). Moreover, there are many studies discussing undergraduate nursing experience at their first visit to hospitals in the Middle East (7, 9, 12) and internationally (1, 13, 14). Clinical practice placements' is an essential element in nursing education and can be a stressful experience for nursing students (15).

There was only one research study done in Australia which explored Saudi postgraduate nursing students experience in studying Master degree in Australia. There were no studies done in Saudi Arabia searching stressors' facing medical and allied health students and more specifically for undergraduate nursing students' experience. Therefore, this research study is unique and is an important field to research.

1.1 Research Problem

The issue of stress is common in all medical, nursing and allied health undergraduates (12-14). Nursing undergraduates' students are facing stress when exposing to clinical setting hospitals. Clinical practice placements' in all nursing specialties is considered stressful experience among nursing undergraduates students (6, 12-14).

1.2 Research Aim

The aim of this research study is to identify the sources and types of stressors among undergraduate nursing students. Also to identify the coping strategies employed by nursing students'.

1.3 Research Objectives

The research objective of this study is to

1. Identify stressors during clinical experience among undergraduate nursing students.
2. Identify sources of stressors among nursing undergraduates students
3. Identify the most common type of stressors, and categorise stressors to following themes;
   - Teachers and nursing staff
   - Assignments and workloads
   - Peers and daily life
   - Lack of professional knowledge and skills
   - Clinical environment
4. Identify the copying strategies employed by nursing students'.

2. Methodology

2.1 Design

This is a Descriptive design study by means of questionnaires. The data collection took place in November and December 2015.

2.2 Setting

All data collection was conducted at Princess Nourah Bint Abdulrahman University (PNU), the college of nursing in Riyadh, Saudi Arabia. PNU is the largest University campus in the world and is inclusive to females' students only (16). A pur-

posive sampling (17) was used to recruit students. All participants' were in their final year 4th year.

2.3 Participants

The sample of this research study was undergraduate females Saudi nursing students who were studying at PNU and in their final year. The eligibility inclusion criteria were Saudi female nursing students who: (1) were in their final year and in the 7th level of the 2015–2016 academic year; (2) Speaks Arabic (Saudi Arabia mother tong language); and (3) consented to take part in the study. In the other hand, the research exclusion criteria were students other than the final year in nursing and not in their 7th level.

A purposive sampling technique was used to recruit students(17). All cohort of nursing students n=55 participants' in their final year 4th year were invited to take part in the study. A purposive sampling technique indicates that the researcher attempts to obtain sample that appears to her to be representative of the population and ensures that a range from one extreme to the other is included (17). The researcher allocated students lectures and permission was obtained from the teachers for data collection to take place in the classroom setting. All students agreed to participate in this research. The response rate was largely positive (90%). Attrition was not found in this study, given that all 55 students were attending their classes at the second data-collection time and filling the questionnaires.

3. Measure

3.1 Demographic data

The validated and modified questionnaire tool was customized to match the research aims and objectives and more specifically for the female Saudi nursing undergraduates' students. Approval to use the tool was confirmed by the original authors (9).

Demographic data section was included in the questionnaire with the following information; students ID, age, marital status, and clinical hours. The questionnaire is designed with 5 Likert scale options. The language of the questionnaire was in Arabic language which is much understood among Saudi nursing students as it is their mother tong language. Data was collected from undergraduate nursing students who are currently enrolled in the nursing college at PNU and after gaining ethical approval from the research ethics committee at the nursing collage.

3.2 Perceived stress scale

The perceived stress scale was previously created by (18). This scale was generated to measure the perceived stress among nursing students in clinical practice environment (18).The questionnaire was designed to measure six main themes related to stress degrees and types with 29 questions Table 1.

3.3 Coping behaviour inventory questionnaire

The coping behaviour inventory questionnaire is a validated tool by (9, 18, 19). The tool consisted of 19 questions on coping strategies' in relation to stress from the clinical setting. Table 2 summarises' the questionnaire groups and number of questions for each group as taken for the original work of (9).

3.4 Ethical considerations

Ethical approval was sought out from the college of nursing research ethics committee IRB at PNU prior to conducting this research. All participants were reassured of their right of maintaining confidentiality of identity and the voluntary nature

Table 1. Number of questions and precived stress scale thems (Sheu et al. (1997).

Perceived stress scale theme	Number of questionnaire questions
Patient care	8
Teachers and nursing staff	6
Assignments and workloads	5
Peers and daily life	4
Lack of professional knowledge and skills	3
Clinical environment	3

of taking part in this research. An information sheet and a description, explanation and answering of participant questions all took place prior to signing the consent form. Each participant was given an identification code and data was kept strictly confidential. No names or personal demographics were included. Participants were informed that results will be published anonymously. The researcher informed all nursing students to discontinue filling the questionnaires at any time if psychological stress became too intense, or if there are any other problems while feeling the questionnaire. In cases where students' shows signs of stress in filling the questionnaires, students were advised to discontinue filling the questionnaire and support were given. No reported cases noticed.

3.5 Data-collection method

The researcher had the timetable of the year 4 students' lectures location. Data collection took place between November and December 2015. All data collection took place in students' class rooms after completing their lectures. The researchers distributed information sheet and consent form to all students. The researcher then explained the research aim, objectives and method. All students in year 4 cohort n=55 nursing undergraduate students were included using purposive sampling technique (17).

3.6 Data Analysis

Descriptive statistics package (SPSS version 16.0; SPSS, Chicago, IL, USA) was used for the data analysis. To satisfy the study aims, it will also describe the study sample and to answer research question. The descriptive statistics use is mean, median, standard deviation, range, frequency, and percentage.

4. Results

4.1 Demographic data

Demographic data of the participants' is shown in Table 3.

According to Table 3, all participants' who took part in this study were females as PNU is an exclusive only University for females. The mean age of the students was 22.436 years and 0.938 standard deviation (SD). The majority of the participants were single 89.1% and 10.9% were married. There were no students working full time and only 7.3% had part time jobs. The majority of students were unemployed with 92.8%.

4.2 Degrees of perceived stress and types of stressors among nursing students'

As shown in Table 4, assignments and workloads were the most perceived stressor among nursing students' (mean = 2.41, SD = 1.108) followed by stressors' from the teachers and nursing staff (mean = 2.17, SD = 1.054). Stressors related to the clinical environment (mean=1.98, SD=1.082) and from the peers and daily life (mean= 1.96, SD=1.153) were ranked 3rd and 4th subsequently. Interestingly, the least stressor perceived by nursing students were stressors' which were related to the lack of professional knowledge and skills (mean= 1.70, SD=0.979) and taking care of patients (mean=1.59, SD=0.909).

4.3 Coping approaches employed by nursing students

As shown in Table 5, The most employed coping approach among nursing undergraduate students' during their clinical training setting was to stay

Table 2. Coping behaviour inventory questionnaire groups and number of questions (AlZayyat and Al-Gamal 2014)

Coping behaviour inventory groups	Number of questions
Avoidance behaviours; efforts to avoid the stressful situation	6 questions
Problem-solving behaviours; efforts to manage or change the stress arising from a stressful situation	6 questions
Optimistic coping behaviours; efforts to keep a positive attitude towards the stressful situation	4 questions
Transference behaviours; efforts to transfer one's attention from the stressful situation to other things	3 questions

Table 3. Demographic data for nursing undergraduate students

Variable	Frequency (%)	Mean	Median	Minimum	Maximum	SD
Age	55	22.43	22.00	21	25	0.938
Academic cumulative score	53	3.92	4.00	3	5	0.549
Academic credit hours	53	17.19	17	12	21	1.144
Marital status • Single • Married • Divorce	55 49(89.1%) 6 (10.9%) 0	0.11	.00	0	1	0.315
Employment status • Full time • Part time • Unemployed	55 0 (5.5%) 4 (7.3%) 51 (92.8)					
Interest in studying nursing • Yes • No	55 53 (96.4%) 2 (3.6%)	0.96	1	0	1	0.189

Table 4. Perceived stress among nursing students' at their clinical placements (n = 55)

Subscale	Ranking	Mean	SD
Taking care of patients	6	1.59	0.909
Teachers and nursing staff	2	2.17	1.054
Assignments and workloads	1	2.41	1.108
Peers and daily life	4	1.96	1.153
Lack of professional knowledge and skills	5	1.70	0.979
Clinical environment	3	1.98	1.082

Table 5. Coping approaches employed by nursing students' during clinical placements (n = 55)

Subscale	Ranking	Mean	SD
Problem solving	2	2.54	1.045
Avoidance	4	1.94	1.319
Stay optimistic	1	2.69	1.199
Transference	3	2.28	1.156

optimistic approach (mean = 2.69, SD = 1.199), followed by problem solving (mean = 2.54, SD = 1.045). The third ranked coping approach was the transference strategy (mean = 2.28, SD = 1.156). Interestingly, avoidance strategy was the least coping approach employed by the nursing undergraduates' students (mean=1.94, SD=1.319).

5. Discussion

5.1 Sources and types of stressors among undergraduate nursing students

The most perceived stressors' among nursing students were from the assignments and workloads followed by stress from teachers and nursing staff and the clinical environment. Interestingly, the least three stressors' were pears and daily life, lack of professional knowledge and skills and taking care of patients. Stress form teachers and nursing staff and workloads' were also reported by (9, 20-22), as the main stressors' for nursing students. Interestingly none of the published studies reported that the stress from assignments and workloads are the most influential stressor among nursing students'.

Nursing undergraduate students' suffer higher levels of stress during their college years than other college students in other disciplines (9, 14). The environmental clinical setting is one of the influential stressor for nursing students. The clinical environment setting was reported as the least stressor

factor by (9). In this research, environment clinical setting is ranked as the top three stressors' among nursing students'. An explanation of this can be due to the lack of orientation programs to the clinical setting environments (4). Moreover, environmental factors can be related to the organisational factors included the number of staff on duty, work pressure, resources, senior and peer support, clinical guidelines reminder system, communication and teamwork (4). More precisely, environmental factors can be also related to equipment, lack of orientation programs and resources (4). Another influential stressor on nursing students was pressure from homework and assignments. Stress from assignments and workloads was identified as the most influential factor in (9) and also by (10, 22). Nursing students in this study reported that the required workload from them is causing them emotional stress. The workload on the student included examinations, portfolios, research projects and assessments' throughout the period of clinical placements.

The results of this research have vital implications for clinical tutors and nursing program directors. Clinical teaching should be aligned with the knowledge and skills taught in classes in order to provide the best evidence-based guidelines on patient quality of care and safety (4). In reality, nurses are expected to be flexible in their work environment and therefore they are usually asked to work in different clinical settings (4). Nursing students', have to be prepared, to have all the necessary knowledge, skills and support in order to adapt to the demanding clinical settings. Furthermore, it is the responsibility of the clinical tutors and teaching staff in nursing faculties to ensure the continuity of emotional, professional and academic support and advice to their nursing students throughout their clinical setting placements (4). There are variations of specialised workshops which target these issues in the hope of minimizing stress among students. These can be in many forms such as live role playing, expert professional talk, clinical visits, orientation programs and simulated videos' (23).

5.2 Coping approaches employed by nursing students

According to the findings' of this research study, the most employed coping approach among nursing students during their clinical training setting was the stay optimistic approach followed by problem solving. According to Alzayyat and Algmala in 2014 and Chen and Hung in 2014 (9, 20), problem solving was the most employed coping strategy for nursing students unlike the nursing students at our study.

In this research study, avoidance approach was the least influential factor for coping with stress in nursing students. This result, contradicts with (10, 19, 24) research results were they reported avoidance as the most common strategy for coping among their students.

In the light of these results, it is important to note that the differences in the results among researches can be due to many reasons such as the differences on the methodology used, participant's demographics and the nursing program. Interestingly, most of our nursing students employ an optimistic approach and having a powerful positive thinking to deal with stress in their clinical setting. Fallowing an optimistic approach to deal with stress with positive thoughts in mind will help students' to look forward in their future with the belief that good things will happen and they are responsible for that by their actions.

6. Conclusion

Stress is common among nursing undergraduates' students during their visit to clinical settings. As a result, it affects the quality of students' learning experience. Nursing students suffers high levels of stress during their studies. Stressors for undergraduate nurses' included; assignments, long hours of studying and pressure from teachers and nursing staff. Nursing students' mostly used optimistic coping approach to deal with stress. Avoidance approach was the least strategy used to cope with stress among nursing students. It is recommended that the nursing academic faculties to; review nursing program requirements', provide nursing student with proper clinical knowledge and skills, update clinical practice guidelines in

accordance to the latest evidence-based research, train clinical professional tutors in the hope that this might assist students to reduce stressors in the clinical setting.

Moreover, it is suggested to undertake this study again through a follow-up cross sectional study with nursing students' in next term and also in their 5th year internship placements. Adding a qualitative research arm with one to one interviews' and focus groups will enhance this research study.

References

1. *Pagana K. The Relationship of Hardiness and Social Support to Student Appraisal of Stress in an Initial Clinical Nursing Situation. Journal of Nursing Education. 1990; 6(29): 255-61.*

2. *Furnham A. The Psychology of Behaviour at Work: The Individual in the Organization. Psychology Press. 2005; Hove.*

3. *Gibbons C. Measuring Stress and Eustress in Nursing Students. Unpublished Doctoral Dissertation, UK: Queen's University Belfast; 2008.*

4. *Ismaile S. Nursing studies: factors promoting and inhibiting adherence to clinical practice guidelines among the nursing profession. Unpublished Doctoral thsis, Durham, UK: Durham University; 2015.*

5. *Al-Zayyat A, E EA-G. A review of the literature regarding stress among nursing students during their clinical education. International Nursing Review. 2014 (61): 406-15.*

6. *Chen Y, Hung C. Predictors of Taiwanese baccalaureate nursing students' physio-psycho-social responses during clinical practicum. Nurse Education Today. 2013; 34(1): 73-7.*

7. *L N, Plummer V. Indonesian student nurses' perceptions of stress in clinical learning: a phenomenological study. Nursing Education and Practice. 2013; 3(5): 56-65.*

8. *Ü Karabacak et al. First day in clinical practice: evaluating stress of nursing students and their ways to cope with it. HealthMED. 2012; 6(2): 596- 602.*

9. *Al-Zayyat A, Al-Gamal E. Perceived stress and coping strategies among Jordanian nursing students during clinical practice in psychiatric/mental health courses. International Journal of Mental Health Nursing. 2014; 23: 325-36.*

10. *Shaban I, Akhu-Zaheya L. Undergraduate nursing students' stress sources and coping behaviors during their initial period of clinical training, A Jordanian perspective. Nurse education in practice. 2012; 12: 204-9.*

11. *McKenna L, Plummer V. Indonesian student nurses' perceptions of stress in clinical learning: A phenomenological study. Journal of Nursing Education and Practice. 2013; 3(5): 56-65.*

12. *Hamaideh S. Gender differences in stressors and reactions to stressors among Jordanian university students. International Journal of Social Psychiatry. 2012; 58(1): 26-33.*

13. *Chou P, Chao Y, Yang H, L Yeh, T L. Relationships between stress, coping and depressive symptoms among overseas university preparatory Chinese students: A cross-sectional study. BMC Public Health. 2011; 11(4): 352-8.*

14. *Pillay A, Ngcobo H. Sources of stress and support among rural-based first-year university students: An exploratory study. South African Journal of Psychology. 2010; 40(3): 234-40.*

15. *Chan C, Fong D. Hong Kong baccalaureate nursing students' stress and their coping strategies in clinical practice. Journal of Professional Nursing. 2009; 25(5): 307-13.*

16. *(PNU) PNBAU. Riyadh, audi Arabia: PNU; 2015 [24/12/2015]. Available from: www.pnu.edu.sa.*

17. *Knafl KA, Patton MQ. Qualitative evaluation and research methods (2nd ed.). Newbury Park, CA: Sage, 532 pp., $28.00 (hardcover). Research in Nursing & Health. 1991; 14(1): 73-4.*

18. *Sheu S, Lin H, S H, Y H, Lou H. The development and testing of perceived stress scale of clinical practice. Nursing Research. 1997; 5(4): 341-51.*

19. *Sheu S, Lin H, Hwang S. Perceived stress and physio-psycho-social status of nursing students during their initial period of clinical practice: The effect of coping behaviors. International Journal of Nursing Studies. 2002; 39(2): 165-75.*

20. *Chen Y, Hung C. Predictors of Taiwanese baccalaureate nursing students' physio-psycho-social responses during clinical practicum. Nurse Education Today. 2014; 43(1): 73-7.*

21. *Lou JH, S Chen, Yang C. The influence of personality traits and social support on male nursing student life stress: A cross-sectional research design. Journal of Nursing Research. 2010; 18(2): 108-16.*

22. *Nolan G, Ryan D. Experience of stress in psychiatric nursing students in Ireland. Nursing Standard. 2008; 22(43): 35-43.*

23. *Penn T. Enhancing student comfort in psychiatric clinical settings. Teaching and Learning in Nursing. (2008); 3(2).*

24. *Tully A. Stress, sources of stress and ways of coping among psychiatric nursing students. Journal of Psychiatric and Mental Health Nursin. 2004; 11(1): 43-7.*

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Faster rate of ethanol elimination from blood in tested drivers with high blood-alcohol concentrations

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Abstract

Determination of blood alcohol concentration at the time of critical event is a continuing challenge in the daily work of the expert witness. The rate of ethanol elimination from blood is important factor when retrograde blood-alcohol calculations in forensic casework are made. Therefore, taking two blood samples in two period of times, about 1h apart, to determine of the rate of alcohol elimination is a forensic doctrine. There are a number of factors affecting the rate of alcohol elimination from blood. High blood-alcohol concentration is also important factor of influence on the rate of alcohol elimination from blood.

The study included 68 male tested persons to whom the blood samples were taken in two period of times, and then alcohol phases and individualy values of the elimination rate were determined.

The rate of blood-alcohol elimination per hour in post-absorptive phase of BAC curve is not the same in all concentration groups, so increasing of values of eliminated alcohol from blood is obvious, although observed groups did not have extreme high concentrations alcohol in blood.

Key words: Alcohol, Blood, Elimination rate, Metabolism

Introduction

The pharmacokinetics of ethanol after oral administration has been studied in details since 1930. Today we know that destiny of alcohol in organism is much more complicated than presented by one-compartment model with pharmacokinetics, in fact elimination of zero level, initially proposed by Widmark [1]. Later on, it has been discovered that majority of parameters pertaining to pharmacokinetics of alcohol (absorption, distribution level and elimination speed) are the reason to individual biological differences [2]. At the beginning of millennium, pharmacokinetics of alcohol was described by three-compartment model with the assumed concentration-dependant absorption and elimination. Determining relevant blood-alcohol concentration (BAC) in times of critical event is the constant challenge in daily work of a court-medicine expert [1]. This is indirectly related to the alcohol elimination speed, whose value determines the relevant blood-alcohol concentration. Elimination of alcohol is done in several ways. Metabolic degradation (biotransformation) eliminates the highest quantity of alcohol (about 90-95%). It is the alcohol oxidation process mainly occurring under the influence of alcohol-dehydrogenase enzymes (ADH). To a smaller extent, metabolic transformation of alcohol is done under the influence of special microsomal system called MEOS – Microsomal Ethanol Oxidizing System, which is considered to be the main cause to variation in alcohol elimination speed. It is usual practice in a routine court-medicine practice to use as elimination measure the expression speed elimination determined by Widmark's beta-elimination factor. The most frequently tested factors of impact to the dynamic of BAC movement are: racial differences, age, gender, body mass and structure, long-term alcohol consumption, physical activity, alcohol consummation speed, liver diseases, glycaemia and insulin values, bleeding, transfusion and infusion therapy, diuretics as well as value of the blood-alcohol concentration. High concentrations of alcohol in blood speed up the alcohol elimination process, which probably pertains to activation of MEOS and increase of concentration gradient at diffusion elimination. This particularly has the effects at severe chronic drunkenness [3].

Material and Methods

68 male examinees were included in the study, whose blood sample was taken in two periods of time. Examinees selection criteria were: that the examinees were in the post-absorptive phase of the BAC curve, that time between blood samples taking was not too short (more than 20 minutes) and that in alcohol elimination prevailed zero level kinetics. Eliminatory phase was determined first. The alcohol phase was determined based on the BAC values movement per time unit. Blood samples were taken in two periods of time. If BAC smpl1> BAC smpl2, and if more than 90 minutes elapsed from the last alcohol consummation, it was concluded that the examinee was not in absorptive phase. Individual value of beta-elimination factor was calculated using the following formula:

$$\beta_{i60} = \frac{(BAC_{smpl1} - BAC_{smpl2}) \cdot 60}{(t_{smpl2} - t_{smpl1})}$$

BAC_{smpl1} – value of alcohol in blood concentration determined in the first time period;
BAC_{smpl2} – value of alcohol in blood concentration determined in the second time period;
$ßi_{60}$ – individual decrease of blood concentration values per hour;
t_{smpl1} – first time period of blood sample taking;
t_{smpl2} – second time period of blood sample taking;

Afterwards, the relation of anthropometric features (weight, height, BMI) and the BAC with the beta-elimination factor values were determined.

The examinees were divided to three groups considering the blood-alcohol concentration value:

- Concentration of alcohol in blood to 1,0g/kg;
- Concentration of alcohol in blood between 1,0g/kg and 2,0g/kg;
- Concentration of alcohol in blood over 2,0g/kg.

All the data used in the study were taken from the secondary sources of information, in fact from court-medicine documentation including:

- Protocols/records of blood sampling to determine the concentration of alcohol in blood of the Biochemistry Institute of the Polyclinic for laboratory diagnostic at the Public Health Institution University Clinical Centre Tuzla,
- Information from the findings and opinions of court-medicine experts taken from the relevant court files.
- Anthropometric and nosologic information taken from medical databases at digital and analogue media of the University Clinical Centre Tuzla, Health Centre Tuzla, Health Centre Gračanica, Health Centre Živinice and Health Centre Lukavac).

Determining concentration of alcohol in blood is done by using the ethyl-alcohol dehydrogenase test method, at Viva E DADE BEHRING SIEMENS analyser, in the laboratory of the Biochemistry Institute at the Polyclinic for laboratory diagnostic of the Public Health Institution University Clinical Centre Tuzla.

For the purpose of statistical data analysis, the software package for statistical data processing SPSS was used (version 12.0 for Windows SPSS, Inc; Chicago, IL).

Results

The tables 1 and 2 show the obtained values of the assessed variables in this study.

The table 2 shows the values of the assessed variables per concentration groups (N = 68).

The biggest mean value of weight is 88.14 in the concentration group 1.0 - 2.0 g/kg, but considering the biggest average height of this group, the BMI mean value (26,80) is very close to the one from the concentration group >2.0 g/kg where it totals 27,35. The mean value of weight of the examinees from the concentration group < 1.0 g/kg although being close to the value of the average height in other groups, leads to the smallest BMI value of 24,60. The biggest mean value of beta-elimination factor of 0,185 g/kg/h was determined at the concentration group > 2.0 g/kg while the smallest value of beta-elimination factor (0,14g/kg/h) was determined at the concentration group < 1.0 g/kg.

All the examinees were adult, and age groups ranged from 18 as the youngest examinee to 66 the oldest examinee, with average age 34,50 years.

In order to determine the correlation between the beta-elimination factor value and the values of anthropometric features and age of examinees, the Spearman ρ (Rho) correlation coefficient was used.

Table 1. Descriptive statistic – assessed variables.

Variable	N	Minimum	Maximum	AS	SD
Decrease of alcoholemy values (g/kg)	68	.09	.26	.1607	.039
Weight (kg)	68	56	130	86.28	15.75
Height (m)	68	1.57	1.96	1.80	.07
Bmi	68	19.40	35.70	26.44	4.02
Age	68	18	66	34.13	12.00

Table 2. Descriptive statistic of concentration groups.

Variable	Groups	N	AS	SD	Minimum	Maximum
Weight(kg)	< 1	15	79.73	12.80	64	102
	1.0 - 2.0	37	88.14	17.13	56	130
	> 2.0	16	88.13	13.97	70	112
Height(m)	< 1	15	1.79	.06	1.70	1.91
	1.0 - 2.0	37	1.80	.08	1.60	1.96
	> 2.0	16	1.79	.08	1.57	1.90
BMI (Body mass index)	< 1	15	24.60	3.21	20.50	30.70
	1.0 - 2.0	37	26.80	4.00	19.40	35.20
	> 2.0	16	27.35	4.43	21.10	35.70
Decrease of alcoholemy values (g/kg/h)	< 1	15	.14	.03	.10	.21
	1.0 - 2.0	37	.15	.03	.09	.22
	> 2.0	16	.18	.04	.12	.26
Age (years)	< 1	15	31.87	12.65	18	66
	1.0 - 2.0	37	33.30	11.15	21	57
	> 2.0	16	38.19	13.10	21	65

The obtained results indicate the strong positive correlation between anthropometric parameters of examinees and values of beta-elimination factor, as follows:

- Strong positive correlation ($\rho = .763$, $p < .00$) was obtained with the body weight
- Medium positive correlation was obtained with the height ($\rho = .481$, $p < .00$),
- Strong positive correlation was obtained with the body mass index ($\rho = .682$, $p < .00$).

Anthropometric parameters have a strong intrusive impact to correlation of BAC and beta-elimination factor values (Table 3). Intrusive factor is the fact that the members of the third concentration group (>2.0 g/kg) had a high mean value of weight (88.13 kg) as well as BMI (27.35). To determine the impact of the blood-alcohol concentration values to the beta-elimination factor value per hour single-factor analysis of covariance was used. Covariance in the analysis of variance was weight and age. During preliminary controls, it was determined that necessary assumptions for use of ANCOV test were not violated. After statistical removal of impact of examinees' weight and age, it was determined that there was statistically important difference between the concentration groups in the values of beta-elimination factor per hour [$F = 10.04$; $p = .00$; η^2 (eta square) = .25]. Also, within this statistical test, particularly strong, statistically important relation was determined between body weight and the value of beta-elimination factor per hour [$p = .00$; η^2 (eta square) = .611], which confirms that the impact of weight is important factor, with variance share of 61%.

No statistically important correlation between age of examinees and value of beta-elimination factor was determined.

In further analysis of multiple comparisons of concentration groups using Bonferroni correction factor, it was determined that the first and the second concentration group were statistically very different from the third one per value of beta-elimination factor per hour, while there were no statistically important differences between the first and the second concentration group (Table 4).

Table 3. Correlation between the beta-elimination factor value at elimination group (N = 68) and the values of their anthropometric features and the age of examinees

Spearman's RHO		Age	Weight	Height	Bmi	Concentration	Beta-elimination factor
Valeus of beta-elimination factor	Correlation Coefficient	.133	.763**	.481**	.682**	.308*	1.000
	Sig. (2-tailed)	.280	.000	.000	.000	.011	.
	N	68	68	68	68	68	68

*Legend: **Statistically important correlation at the level p ≤ 0.01.*
**. Statistically important correlation at the level p ≤ 0.05.*

Table 4. Multiple comparisons of concentration groups in alcohol elimination speed.

	Concentration group < 1 (N = 15)		Concentration group 1.0 - 2.0 (N = 37)		Concentration group > 2.0 (N = 16)	
	AS	SD	AS	SD	AS	SD
Decrease of alcoholemy values	.1453*	.030	.156*	.037	.185	.043

*Legend: *- Statistically important difference in relation to the third concentration group (p ≤ .05)*

Discussion

Determining relevant blood-alcohol concentration in time of critical event is a constant challenge in daily work of court-medicine expert. This is indirectly related to the alcohol elimination speed, whose value is used in formula. In a routine court-medicine practice the blood samples taken in two periods of time are used. To measure elimination, the expression speed elimination determined by Widmark's beta-elimination factor is used. There are numerous factors influencing the alcohol elimination process. The most frequently tested factors of impact to the dynamic of BAC movement, in fact to ß-elimination factor are: racial differences, age, gender, body mass and structure, long-term alcohol consumption, physical activity, alcohol consummation speed, liver diseases, glycaemia and insulin values, bleeding, transfusion and infusion therapy, diuretics as well as level of alcohol concentration. Even in thirties of the last century, Widmark determined undoubtable correlation between the body weight and BAC value by postulating the Widmark's formula. Since then, several studies addressed the issue of impact of body weight and beta-elimination factor value. There is surely a very strong influence of anthropometric parameters and in order to assess other variables, those parameters must be put under control.

Blood-alcohol concentration level has been imposed for a very long period of time as a very important factor of impact to the elimination speed. The impact of this variable was determined by several studies, including the study from 1995 by Brennan DF and associates; Jones AW in the study from 2008.

Impact of anthropometric features was determined in this study with correlation between beta-elimination factor values and the values of anthropometric features. At the same time, the correlation between the age of examinees and the values of beta-elimination factor was determined. The used Spearman ρ (Rho) correlation coefficient indicates the strong positive correlation between anthropometric parameters of the examinees and the value of beta-elimination factor. No statistically important correlation between age of the examinees and the value of beta-elimination factor was determined. It means that in this case as well, the anthropometric parameters have a strong intrusive impact to correlation of the BAC and beta-elimination factor values (Table 3). After statistical removal of impact of examinees' weight and age, it was determined that there was statistically important difference between the concentration groups. Actually, using Bonferron correction factor, it was determined that the first and the second concentration group were statistically very different from the third one in terms of the impact to the value of beta-elimination factor, while there were no statistically important differences between the first and the second concentration group (Table 3).

This indicates very strong impact of high blood-alcohol concentration value to the value of beta-elimination factor, and that these values over 2,0 g/kg significantly increases elimination with average value of beta-elimination factor of 0,185 g/kg. High concentrations of alcohol in blood speed up the alcohol elimination process probably due to activation of MEOS. This particularly has the effects at severe chronic drunkenness. However, the proofs to this are rather scarce. [3]

Conclusion

The speed of ethanol elimination from blood was determined based on the blood sampling in two periods of time. The cases were divided to three concentration groups in order to determine the impact the level of blood-alcohol concentration to elimination speed. In practical sense, this problem deserves a bigger attention during retrograde calculation of alcohol in blood during a critical event. High concentrations of alcohol in blood speed up the alcohol elimination process, which probably pertains to the activation of MEOS and increase of concentration gradient at diffusional elimination. This particularly has the effects at severe chronic drunkenness.

References

1. *Simić M, Tasić M, Stojiljković G, Budakov B, Vuković R. „Cognac alibi" as drunk-driving defense and medico-legal challange. Med Law 2004; 23(2): 367-78.*
2. *Jones AW, Jonsson KA. Between-subject and within-subject variations in the pharmacokinetics of ethanol. Br J Clin Pharmacol 1994; 37: 427-31.*
3. *Jones AW. Ultra-rapid rate of ethanol elimination from blood in drunken drivers with extremely high blood-alcohol concentrations.Int J Legal Med. 2008; 122(2): 129-34.*
4. *Agarwal DP, Goedde HW. Pharmacogenetics of alcohol metabolism and alcoholism.Pharmacogenetics. 1992; 2(2): 48-62.*
5. *Barinskaia TO, Smirnov AV, Salomatin EM, Shaev AI.Comparison of beta60, beta-slope elimination rates in different periods after alcohol intake. 2009; 52(3): 16-21.*
6. *Barinskaia TO, Smirnov AV, Salomatin EM, Shaev AI.Ethanol elimination rate beta60, beta-slope in different age groups after intake of a moderate or high dose of alcohol. 2009; 52(5): 23-7.*
7. *Ensor T. Godfrey C. Modelling the interactions between alcohol, crime and the criminal justice system. Addiction 1993; 88: 477-87.*
8. *Gillberg RG, Jones AW. Guidelines for estimating the amount of alcohol consumed from a single measurement of blood alcohol concentration: re-evaluation of Widmark`s eqation. Forensic Sci Int. 1994; 69(2): 119-30.*
9. *Jones AW. Disappeareance rate of ethanol from blood of human subjects: implications in forensic toxicology. J Forensic Sci 1993; 38(1): 104-18.*
10. *Neuteboom W, Jones AW. Disappearance rate of alcohol from the blood of drunk drivers calculated from two consecutive samples; what do the results really mean? Forensic Sci Int 1990; 45 (1-2): 107-15.*
11. *Piekoszewski W, Gubała W. Inter- and intra-individual variability of ethanol pharmacokinetics over a long period of time. Pol J Pharmacol. 2000; 52(5): 389-95.*
12. *Pieters JE, Wedel M, Schfaazma G. Parameter estimation in a tree-compartment model for blood alcohol curves. Alcohol Alcohol. 1990; 25: 17-24.*
13. *Simić M, Tasić M, Budimlija Z. Re-evaluation of alcohol disappearance rate (beta slope) on the basis of ten-year data. Medicina forensis 2000; 7: 21-24.*
14. *Wedel M, Pieters JE, Pikaar NA, Ockhuizen T. Application of a three-compartment model to a study of the effects of sex, alcohol dose and concentration, exercise and food consumption on the pharmacokinetics of ethanol in healthy volunteers. Alcohol. 1991; 26(3): 329-36.*
15. *Winek CL, Esposito FM. Blood alcohol concentrations: factors affecting predictions. Leg Med. 1985; 34-61.*

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Radiotherapy Perception and Initial Experiences of Turkish Patients: A Qualitative Study

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Abstract

Radiotherapy (RT) is a treatment technique that is used extensively in the treatment of cancer.

Objectives: The aim of this study was to describe patients' personal experiences during their first week of RT.

Methods: The study used purposeful sampling and followed saturation principles. Five male and six female participants were treated in a radiation oncology department were interviewed. Data were analyzed following a hermeneutical process.

Results: Four main themes emerged from the process: RT for the patients, patients' initial RT experiences, patients' concerns, and patients' need for information. The results indicated that patients had a positive view of RT as a treatment method. However, they expressed some concerns about disease prognosis, treatment success, and treatment side effects. They indicated that the radiation oncology team was caring and attentive, but not informative.

Conclusion: These findings create the opportunity to understand patients' thoughts and emotions related to this therapy. The results of this study will help health professionals be aware that they must develop care interventions based on the needs of the patient.

Key Words: Cancer patient, radiotherapy, experince, qualitative.

Introduction

Cancer is the second leading cause of death in many countries, including Turkey (1). Along with the physical problems, a diagnosis of cancer often causes psychological problems. These include patients' inability to accept their cancer diagnosis, struggles with treatment side effects, and difficulties associated with adaptation to the illness and the cancer treatments (2, 3). Radiotherapy is just one of many ways to treat cancer. It is delivered in consecutive treatments, and for a certain amount of time. Radiotherapy patients are already in a vulnerable situation when they enter the radiation therapy department. In addition to many fears they are experiencing, patients become quite concerned about the treatment's side effects and whether or not it can actually eradicate their cancer (4, 5, 6).

If cancer patients are able to successfully adapt to the treatment process, they may experience positive results in decreasing the progression of the disease and treatment-related problems. Recognizing and acknowledging aspects of the patient's psychosocial characteristics can improve the therapeutic relationship between the patient and medical personnel. Because of the multidisciplinary aspect of cancer treatment, recognition of the patient's feelings by medical personnel (especially those in direct contact) is very important. Medical personnel who recognize and evaluate the positive and negative feelings and thoughts of the patient can help the patient adapt and respond to the treatment. A strong patient-health team relationship leads to better clinical results (6, 7).

The patient's feelings and thoughts that result from his or her perceptions about the treatment are important factors related to compliance with the treatment process. Understanding the patient's viewpoint towards treatment is important for guiding development of approaches that can be used for patient care and for planning treatment education.

Many studies have been published about RT. These have dealt primarily with the treatment's side effects, but no studies about the patients' perception of the treatment have been published in Turkey. The objective of this phenomenologic

study was to examine the personal experiences of patients during the early stages of RT. Our aim was to gain a deeper understanding of patients' individual experiences and what these experiences meant to them.

Methods

Research design

The study was performed using a phenomenological approach. The goal of this qualitative research method is to describe life experiences or to understand the essence of a phenomenon as experienced by individuals. The Heideggerian hermeneutical perspective was used in this study.

Sampling

Purposive convenience sampling was used to recruit 11 participants who were in the first week of RT and were receiving the treatment at Karadeniz Technical University Medicine Faculty's Hospital Radiation Oncology outpatient clinic in Turkey. We included patients in their first week of treatment because treatment side effects that develop at later stages of treatment could affect patient perception. Inclusion in the study required that patients be diagnosed with primary cancer, be >18 years of age, know the diagnosis, have an Eastern Oncology Cooperative Group (ECOG) performance score between 0 and 2, speak and understand the Turkish language, had never previously received RT or been a caregiver to a patient receiving RT, have a life expectancy >6 months, and volunteer to participate in the study. Excluded from the study were patients with psychiatric conditions requiring treatment or use of psychiatric medication, those with visual or auditory loss, and anyone who had been employed as a health care worker.

Ethical permissions

Approval to perform the study was obtained from the institution's ethics committee, and written informed consent was obtained from all participating patients.

Data collection

After securing approval, the lead researcher phoned and invited each potential participant to join the study. The second and third researchers then arranged for an interview time according to the participant's preference. The participants were reminded that their participation was voluntary and that they could decline or withdraw from the study at any time without any obligation. The data were collected using the "in-depth interview" method and semi-structured questions. The intent of the questions was to ask patients' opinions related to this therapy. They were asked to describe what radiotherapy is, what their thoughts were, and how they felt about the treatment method etc.

The interviews were conducted in a suitable room in the outpatient clinic, and the participant was the main speaker during each interview. The interviews were between 30 and 45 minutes in length, and all were recorded using an audio recording device. Personal and medical information was obtained from the medical records maintained in the radiation oncology office.

Data analysis

The researchers recorded all of the raw data exactly as expressed by the participants. Narratives (texts) were interpreted using a seven-stage hermeneutical process described by Diekelmann and Ironside; 1998 (8). Data analysis began with a verbatim transcription of each of the 11 audiotaped interviews. During the first stage, each researcher examined the texts as a whole to gain an overall understanding of the participants' perceptions of their RT experiences. Possible common meanings were identified from the texts at the second stage of the analysis. At third stage, the researchers compared their interpretations for similarities and differences at biweekly intervals.

The researchers then read and reread all of the texts to link the themes (Stage four). At Stage fivethey described constitutive patterns that portrayed the relationships among themes across all texts. The themes were validated by the study participants at Stage six. A final summary was then written and included quotes (for validation) for the reader. This multistage process permitted clarification and validation, which helped to eliminate unconfirmed meanings. The hermeneutic circle involved constant checking of whole texts, parts of texts, and constant reference to the texts. The continuous reference to the texts guaranteed that interpretations were grounded and focused (8).

Results

Sample demographics

The results for the descriptive characteristics of the 11 patients are presented in Table 1. The mean patient age was 53 years (range, 25–75 years). Six of the patients were women and five were men. Seven patients were elementary school graduates. All of the women were housewives, and the men worked at different types of employment.

Results of the interviews yielded four main themes: RT for the patients, patients' initial RT experiences, concerns, and information need**.**

Radiotherapy for the patients

All of the patients stated that they viewed RT as one of the treatment modalities for their illnesses. Some patients described RT as a treatment modality that would cure their disease or stop their pain. One patient said, *" I am coming here because I would like to not have pain if I am to live longer."* (P3). Some of the patients used expressions that revealed conflicted feelings related to the RT. One patient said, *"I've said I wish I hadn't received the treatment. I wanted to end my treatment early, so I said I wish I hadn't received the treatment. Then I said my treatment will be finished with radiotherapy; I am getting used to it."* (P6).

All patients, who also were treated with surgery or chemotherapy, compared these treatment methods with RT. Most of them stated that when they compared RT with surgery, they found that RT was a more comfortable procedure. The patients who had RT without surgery said that they were satisfied to have undergone RT rather than surgery. For example, one patient said that RT was a "*Better technique than surgery. I see some people with holes in their throats; it is not a nice look. Another doctor told me that they would cut my throat; when it comes to radiotherapy there is no cutting."* (P9). When the patients treated with chemotherapy compared chemotherapy with RT, they responded that they found that RT was easier and more acceptable. One patient stated, "*After chemotherapy everything is acceptable."* (P4).

Patients' initial RT experiences

The participants did not view the need to wear a mask for the procedure and marking of the treatment

Table 1. Patient's Characteristics

Patient No	Age	Gender	Diagnosis	Operation	Stage	Education status	Occupation	RT (day)	Time between diagnosis and interview (month)
1	24	F	Breast Ca*	Breast Conservative Surgery	1	High School	Housewife	8	2
2	54	F	Nasopharynx Ca	Biopsy	3	Elementary	Housewife	8	1
3	60	M	Lung Ca	Biopsy	3B	Elementary	Night Guard	7	5
4	75	M	Thyroid Ca	Total Thyroidectomy	4A	Elementary	Driver	7	2
5	47	M	Pancreas ca	Whipple	2B	Elementary	Self Employment	8	2
6	43	F	Breast ca	Mastectomy	3B	Middle Grade	Housewife	7	6
7	54	F	Nasopharynx Ca	Biopsy	3	Elementary	Housewife	8	1
8	57	F	Pancreas Ca	Whipple	3B	High School	Housewife	8	2
9	75	M	Lung Ca	Biopsy	3B	Elementary	Lather	7	2
10	47	F	Cervix Ca	Biopsy	3	Elementary	Housewife	8	1
11	55	M	Stomach Ca	Total Gastrectomy	3C	University	Engineer	9	2

**Ca=Cancer*

regions as upsetting. One patient stated, "*Lines on my body don't bother me, I know everything is for the treatment."* (P2). Only one patient stated that he was feeling uncomfortable being in the treatment room as a result of the use of the mask.

Not being able to bathe because of the presence of the lines was disturbing for all patients. One patient stated, "*One thing bothers me; I couldn't bathe. The lines on my body don't bother me, I know everything is for the treatment."* (P5).

The sounds from the machines and the treatment environment itself were not bothersome to the patients. When they were asked to name the treatment device, they used names that implied that the device would save them from a progression of their disease. The responses that included the device names were, *"I call it a lifesaver; you should name it lifesaver, it saves us."* (P10), *"It is like Luqman the Wise; it makes fewer mistakes than men."* (P3), *"It is my light of life."* (P7), *"It looks like a bird, flying around me."* (P8), and *"It is like a fire but you don't feel its heat, a secret fire."* (P11). It was also described as *"a ferris wheel"* (P5) and *"a robot"* (P4).

Most of the patients responded that they were satisfied with the professionalism of the RT team. They expressed trust, especially in their doctors, "*For the first time in my life I had so much attention, I asked everything I wanted to ask."* (I1).

Patients' concerns

The patients stated that they were anxious about the treatment itself and the course of their disease. Their concerns about the RT were related to skin burns and other side effects of the treatment. They were worried because they did not understand the process. One patient stated, "*The lines were too wide, so I was anxious about the width of burns."* (P6). Most of the patients expressed anxiety about skin burns. One patient said, "*I was scared of getting burned; will they burn me, and will they give the treatment to the wrong place?"* (P8). Some of the patients were concerned about adverse treatment effects. One said, *"I have concerns about the side effects. I have nausea right now but I haven't vomited yet. I am concerned about its getting worse."* (P11).

Some of the patients expressed concerns related to their cancer diagnosis and disease prognosis. One patient said, "*I cannot accept cancer, radiotherapy reminds me of the disease."* (P4). Only one patient mentioned concerns about the hygiene level of the treatment area, "*Everyone lies on the device naked; lying down knowing that bothers me. I bring muslin and spread it first, and then I lie down."* (P10).

Patients' need for information

The patients described RT as a treatment method that killed cancer using a "beam" or "light". Many of the patients called RT a "ray treatment". Some of them responded that they used the same name for the RT that the medical personnel used. Most of the participants described RT as the "burning of a region". One patient stated that "*I understand it as treating the region by burning without excision."* (P8). Patients indicated that they did not know how this method treated the disease. For example, one said, "*I had no idea at first, it was like a film or light device, I still do not know how it will burn, how it will melt."* (P1). Another patient said, *"They give a high voltage, like a shock, such a thing comes into my mind."* (P2). Some patients associated therapy with the machine. One patient said RT was, *"Treatment with a machine before an operation, without cutting me open."* (I4).

Some of the patients stated that the information that was supplied by medical personnel was adequate; others felt it was not enough. One patient said, *"No information was given, no one sat and told me what was going to happen, what I should eat during the treatment, what I should do, these need to be told in detail."* (P8). Some patients responded that they couldn't ask about some of their concerns, *"There was no time to ask questions about my concerns."* (P2).

Most of the patients responded that the medical personnel instructed them to not wash the drawn lines, but that the instructions were incomplete. The patients indicated that in addition to the information from the RT team, they also received information from others who had previously been treated with RT.

Discussion

Radiotherapy has been used for many years for curative and palliative treatment of cancer patients. Although it yields positive results, it also

causes various side effects during and after treatment. Consequently, these unpleasant side effects can decrease patients' compliance to treatment and have a negative impact on their quality of life. Therefore, the RT team must be aware of the patient's expectations about the treatment and the patients' need to be informed about the care that they will receive from medical personnel. This study was performed in order to more fully understand the RT experiences of cancer patients.

The patients' statements revealed that while some had positive feelings towards RT, others were confused about it. At the beginning of the RT treatment period, many patients have already lived a period with their illness, have accepted their disease, and are focusing their attention on recovery (9). Therefore, a patient who is to receive RT is likely to be more focused on health rather than illness. The patients indicated that compared with chemotherapy and surgery, RT was a preferred treatment. This perspective may be an advantage of RT, which requires patient compliance during a specific period of time.

The actual radiotherapy equipment and the pauses that occur during the radiotherapy treatment cause a great deal of anxiety for patients, and this affects their treatment experience (10, 11). Karhu-Hämäläinen's study (2002) in Finland found that the physical environment affects the patients' sense of well-being (12). But the participants in our study responded positively to their first radiotherapy experiences. All patients stated that the treatment preparations (e.g., drawing lines, mask preparation) and the duration of time in the treatment device were not stressful. Ekfors and Peterson (2004) found that half of the patients did not experience distress or experienced much less distress during RT than they had expected. Our study showed similar results (13). When the patients in our study were asked to assign a name to the treatment device, they used names associated with hope.

The RT team can use this optimistic view to support the patient's psychological state, increase treatment compliance, and improve patient willingness to fight treatment side effects. In this study many patients stated that they were satisfied with the medical personnel's actions and professionalism and described them as friendly and helpful. Cancer is a long-term disease with a difficult treatment regimen. The quality of the relationship between the patient and health care team plays a vital role in this journey. In 2008 Siekkinen, Salanterä, et al. found that medical personnel's neatness, kindness, friendly approach, precision, and attention received the highest scores when patients evaluated them. (14). Other studies have shown similar results. Radiotherapy departments and teams who offer social support can significantly improve patients' quality of life (15, 16, 17).

The patients in this study also experienced concerns about the treatment and their prognosis (4, 6, 9). As found in previous studies, anxiety, depression, and hopelessness are the most common psychosocial problems that cancer patients experience during the treatment period (11, 16).

We found that patients did not understand the function of RT and how it could help them. When asked to explain RT, most patients described this therapy as burning specific regions of the body. Ekfors and Peterson reported that many patients described radiation as a therapy which attacks cancer cells, and they used war-like expressions in their descriptions (9). Patients associate radiation with killing and burning, thus they associate radiation's use in war with its use in medicine. The patients' responses indicated that the information given by the medical personnel was not planned and organized. After a cancer diagnosis, patients would like to be informed about treatment options and what they should expect during the treatment process (17, 18). According to earlier studies, when patients are given accurate and relevant information about radiotherapy, their emotional distress and anxiety are lessened (18, 19). Information provides knowledge, builds alliances, reduces uncertainty, and improves treatment compliance. The professional characteristics of radiotherapy department staff are closely communicated in many ways while caring for patients receiving radiotherapy. Caring activities include providing information, patient education, and technical implementation of radiotherapy. These interactions with the patients influence their experiences of treatment and also its quality (18, 19, 20). Patients in this study explained that they were unable to obtain information from medical personel and doctors were their only source of information. One study revealed that nearly all patients prefer to receive detailed information about the treatment they

will receive from the radiation oncologist. They prefer that the radiation oncologist use easy-to-understand language when the treatment is discussed (1). Patients would also like to obtain information from doctors. This is particularly important for issues regarding patients' treatment plan. Each person on the RT team is responsible to give information regarding their specialty. Skills such as open questioning, listening, and showing empathy can be used by the radiation team to relieve patients' concerns (21).

Conclusions

This study had some limitations. Experiences are related to early period of RT. The sample was not representative in the quantitative sense, but in qualitative research any subject belonging to a specified group is considered to represent that group. The resulting descriptive interpretation can also be applied to other groups of cancer patients. In addition, the findings may not be applicable to patients in different healthcare settings or from different cultural backgrounds.

Cancer is a serious health problem that requires a professional approach during the treatment period. During this process, approaching RT as "applying x-ray to the treatment region via machines" is far from a holistic treatment and caregiving methodology. Many studies about the negative effects of RT and how they affect patients' lives have been published. However, only a very limited number of studies have described patients experiences during the treatment process.

To our knowledge, this is the first study in Turkey to perform an in-depth analysis of the RT experience from the patient's perspective. The results of this study provide us with the opportunity to understand patients' experiences as they begin RT. Hearing about the disease and treatment journey from the patient's perspective can broaden the health professional's perspective. We hope that these findings will help patients undergoing RT to recognize their tendency to self-criticize and to be more accepting and more forgiving of themselves. To understand the later stages of the RT treatment experience from the patient's perspective, this study could be repeated using a patient population that is near the end of or has completed the treatment.

References

1. *Bhatnagar AK, Land SR, Shogan A, Rodgers EE, Heron DE, Flickinger JC. What do patients want from their radiation oncologist? Initial results from a prospective trial. Int J Radiat Oncol Biol Phys 2007; 69(5): 1527-33.*
2. *Eades M, Chasen M, Bhargava R. Rehabilitation: long-term physical and functional changes following treatment. Semin Oncol Nurs 2009; 25(3): 222-30.*
3. *Mallack I, Waldron JN. Radiation therapy for head and neck cancers. Seminars in Oncology Nursing 2009; 25: 193–202.*
4. *Halkett GKB, Kristjanson LJ. Patients' perspectives on the role of radiation therapists. Patient Education and Counseling 2007; 69: 76–83.*
5. *Long LE. Being informed undergoing radiation therapy. Cancer Nursing 2001; 24: 463–468.*
6. *Halkett GKB, Kristjanson LJ, Lobb EA. If we get too close to your bones they'll go brittle: women's initial fears about radiotherapy for early breast cancer. Psycho-Oncology 2008; 17: 877–884.*
7. *Eton D, Lepore S, Helgeson V. Early quality of life in patients with localized prostate carcinoma: in examination of treatment-related, demographic and psychosocial factors. Cancer 2001; 92: 1451–1459.*
8. *Diekelmann N, Ironside P. Hermeneutics In: Fitzpatrick J, ed. Encyclopedia of Nursing Research. New York, NY: Springer 1998; 50-68.*
9. *Houldin AD. Patients with cancer: Understanding the psychological pain. Philadelphia: Lippincott Williams and Wilkins 2000.*
10. *Hinds C, Moyer A. Support as experienced by patients with cancer during radiotherapy treatments. Journal of Advanced Nursing 1997; 26: 371–379.*
11. *Karhu-Hämäläinen A, Eriksson E. Environment in the department of radiotherapy experienced by outpatient. Hoitotiede 2001; 13: 247–257.*
12. *Ekfors H, Petersson K. A Qualitative Study of the Experiences during Radiotherapy of Swedish Patients Suffering From Lung Cancer. Oncology Nursing Forum 2004; 31(2): 329-334.*
13. *Karhu-Hämäläinen A. Patient with Cancer: Expectations and Experiences during Radiation Therapy. Annales Universitatis Turkuensis Series C 188. Department of Nursing Science, University of Turku, Turku, Finland 2002.*

14. *Siekkinen M, Laiho R, Ruotsalainen E, Katajisto J, Pyrhönen S, Leino-Kilpi H. Quality of care experienced by Finnish cancer patients during radiotherapy. Eur J Cancer Care 2008; 17: 387-393.*

15. *Rose P, Yates P. Quality of care experienced by Finnish cancer patients during radiotherapy. Cancer Nurs 2001; 24(4): 255-63.*

16. *Ledeboer Q, Van der Velden LA, de Boer MF, Feenstra L, Pruyn JFA. Physical and psychosocial correlates of head and neck cancer: an update of the literature and challenges for the future 1996–2003. Clinical Otolaryngology 2005; 30: 303–319.*

17. *Hegney D, Pearce S, Rogers-Clark C, Martın-Mcdonald K, Buıkstra E. Close, but still too far. The experience of Australian people with cancer commuting from a regional to a capital city for radiotherapy treatment. European Journal of Cancer Care 2005; 14: 75–82*

18. *Kelsey SG, Owens J, White A. The experience of radiotherapy for localized prostate cancer: the men's perspective, European Journal of Cancer Care 2004; 13: 272–278*

19. *Skalla K, Bakitas M, Furstenberg C, Ahles T, Henderson J. Patients need of information about cancer therapy. Oncology Nursing Forum 2004; 31: 313–319.*

20. *Christman N, Cain L. The effects of concrete objective information and relaxation on maintaining usual activity during radiation therapy. Oncology Nursing Forum 2004; 31: 39–45.*

21. *Martin KL, Hodgson D. The role of counselling and communication skills:how can they enhance a patients' first day experience? Journal of Radiotherapy in Practice 2006; 5: 157–164.*

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Empirical Analysis of the Main Input and Output of China's Healthcare Reform from 2009 to 2013

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Abstract

Objective: To analyze the main input and output of healthcare reform in China, and to provide references for improving the policies and measures of healthcare reform in China in future.

Methods: Data from the National Health Services Survey, and the China Statistical Yearbook etc. was collected to compare and analyze the allocation of health resources, health status of residents, health service utilization, and medical burden before and after healthcare reform.

Results: During the reform from 2009 to 2013, hospital health and technical personnel increased year by year. In 2013, the proportion of health and technical personnel in hospitals was up to 61.4% of the total national health technical personnel. In 2013, 65.19% of government expenditure on healthcare was used for disease treatment, and only 14.59% was used for disease prevention. Compared with the year of 2008, the two-week prevalence rate of residents increased by 5.2%, the chronic disease prevalence rate increased by 9% in 2013. Compared with the year of 2009, the annually diagnosed and treated patients increased 18.2 billion person-time, the annually discharged patients increased 59.65 million person-time in 2013. The individual residents paid 52.49% of total medical expenses.

Conclusion: Since the healthcare reform, China's central and local governments have imputed a large number of health resources into hospitals for "disease treatment". That partly improved the utilization of residents' health service, but the two-week prevalence rate and chronic disease prevalence rate are rapidly growing. There is still high burden of medical expenses for the residents.China's healthcare model should be changed from "treatment-centered" to "prevention-centered" in future.

Key words: China; Healthcare model; Healthcare reform; Transformation

1. Introduction

China, the country with the most population in the world, has made remarkable progress in economic and public health over the past 20 years, including prolonged life expectancy by one third, decreased childhood mortality rates by more than half, and increased hospital beds by three times[1]. However, China still faces challenges in many aspects of healthcare system[2]. Therefore, The Chinese government launched a health care reform in 2009, which goaled to establish a basic universal healthcare system to China's more than 1.3 billion citizens, planning to achieve the overall goal to 2020[3].(1) China's healthcare reform has several achievements at its middle stage in 2013. Over 90% of residents were covered by basic health insurances across the nationwide[4].(2) However, the dissatisfaction of patients was high, and the conflicts between patients and doctors or hospitals were kept increased[5].(3) Furthermore, the prevalence of chronic diseases was rising along with population aging[6].

The present study was to retrospectively examine the changes of China healthcare system in the distribution of healthcare resources, the contributions of healthcare expenditures among government, residents and other sources, and the prevalence of chronic diseases. We expected to provide evidence of achievement at the mid-term of healthcare reform by comparing the numbers each year, which might give us direction for future.

2. Data and methods

2.1 Data source

The data for present study were collected from the following four public resources: (1) The data of distribution of healthcare professionals were obtained from "the Statistical Bulletin of China's Health Development" issued by National Health and Family Planning Commission every year during 2009-2014; (2) The data of government health expenditure were obtained from Annual National Public Fiscal Expenditure Data released by the Financial Ministry of the People's Republic of China from 2009 to 2014; (3) The data on the prevalence rate of chronic diseases, two-week prevalence rate, residents' medical service demand and utilization of health service were obtained from the Fourth and Fifth National Health Care Survey in 2008, and 2013; (4) The data of the total healthcare expenditures, medical expenditures, and out-of-pocket payment were obtained by China statistical yearbook in 2015.

2.2 Definitions

In China, health care human resources include medical and healthcare professionals (physicians, physician assistants, dentists, obstetrics, registered nurses, pharmacists, physiotherapists, optometrists, and others.) and healthcare-associated professionals, who support implementation of health care, include public health administrations, medical educators, medical research scientist, and other supportive staffs who work at hospital.

The health care human resources allocate to hospitals, primary care facilities, and public health institutes (PHIs). Hospitals in China are organized as a 3-tier system as Primary, Secondary or Tertiary institutions, according to hospital's ability to provide medical care, medical education, and conduct medical research[2].The primary care facilities include township health care clinics at rural districts, community health care clinics and service center at urban areas. PHIs are nonprofit organizations that improve the public's health by fostering innovation, leveraging resources, and building partnerships across sectors, including government agencies, communities, the health care delivery system, media, and academia.

Total health care expenditures included government expenditures, social expenditures, and out-of-pocket payments of the populations. Government expenditures referred to expenditures incurred by the central and local government authorities, including spending on healthcare and population and family planning, subsidy to health insurance, and health administration costs; Social expenditures referred to expenditures incurred by social funds, including spending on social health insurances, private health insurance, and social-medical assistance and donation, and administration cost; Out-of-pocket expenditures for health care that weren't reimbursed by any kinds of insurance scheme, including deductibles, coinsurance, and copayments for covered services plus all costs for services that weren't covered. Out-of-pocket health care expenditures per capita were calculated as the sum of total health care expenditure of the population divided by the number of population. The social health insurance scheme in China health care system included new rural cooperative medical scheme (NCMS), the urban resident basic medical insurance (URBMI), and urban employee basic medical insurance (UEBMI).

2.3 Indicators

(1) Two-week prevalence of illness referred to the number of the diagnosed patients among subjects during the two-week survey, divided by the total subjects of survey;

(2) Chronic disease was defined as any non-communicable conditions that typically lasted for a year or more and required ongoing medical attention and/or limited activities of daily living. The prevalence of chronic diseases referred the numbers of patients suffering from chronic conditions within half a year of the survey in the total population of that year;

(3) The annual average number of visiting = the total number of visiting of the year/ the population of the year;

(4) The annual average in-hospital rate = the total number of the discharged from hospital of the year / the total population of the year ×100%;

(5) Percentage of out-of-pocket health care expenditures per capita in total health care expenditures = out-of-pocket health care expenditures

per capita / (out-of-pocket health care expenditures per capita + Social insurance expenditures (NCMS + URBMI + UEBMI) ×100%.

(6) The out-of-pocket health care expenditure per capita as a percentage of average annual household living consumption expenditure per capita was used as a proxy indicator to estimate the financial burden of healthcare placed on population. Annual household living consumption expenditure per capita was defined as total consumption expenditure for daily life including food, clothing, housing, education, health care, transportation etc.

3 Results

3.1 Main Input of China's health care reform from 2009 to 2013

3.1.1 The health care human resources

In China, above half of professionals allocated in hospitals, and over one third of them allocated in primary care facilities, and about 10% of professionals worked in the public health institutions. Most important, the allocation of professionals had one-direction changes during 2009-2013. As shown in Table 1, about 4% of medical and healthcare professionals and 3.5% of healthcare-associated professionals migrated from primary health care facilities to hospitals or the public health institutions. The professionals in public health care institutes have no significant changes. Among them, the healthcare-associated professionals were 1.4 fold of medical and healthcare professionals, and had no significant changes between 2009 and 2013 (1.4 vs. 1.36 fold) as shown in Table 1.

3.1.2 Healthcare financial resources

From 2009 to 2013, the total healthcare expenditures in China increased about 1.8 fold from 17.5 to 31.7 Trillion RMB, progressively. All sources of expenditures, including government expenditures, social expenditures, and out-of-pocket expenditures of the populations, had significant increases, 1.98, 1.85, 1.63 fold, respectively, as shown in Table 2. Moreover, the percentage of government expenditures in total expenditures was increased progressively from 27.5 to 30.1%, but the percentage of out-of-pocket expenditures was decreased progressively from 37.5 to 33.9%, while social expenditures has no significant changes, between 34.6 and 36.0%. In 2009, the percentage of government expenditures was slightly above one quarter of total expenditures.

3.1.3 Components of China government health care expenditure

As shown in Table 3, China government health care expenditure had increased over 2 fold from 399 to 827 billion RMB. Figure 1 depicted the top 4 categories comprised the majority of the expenditure (about 80-90% of the total), including Hospitals, Primary Care, Public Health care, Social Basic Medical Insurance. The 5-year growth trends of these top 4 components of China government health care expenditure was shown in Figure 1A. The same top 4 components as a percentage was shown in Figure 1B. Social Basic Medical Insurance had always been the dominant expenses in percentage of government health care expenditure, and had a rapid increase over 2 folds in absolute spending and over half of government health care expenditure in percentage. From 2009-2013, the cost of hospital facilities (19% to 14% of government health care expenditure) had been growing steadily, but had been overtaken in importance by public health care (from 7% to 15% of government health care expenditure). The primary care maintained the lowest and relatively constant share of overall cost (10% of government health care expenditure) from 2009-2013. (Table 3.)

3.2 Main Output of China's healthcare reform from 2009 to 2013

3.2.1 Two-week prevalence and chronic disease prevalence

The data of population two-week prevalence came from the Chinese Fifth National Health Service Survey, which conducted in 2013. The population of two-week prevalence was 24.1% in 2013, which increased 5.2 % compared to that of the fourth survey in 2008. The population of the chronic disease prevalence in age 15 and over in 2013 was 33.1%, which 9% more than that in 2008[7].

3.2.2 Healthcare service utilization rate

As shown in Table 4, the overall annual patient visiting increased progressively between 2009 and 2013 (54.9 vs. 73.1 billion visitors per year). Adjusted to population, the average annual clinic visiting per person was increased as well, 4.2 visits in 2009, vs. 5.4 visits in 2013. The overall number of annual hospital discharged also increased from 133 million in 2009 to 192 million in 2013. The hospital admission rates had significant and progress increases from 9.9% in 2009 to 14.1% in 2013. The total number of annual discharged also increased yearly, from 132 million in 2009 to 192 million in 2013, corresponding hospitalization rate from 9.9% to 14.1%.

3.2.3 Residents' medical burden

At present, China's medical aid and commercial health insurance spending less. According to data released by the Ministry of finance of the people's Republic of China and the China Insurance Regulatory Commission, 2013 China Medicaid spending 186.84 billion Yuan RMB [8], health insurance indemnity and payment 41.113 billion US dollars [9], and accounted for only when personal cash health expenditures and health care spending sum of 2.9% (597.97/20 439.54 billion Yuan RMB). As a result, the medical expenses of Chinese residents are mainly borne by the individual and the basic medical insurance. As shown in Table 5, in 2009, China spent 1.8 trillion, or 5.15 percent of its gross domestic product (GDP), on health care. However, it rapidly increased to 3.2 trillion at 2013, but the percentage in GDP slightly increased to 5.57%. Furthermore, out-of-pocket money from individual as a financial burden increased from 0.7 trillion in 2009 to 1.1 trillion in 2013. Furthermore, as largest part of healthcare spending pie, its share as a percentage of total spending for healthcare was declining, from 64.9% in 2009 to 52.5% in 2013. It also noted that the major portion of spending in healthcare went toward basic medical insurance, and those funds were rising significantly from 355 billion to 971 billion. Other contributions came from social insurance expenditures (NCMS + URBMI + UEBMI), increased as well, including NCMS from 92 billion to 291 billion, URBMI from 41 billion (since 2011) to 97 billion, and UEBMI 263 billion to 583 billion.

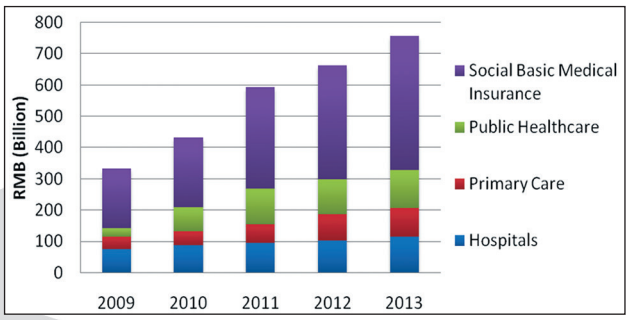

Figure 1 A

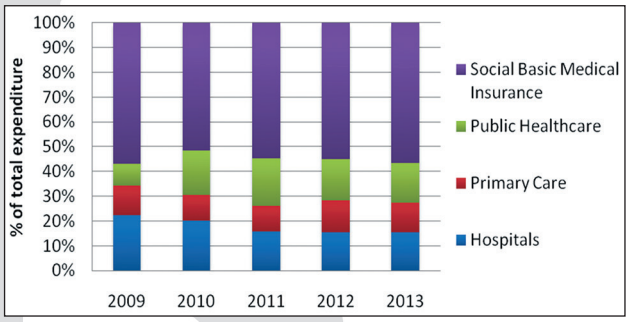

Figure 1 B

4. Discussion

In present retrospective study, we found that since China health care reform in 2009, the resources of health care, including human and financial resources, migrated towards disease "treatment" from disease "prevention". Along with extremely increased the healthcare expenditures, the public healthy was not improved as expected, and the resident out-of-pocket payment for healthcare was increased significantly, especially in rural population.

Healthcare resources migrated from "prevention" to "treatment"

From 2009 to 2013, the healthcare professionals had relocated to hospitals significantly for "treatment" disease from primary facilities. Professionals in public health institutions, increased slightly, but the primary care professionals, who served as "gatekeeper" for residents' healthy, declined progressively.

Moreover, the expenditures for healthcare mainly spent at hospital for disease "treatment". One of the potential reasons might relate to the

Table 1. The health care resource allocation during healthcare system reform from 2009 to 2013

Year	Medical And Healthcare Professionals							Healthcare-Associated Professionals						
	Total workers	Hospital		Primary Care Facilities		Public Health Institutions		Total workers	Hospital		Primary Care Facilities		Public Health Institutions	
		Numbers	%	Numbers	%	Numbers	%		Numbers	%	Numbers	%	Numbers	%
2009	778.1	395.8	50.9	315.2	40.5	60.1	8.6	553.5	320.0	57.8	183.3	33.1	46.6	8.4
2010	820.8	422.7	51.5	328.2	40.0	62.5	8.5	587.6	343.8	58.5	191.4	32.6	48.7	8.3
2011	861.6	452.7	52.5	337.5	39.2	64.1	8.3	620.3	370.6	59.7	196.3	31.6	49.8	8.0
2012	911.9	493.7	54.1	343.7	37.7	67.0	8.2	667.9	405.8	60.8	205.2	30.7	53.2	8.0
2013	979.0	537.1	54.9	351.4	35.9	82.6	8.4	721.1	442.5	61.4	213.8	29.6	60.9	8.4

Data resources: the Statistical Bulletin of China's Health Development" issued by National Health and Family Planning Commission every year during 2009-2013. Unit of numbers: 10,000.

Table 2. Contribution of China healthcare financial resources from 2009 to 2013

Year	Expenditures						
	Total	Government	%	Social	%	Out-Of-Pocket	%
2009	1754.2	481.6	27.46	615.4	35.08	657.1	37.46
2010	1998	573.2	28.69	719.7	36.02	705.1	35.29
2011	2434.6	746.4	30.66	841.6	34.57	846.5	34.77
2012	2811.9	843.2	29.99	1003.1	35.67	965.6	34.34
2013	3166.9	954.6	30.14	1139.4	35.98	1072.9	33.88

The data of government health expenditure were obtained from Annual National Public Fiscal Expenditure Data released by the Financial Ministry of the People's Republic of China from 2009 to 2013; Unit: Billion RMB (￥).

Table 3. Components of China government health care expenditure from 2009 to 2013

Year	Government Health Care Expenditures	Hospitals		Primary Care		Public Healthcare		Social Basic Medical Insurance	
	RMB	RMB	%	RMB	%	RMB	%	RMB	%
2009	**399.4**	74.2	18.6	39.5	9.9	29.3	7.3	189.2	47.4
2010	**480.4**	87.6	18.2	44.8	9.3	76.9	16.0	222.8	46.4
2011	**643.0**	94.0	14.6	61.4	9.6	111.7	17.4	325.1	50.6
2012	**724.5**	101.3	14.0	86.3	11.9	110.2	15.2	365.7	50.5
2013	**828.0**	115.7	14.0	91.8	11.1	120.6	14.6	429.4	51.9

Data sources: Annual National Public Fiscal Expenditure Data released by the Financial Ministry of the People's Republic of China from 2009 to 2013. %, percentage of Government Health Care Expenditures; Unit: Unit: Billion RMB (￥)

Table 4. Healthcare service demands and utilization rate

Year	Annual Patient Visiting (Billion Times)	Annual Clinic Visiting Per Person (Times)	Annual Hospital Discharged (Million person)	Hospital Admission Rates (%)
2009	54.90	4.20	132.50	9.90
2010	58.40	4.34	141.74	10.50
2011	62.70	4.63	152.98	11.30
2012	68.90	5.10	178.12	13.20
2013	73.10	5.40	192.15	14.10

Data sources: the Statistical Bulletin of China's Health Development" issued by National Health and Family Planning Commission every year during 2009-2013.

Table 5. Contributions of healthcare expenditures

Year	Total Healthcare Expenditures (Trillion)	Healthcare Expenditures In GDP (%)	Out-Of-Pocket Money (Billion)	NCMS (Billion)	URBMI (Billion)	UEBMI (Billion)	Basic Medical Insurance (Billion)	Percentage of out-of-pocket health care expenditures per capita in total health care expenditures (%)
2009	1.75	5.15	657.1	92.3	---	263.0	355.3	64.91
2010	1.99	4.98	705.1	118.8	---	327.2	445.9	61.26
2011	2.43	5.15	846.5	171.0	41.3	401.8	614.2	57.95
2012	2.81	5.41	965.6	240.8	67.5	486.9	795.2	54.84
2013	3.17	5.57	1072.9	290.9	97.1	583.0	971.0	52.49

Data sources: China statistical yearbook in 2014.

strategies of China's healthcare reform. Chinese health-care reform plan (2009), the total of the five key reform tasks, four for "diseases" design, including: the establishment of universal coverage of basic medical insurance system, the establishment of national essential drug system, the reform of public hospitals, improve the basic medical and health service system. However, only one for the "disease prevention" of reform measures that promote basic public health services gradually equalization[10]. Obviously, the focus of China's health care reform is "diseases", belittled a very important job, and that is disease prevention. The chronic disease hazards were studied and predicted by Haichao Lei in early 1996[11, 12]. The "alarm" about Chinese prevalence rate of chronic diseases increasing rapidly has been mentioned as early as in 2003[13]. Chinese chronic disease prevalence increased by 5 percentage points from 2003 to 2008[14]. Previous studies suggested that, to against rapid increase in the prevalence rate of chronic diseases, the elimination and/or control of the risk factors were the critical steps in chronic disease prevention and intervention, instead of the treatment[15, 16]. Another reason might be due to the reimburse policy of healthcare insurance in China. In tradition, "treatment" was paid more attention to "prevention". Therefore, most health insurance paid cost in-hospital patients only. Then there was a rapid increase in demand of in-hospital services (Table 4), which caused the overuse of medical services, and increased total health expenditure and medical costs obviously. Comparing the data between the Fourth and Fifth National Health Services Survey in 2008 and 2013 respectively, all clinic visiting increased from 62.4% in 2008 to 84.4% in 2013[14,17].

Increased prevalence of chronic diseases

Lacking an effective primary care system, most hospitals were severely overwhelmed. This problem has been accelerated by reimbursement policy, aging and expansion of healthcare insurance coverage. In China, most patients sought treatment in the highest-level hospital (class III), because the other hospitals or facilities were thought to deliver poor healthcare, including, doctor's skill, facility equipment, medicine.

Therefore, the government launched a new strategy to improve healthcare at "gatekeeper" by establish community healthcare center, and primary care facilities in rural area. Also, the government recently announced resident standard training program to link the class III hospitals with primary care facilities to improve the technics of general physicians. Another factor attracted patients to Class III hospitals is the essential drug list. In primary care facilities, prescription on the expensive drug was limited. Therefore, the adoption of standard treatment guideline, installment of performance-monitoring mechanism, and minimization of variations in doctors' skill will be the major direction for China healthcare reform. It is particularly important, China should strengthen the primary health care personnel.

In reality, although the primary prevention of the disease after treatment compared with the disease, we can save more lives, most of the resources of the health system is still mainly spent on the treatment of disease[18]. In many countries, although the residents have health insurance, but they still face the risk of catastrophic health expenditure[19,20]. World experience and lessons show that healthy development objectives and strategies of selection improper and wrong the first choice, not only to the life and health system performance at the expense of health will also be misconfigured lot of resources and low efficiency costs. If the continuation of treatment based health care model, not an elixir can save the current resource misallocation and inefficient health care system. To address this problem, many countries in the health policy objectives and its implementation at the national level as well as ways to reform the health system direction, showing a new trend, stressing that "prevention first" and pay attention to the role of preventive health care, to promote clinical the integration of medicine and public health, the health of the overall concern of the priority allocation of resources on preventive health interventions with good cost-effectiveness, by primary health care providers rather than relying on top-level medical institutions, to change the health system lack of integration, lack of sustainability, inefficient, unfair and costly situation[21].

As a developing country, China faces an aging population, high incidence of non-communicable diseases such as multiple challenges, the Chinese health care model from "treatment" to "prevention" should be taken as soon as possible. Experiences in many developed countries, such as Finland, Britain, Canada, France and Germany's proved that many interventions for chronic disease prevention measures recommended in " Frame Convention of Tobacco Control " and multiple drug therapy interventions used for cardiovascular disease of high risk population are very economic and effective[22-24]. Moreover, control effect often appears in much shorter time than expected. Some Chinese chronic disease intervention proved that chronic disease intervention is not only cost effective, but also has long term effects on health improvement[25, 26]. The experience from developed countries shows that by reducing or eliminating risk factors, the residents' health will be improved in China in a year or several years, rather than decades usually imagined by people[27, 28]. Many studies suggest that the challenge of chronic diseases such as diabetes rate continues to rise, and to strengthen the non-communicable disease risk factors than focus on disease treatment interventions more important[15, 29].

Increased healthcare expenditures and resident financial burden

Based on the goal of healthcare reform, China has achieved near-universal health insurance coverage by end of 2011[30]. Surveillance data from 2009 to 2013 indicated that there had been a significant increase in the total healthcare expenditures[31]. Government share the most of expenditures increased about 2 fold, which might due to development of universal basic health insurance coverage by government31. However, the out-of-pocket payment for healthcare remains a major expense for most of Chinese. Although the coverage of depth was increased by involvement of other social insurance, like NCMS, URBMI, UEBMI, the proportion of personal health cash disbursement to the sum of personal health cash disbursement and medical insurance expenditures remained high. Over 50% of all healthcare costs were paid as premiums or out-of-pocket payments. Furthermore, the expenses were varies depending where that person lives, and the type of insurance for people with URBMI or UEBMI, which were funded by the central government, lo-

cal governments, and individual paid premiums. Therefore, the populations in rural area paid more than populations in urban area. The disparities in healthcare expenses might become smaller, along with the economic development in rural area.

Hints for future

Based on the above analysis and discussion, the following policies were recommended. *Firstly,* the health care mode transformation from "treatment" to "prevention" in the future should be chosen for the priority strategy in Chinese medical reform, rather than the reform in public hospitals of "disease-treatment". It is impossible that this transformation depends on markets, which needs the government to actively take the main responsibility. At present, the more pressing tasks are: to increase the number of personnel system of disease prevention and control, to improve the quality of personnel engaged in disease prevention and control, to strengthen the work input for disease prevention and control, and to do a good job of prevention and control work for key epidemic, especially in the prevention and control for chronic disease. At the same time, to play their full role in prevention and health care by increasing the professional and technical personnel in health institutions at grassroots. *Secondly,* with the opportunity of promoting the rules of law, determine residents' health goals by legislation, integrate health into all policies and play the full role of all aspects of society to improve the health level of residents. *Thirdly,* China should focus on residents' health goals, integrating the government policy, resources and fund dispersed in all departments to pay attention to people's health, integrating clinical medicine with public health to allocate resources priority in interventions of preventive health with good cost effect.

5. Conclusion

Since the implementation of healthcare system reform, the China government has extremely increased investment in healthcare resources to achieve universal basic health insurance coverage. Therefore, utilization of healthcare serves had substantially increased. However, the increase was unbalanced between hospitals and primary care facilities, and between diseases "treatment" and "prevention", which increased the expenditures and the out-of-pocket payments, decreased the efficiency of service delivery. Given above analysis, the priority strategy for China healthcare system reform was to transform from diseases "treatment" to "prevention".

6. Authors' contribution

As the first author, Feng Deng is responsible for the overall design and study of this paper. Juhong LV, Honglin Wang, participated the research of this paper. Jianming Gao participated the research of this paper, and the proposed amendments, is the paper's corresponding author.

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References

1. *Chen Z. Launch of the health-care reform plan in China[J]. Lancet, 2009; 373: 1322-4.*
2. *Qide Han. China's health care development is still facing serious challenges[J]. Chinese Journal of Health Policy, 2010; 3(5): 41.*
3. *The Central People's Government of People's Republic of China. Chinese government's health care reform plan[OL]. http://www.gov.cn/test/2009-04/08/content_1280069.htm.*
4. *Winnie Chi-Man Yip, William C Hsiao, Wen Chen, Shanlian Hu, Jin Ma, Alan Maynard. Early appraisal of China's huge and complex health-care reforms[J]. Lancet, 2012; 379: 833–42.*
5. *Hui Wu, Li Liu, Yang Wang, Fei Gao, Xue Zhao, Lie Wang. Factors associated with burnout among Chinese hospital doctors: a cross-sectional study[J]. BMC Public Health, 2013; 13: 786.*

6. *Gonghuan Yang, Lingzhi Kong, Wenhua Zhao, Xia Wan, Yi Zhai, Lincoln C Chen, et al. Emergence of chronic non-communicable diseases in China[J]. Lancet, 2008; 372: 1697–1705.*

7. *Xuling Menqun. The fifth Chinese national health services survey results of two - health service need, demand and utilization [J].Chinese Journal of Health Informatics and Management, 2014; 11(3): 193-194.*

8. *Ministry of Finance of the people's Republic of China.China's public expenditure statement in 2013[OL]. http://yss.mof.gov.cn/2013qgczjs/201407/t20140711_1111874.html.*

9. *China Insurance Regulatory Commission. China insurance statistics report in 2013[OL]. http://www.circ.gov.cn/web/site0/tab5257/info3901864.htm.*

10. *National Health and Family Planning Commission of the People's Republic of China. China's health care reform the recent focus on the implementation of the program (2009-2011)[OL]. http://www.nhfpc.gov.cn/tigs/s9660/200904/4f690ccd55c348ddabd3a3e6ad4d79f7.shtml.*

11. *Lei hai-chao,Liuxing-zhu,Bian Ying. Study on prediction of costs of chronic diseases treatment in China[J]. Chinese Health Economics,1996; 10: 18-19.*

12. *Lei hai-chao,Liuxing-zhu,BianYing,etc. Study on morbidity of chronic diseases in the future trend in China[J]. Chinese Health Economics, 1996; 10: 7-9.*

13. *Republic of China Ministry of Center for Health Statistics and Information. An Analysis Report of National Health Services Survey in China, 2003.[M]. Peking Union Medical College press, 2004; 1.*

14. *Republic of China Ministry of Center for Health Statistics and Information.An Analysis Report of National Health Services Survey in China, 2008[M]. Peking Union Medical College press, 2009; 12.*

15. *Gonghuan Yang, Yu Wang, YixinZeng, et al. Rapid health transition in China, 1990–2010: fi ndings from the Global Burden of Disease Study 2010[J]. Lancet, 2013; 381: 1987–2015.*

16. *Meng Q, Xu L, Zhang Y, et al. Trends in access to health services and financial protection in China between 2003 and 2011: a cross-sectional study[J]. Lancet, 2012; 379: 805-14.*

17. *National Health and Family Planning Commission of the people's Republic of China. China Health and Family Planning Statistics Yearbook 2015[M].Peking Union Medical College press, 2015: 10.*

18. *Woolf S H. The need for perspective in evidence-based medicine [J].JAMA, 1999; 282: 2358-2365.*

19. *Christine Goeppel, Patricia Frenz, Peter Tinnemann, et al. Universal health coverage for elderly people with non-communicable diseases in low-income and middle-income countries: a cross-sectional analysis. Lancet, 2014; 384: S6.*

20. *Qun Meng, Ling Xu, Yaoguang Zhang, et al. Trends in access to health services and financial protection in. Lancet, 2012; 379: 805–14.*

21. *REN Ran. The New Direction for Health & Health Reform Internationally: Enhancing the Role of Prevention Care[J]. Medicine & Philosophy (Humanistic & Social Medicine Edition), 2010; 31(4): 5-8.*

22. *Asaria P, Chisholm D, Mathers C, et al. Chronic disease prevention: Health effects and financial costs of strategies to reduce salt intake and control tobacco use[J]. Lancet, 2007; 370(9604): 2044-2053.*

23. *Lim SS, Gaziano TA, Gakidou E, et al. Prevention of cardiovascular disease in high risk individuals in low-income and middle-income countries: Health effects and costs[J]. Lancet, 2007; 370(9604): 2054-2062.*

24. *Jamison, DT, Breman JG, Measham AR, et al. Disease control priorities in developing countries[M]. New York: Oxford University Press, 2006.*

25. *Wu X. G, Gu D F, Wu Y. F, et al. An evaluation on effectiveness of worksite based intervention for cardiovascular disease during 1974-1998 in Capital Iron and Steel Company of Beijing[J]. Journal of China Preventive edicine, 2003; 37(2): 93-97.*

26. *Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: A 20-year follow-up study[J]. Lancet, 2008; 371(9626): 1783-1789.*

27. *Puska P. Successful prevention of NCDs: 25 year experience with North Karelia Project in Finland[J]. Public Health Medicine, 2002; 4(1): 5-7.*

28. *PatricioV, Marquez P. Lead Health Specialist, et al. 2005. Dying too young. Addressing premature mortality and ill health due to non-communicable diseases and injuries in the Russian Federation[M]. Washington, DC: The World Bank, 2005.*

29. *Juliana CN Chan, Yuying Zhang, Guang Ning. Diabetes in China: a societal solution for a personal challenge. Lancet Diabetes Endocrinol 2014; 2: 969–79.*

30. *National Bureau of Statistics of the People's Republic of China. China Statistical Yearbook 2012[M]. China Statistics Press, 2012; 9.*

31. *National Bureau of Statistics of the People's Republic of China. China Statistical Yearbook 2015[M]. China Statistics Press, 2015; 10.*

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Gray zone patients in our clinical data

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Abstract

Objective: To determine the relationship between the prostate volume and the serum values of prostate specific antigen among patients in the "grey zone , "classified according to their age group. Gray zone represents serum prostate specific antigen values between 4. 1 to 10 n g/ml.

Material and Methods: Prospective and retrospective 1420 patients classified in four age-groups with LUTS (Lower urinary tract symptoms) were analyzed. Patients were treated for BPH in the urology clinical at the University Clinical Center of Kosovo during the period of January 2008 - October 2014. Data were recorded from patients according to age, prostate size estimated by trans abdominal ultrasound using 3. 5MHz *ultrasonography,* according to the ellipsoid formula, V = D1xD2xD3/2. 5, volume of prostate, V=T x AP x CC x Pi /6 where T = transverse diameter, AP = antero -posterior diameter, CC = cranial caudal diameter. Patients with confirmed prostate cancer were excluded from the study. Statistical analyses used t-test and ANOVA with 95 and 99% confidence intervals.

Results: For the grey zone patients, these mean values were 44. 6 cm3 and 5. 9 ng/mL.

Conclusions: The data provide evidence to support that prostate volume and serum PSA concentration significantly correlate with aging and within the grey zone patients.

Key words: Grey zone , benign prostate hypertrophy, prostate specific antigen (PSA) , volume of prostate.

Introduction

Benign prostate hyperplasia (BPH) disease is rare before the age of 30 years old in men. After the age of 50, the disease appears more often, and the obstructive symptoms are present in around 50% of men at the age of 75 and in 30% of men at the age of 80 at which prostatectomy intervention is required. The presence of testicular androgens and estrogens hormones are necessary in the development of the prostate in the embryo and its intensive growth until puberty.

Of all markers used in for prostate cancer screening the most important is the prostate specific antigen (PSA). As tumor markers may serve specific products of tumor cells, their metabolites including also molecular markers. Since PSA is produced by benign cells and is also found in malignant prostate cells, they certainly do not represent an ideal tumor marker. An ideal tumor marker should be strongly specific and positive only in the presence of prostate cancer and adverse to other diseases. PSA is not quite sensitive which comes from the fact that 38% to 48% of patients with intra-prostatic carcinoma have normal PSA levels.

If the upper limit of normal PSA serum levels is considered to be 4ng/ml, PSA as a prostate cancer tumor marker compared to BPH has a specificity of 49% and sensitivity of 71%. Despite these shortcomings in clinical practice, PSA currently represents the best tumor marker for prostate cancer detection (7). It is observed that PSA levels increases with age even without cancer existence. The reason for this occurence is that the prostate volume growth is due to the development of BPH, but also contribute to the sub-clinical prostatitis , ischemia , infarct of the prostate and "leakage" of PSA, which is higher in old age man.

Starting from the 5th decade of life, PSA levels rise even in the absence of prostate cancer. Its level will increase also in the next decade. Older men have higher PSA values compared to younger males (7).

Today, there is a large number of tests for the PSA assessment, among them of which the most common is the Tandem R, where 100% of healthy people younger than 40 years and 97% of healthy people older than 40 years having PSA values up

to 4. 0ng/ml. The examined persons older than 40 years do not have the PSA value above 10ng/ml (8).

Similar to this test, there is the tandem E test which differs from the previous one where, instead of radioactive antibodies, alkaline phosphatase enzyme associated with the antibody is used, even when normal values for this test are 0 to 4 ng/ml (7).

PSA "gray zone " represents serum PSA values between 4. 1 to 10 n g/ml. It is named gray zone because the cause of serum PSA levels to increase may be due to different clinical conditions such as prostate cancer, BPH , prostatitis , ischemia and prostate infarct as well as various changes caused by age. To distinguish the causes of high serum PSA levels from prostate cancer, in clinical practice, prostate biopsy is necessary(7).

Materials and methods

Prospectively and retrospectively 1420 patients with LUTS (Lower Urinary Tract Symptoms) were analyzed. Patients were treated for BPH in the University Clinical Center of Kosovo – Urology Clinic, during the period of time: January 2008 - October 2014. Data recorded from patients: age, prostate size estimated by transabdominal ultrasound using 3. 5MHz sonde, according to the ellipsoid formula, where V = D1xD2xD3 \ 2. 5 or Volume of prostate formula = TxAPxCCxPi \ 6 where T = transverse diameter, AP = Antero-posterior diameter, CC = cranial caudal diameter. Also a digito-rectal (DRE) examination of prostate was performed. In cases suspected for prostate malignity ultrasound guided biopsy was performed.

Patients in which prostate cancer was confirmed were excluded from the study.

PSA values were calculated using IRMA method (Immunoradioassay) monoclonal antibodies were obtained by a manufacturing company . The manufactured product is IMMUNOTECH - manufacturing company (Czech Republic) . Laboratory analysis was conducted at the Institute of Physiology and Immunology in UCCK in Pristina. Determination of PSA levels was based on the use of two different types of mouse monoclonal antibodies. Samples of serum or plasma were placed in test tubes incubated with monoclonal antibodies, which were present in the inner wall of the tube, in the presence of a second monoclonal antibody, which was marked with J125. After incubation the content of the test tube was washed so that antibodies tagged with J125 are left and not connected. Afterwards radioactivity was detected with gamma meters. These values are determined by a standard curve. Total PSA concentration in sample is proportional to the radioactivity. Radioactivity was measured by gamma radiation meter type DPC.

The concentration of total PSA in the range of 146 healthy people is determined by this method. PSA average concentration was 0. 77 n g/ ml with a standard deviation of 0. 76 ng/ml. 95% of the samples had total PSA below 1. 8 n g/ml, and 99% of samples below 4. 2ng/ml.

Statistical parameters were calculated for the index of structure, the arithmetic average, standard deviation, minimum and maximum values, as well as linear correlation. Statistical analyses used t-test and ANOVA with 95 and 99% confidence intervals.

Results

The research included 1420 patients with benign prostate hyperplasia.

The average age of the patients involved in the research was 67. 33 years old (standard deviation ± 8: 07 years). The youngest patient with benign prostate hyperplasia was 50 years old and the oldest 87 years old. Divided by age group, the largest number of patients 670, or 47. 2% belonged to the age group 60-69 years old and 420 patients, or 29. 6% to the age group 70-79 years old, 210 of them, or 14. 8% to the age group 50-59 years and 120 patients, or 8. 5% of the age group 80-89 years (Table 1 and Figure. 1).

Table 1. Patients included in the survey classified by age group

Age group	N	%
50-59	210	14. 8
60-69	670	47. 2
70-79	420	29. 6
80-89	120	8. 5
Total	**1420**	**100. 0**
Mean ± SD (vjet)	67. 33 ± 8. 07	
Range	50 - 87 years	

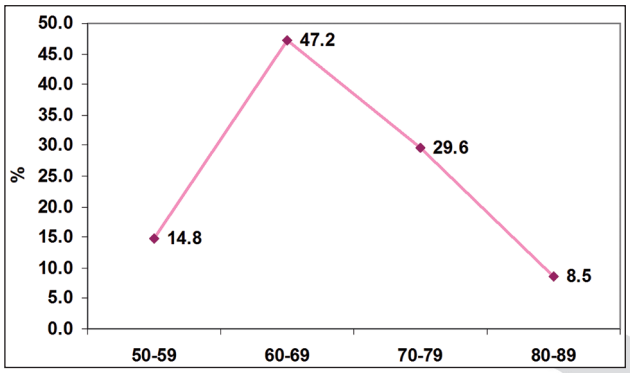

Figure 1. Structure of patients according to the age group

Table 2. Patients according to the concentration of PSA values

PSA values	N	%
<4. 1 ng/ml	1030	72. 5
4. 1-10 ng/ml	360	25. 4
>10 ng/ml	30	2. 1
Total	**1420**	**100. 0**

In our clinical material, most patients - 1030 of them, or 72. 5% had serum PSA concentration below 4. 1 ng / ml, 360 or 25. 4% of 4. 1-10 ng / ml ie belong gray zone (Table 2 and Graf. 2).

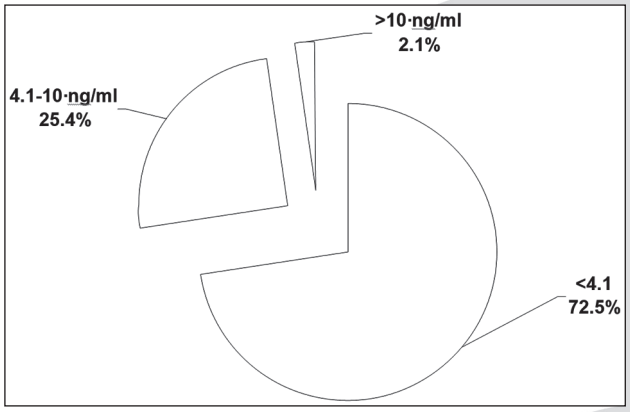

Figure 2. Structure of patients belonging to the "gray zone"

Table 3. Values of PSA and prostate volume in "gray zone" patients

PSA Values	Volume of prostate cm3		T-test p-value
	Mean	SD	
<4. 1 ng/ml n=1030	36. 9	8. 2	t=4. 328 p<0. 0001
4. 1-10 ng/ml n=360	44. 6	11. 6	

Table 3. The average prostate volume of gray zone patients and patients with PSA concentration <4. 1 ng / ml. The average prostate volume for gray zone patients was 44. 6 cm3 (standard deviation ± 11. 6 cm3), while the average prostate volume patients with PSA values <4. 1ng / ml was 36. 9 cm3 (standard deviation ± 8. 2 cm3). T-test obtained a distinction with a high statistical significance between prostate volume of the two groups (t = 4328, p <0. 0001).

Table 4. PSA values and age in "gray zone" patients

PSA Values	Age Years		T-test p-value
	Mean	SD	
<4. 1 ng/ml n=1030	66. 00	8. 00	t=3. 329 p=0. 001
4. 1-10 ng/ml n=360	71. 00	7. 00	

Table 4 shows the average age of gray zone patients and patients with PSA concentration <4. 1 n g / ml. The average age of gray zone patients was 71. 00 years (± standard deviation 7: 00 years), whereas the average age of patients with PSA values <4. 1ng / ml was 66. 00 years (standard deviation ± 8: 00 years). With T-test it is shown a distinction with high statistical age significance between patients in both groups (t = 3329, p <0: 01).

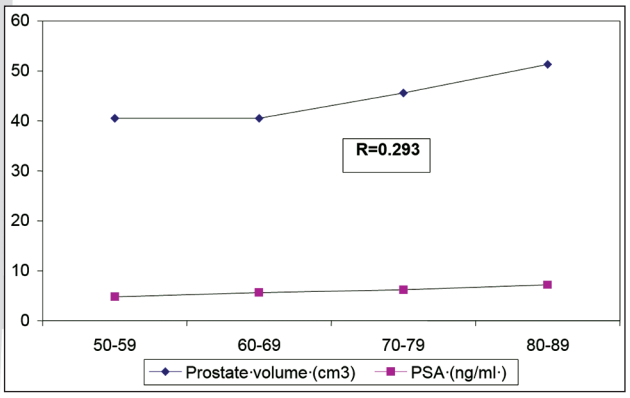

Figure 3. Correlation between age, prostate volume and PSA value to gray zone patients

In "gray zone" patients using a MULTIPEL correlation a positive correlation of a low level (r = 0, 293) between age, prostate volume and serum PSA values was gained. I. e. by aging – prostate and serum PSA levels increase.

Table 5. Average prostate volumes and average values of serum PSA of gray zone patients

Age group	N	%	Volume of prostate (cm3)	PSA (ng/ml)
50-59	20	5. 6	40. 5	4. 8
60-69	100	27. 8	40. 5	5. 6
70-79	200	55. 6	45. 6	6. 2
80-89	40	11. 1	51. 3	7. 2
Total	**360**	100. 0	**44. 6**	**5. 9**

Discussion

Despite the fact that PSA today is considered the leading tumor marker in prostate cancer detection, it is still far away as being an ideal tumor marker. Ideal tumor markers should be strongly specific to prostate cancer and negative to other diseases (7. 11). in the present study, PSA does not fulfill this condition. PSA also is not very sensitive, from the fact that 38% to 48% of patients with intra-prostatic cancer have normal PSA values. Despite these shortcomings PSA is still considered the main tumor marker tool in prostate carcinoma detection (7, 9, 11).

PSA is strongly correlated with prostate volume and age in patients with BPH. It is proven that at the age of 60, the incidence of BPH is around 60%, whereas in the eighth decade approximately in 95. 5% of men BPH is present (7. 11).

Increased serum PSA values except BPH and prostate cancer also affects many other factors such as urethral catheterization, acute prostate inflammation, AUR (acute urinary retention) , then endourologic interventions such as cystoscopy, TUR of prostate, and prostate biopsy (4). A correlation between AUR and PSA was determined in patients with chronic prostate inflammation (4).

PSA level above 4ng/ml were detected in 64% of AUR patients and 38% in patients without AUR. Mean PSA levels in patients with chronic prostate inflammation in AUR was 7. 75 ng / ml while in patients without AUR was 5. 32 ng /ml (4).

Nadler and colleagues also suggested that prostate chronic inflammation increased PSA levels and these data were more compatible with other authors results such as Iran and colleagues who also demonstrated that inflammation in the prostate biopsy has significantly increased PSA levels as a result of damaged glandular epithelium (4).

Damage to the integrity of the prostate gland from inflammation may be the main cause of increased PSA values in the group with AUR (acute urinary retention).

Every pathology that damages the prostate glands leads to distribution of prostate intraluminal secretion through stromal vascular structures and thus increases serum PSA levels. For that particular reason we suggest that prostate chronic inflammation seems to play a very important role in patients with AUR as a result of BPH and consequently increases PSA serum levels (4).

Conclusions

The data confirms that prostate volume and PSA concentration of serumic PSA have significant correlation and rises with aging among the “grey zone” patients.

References

1. *Vesely S et al. Relationship Between Age, Prostate Volume, Prostatespecific Antigen, Symtome Score and Urofflowmetry in Men with Lower Urinary Tract Symptoms. Scand J Urol Nephrol 2003; 37: 322-328.*

2. *Chung BH, Hong SJ, Cho JS et al. Relationship between serum prostate-specific antigen and prostate volume in Korean men with Benign prostatic hyperplasia: a multicentry study. BJU International 2006; 97: 742-746.*

3. *Hedelin H, Johansson N, Stroberg P. Relationship between benign prostatic hyperplasia and lower urinary tract symptoms and correlation between prostate volume and serum prostatic-specific antigen in clinical routine. Scandinavian Journal of Urology and Nephrology, 2005; 39: 154-159.*

4. *Kefi A, Koseoglu H, Celebi et al. Relation between acute urinary retention, chronic prostatic inflammation and accompanying elevated prostate-specific antigen. Scandinavian Journal of Urology and Nephrology, 2006; 40: 155-160.*

5. *Tanagho EA, McAninch JW. Smiths General Urology. USA. Prentice-Hall International. Fourteenth edition. 1998;: 8-11: 410-434.*

6. *Heidennreich A, Aus G, Abbou CC et al. Guidelines on prostate Cancer. EAU, 2007 edition: 9-19.*

7. *Mochtar CA, Kiemeney LA, Van Riemsdijk MM et al. Prostate –specific antigen as an estimator of prostate volume in the management of patients with symptomatic benign prostatic hyperplasia. Eur Urol, 2003 Dec; 44(6): 695-700.*

8. *Marberger MJ, Andersen JT, Nickel JC et al. Prostate volume and serum prostate-specific antigen as predictors of acute urinary retention. Combined experience from three large multinational placebo-controlled trials. EUR urol, 2000 Nov; 38(5): 563-568.*

9. *Roehrborn CG, Boyle P, Gould AL et al. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. Urology, 1999 Mar; 53(3): 581-589.*

10. *Jacobsen SJ, Jacobson DJ, Girman CJ et al. Natural history of prostatism: risk factors for acute urinary retention. J Urol 1997; 158: 481-487.*

11. *Boyle P, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology1996; 48: 398-405.*

12. *Roehrborn CG, Malice M, Cook TJ et al. Clinical predictors of spontaneous acute reteention in men with LUTS and clinical BPH: a comprehensiv analysis of the pooled placebo groups of several large clinical trials. Urology 2001; 58: 210-216.*

13. *Roehrborn CG, Boyle P, Bergner D et al. Serum prostate-specific antigen and prostate volume predict long term changes in symptoms and flow rate; results of four-year, randomized trial compering finasteride versus placebo. PLESS study Group. Urology 1999; 54: 662-669.*

14. *Bo M, Ventura M, Marinello et al. Relationship between prostatic antigen(PSA)and volume of the prostate in benign prostatic hyperplasia in the elderly. Crit Rev Oncol Hematol 2003; 47: 207-211.*

15. *Hochberg DA, Armenakas NA, Fracchia JA. Relationship of prostate-specific antigen and prostate volum in patients with biopsy proven benign prostatic hyperplasia. Eur Urol 2003; 44: 695-700.*

16. *Di Silverio F, Sciarra A, D Eramo G et al. Relationship among age, prostate specific antigen in men with lower urinary tract symptoms(LUTS)and in different groups of men with and without benign and malignant prostate diseases. Prostate 1998; 36: 1-7.*

17. *Jacobson SJ, Jacobson DJ, Girman CJ et al. Natural history of prostatism; risk factors for acute urinary retention. J Urol 1997; 158: 581-487.*

18. *Emberton M, Anson K. Acute urinary retention in men: an age old problem. Br Med J 1999; 318: 921-925.*

19. *Gustafsson O, Mansour E, Norming U. Prostate –specific antigen(PSA), PSA density and age –adjusted PSA reference values in screening for prostate cancer –a study of a randomly selected population of 2. 400 men. Scand J Urol Nephrol 1998; 32: 373-377.*

20. *Anjum I, Ahmed M, Azzopardi A et al. Prostatic ifarcton\infection in acute urinary retention secondary to benign prostatichyperplasia. J Urol 1998; 160: 792-793.*

21. *Nadler RB, Humphrey PA, Smith DS. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. J Urol 1995; 154: 407-413.*

22. *Kessler OJ, Keiseri Y, Servadio C et al. Role of chronic inflammation in the promotion of prostatic hyperplasia in rats. J Urol 1998; 159: 1049-53.*

23. *Hasui Y, Marutsuka K, Asada Y et al. Relationship between serum prostate specific antigen and histological prostatitis in patients with benign prostatic hyperplasia. Prostate 1994; 25: 91-6.*

24. *Powell PH, Smith PJ, Fenely RC. The identification of patients at risk from acute retention. Br J Urol 1980; 52: 520-522.*

25. *Klarskov P, Andersen JT, Asmussen CF et al. Symptoms and signs predictive of the voiding pattern after acute urinary retention in men. Scand J Urol Nephrol 1987; 21: 23-8.*

26. *Kohnen PW, Drach GW. Pattern in inflammation in prostatic hyperplasia: a histologic and bacteriolog study. J Urol 1979; 121: 755-60.*

27. *Irani J, Levillain P, Goujon JM et al. Inflammation in benign prostatic hyperplasia : correlation with prostate specific antigen value. J Urol 1997 ; 157: 1301-3*

28. *Scattoni V, Raber M, Montorsi F et al. Percent of free serum prostate-specific antigen and histological findings in patients undergoing open prostatectomy for benign prostatic hyperplasia. Eur Urol 1999; 36: 621-30.*

29. *Nickel JC, Downey J, Yung I et al. Asymptomatic inflammation and infection in benign prostatic hyperplasia. BJU Int 1999; 84: 976-81.*

30. *Berry SJ, Coffey DS, Walsh PC et al. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132: 474-9.*

31. *Partin AW, Oesterling JE, Epstein JI et al. Influence of age and endocrine factors an the volume of benign prostatic hyperplasia. J Urol 1991; 145: 405-9.*

32. *Collins GN, Lee RJ, McKelvie GB et al. Relationship between prostate specific antigen, prostate volume and age in the benign prostate. Br J Urol 1993; 71: 445-50.*

33. *Uygur MC, Erol D, Cetinkaya M et al. Analysis of prostate –specific antigen values from 4. 846 Turkish men with symptomatic benign prostatic hyperplasia. The correlation between prostate-specific antigen and age. Eur Urol 1997; 32: 416-9.*

34. *Morote J, Encabo G, Lopez M et al. Prediction of prostate volume based on total and free serum prostate-specific antigen: is it reliable? Eur Urol 2000; 38: 91-5.*

35. *Eckhardt MD, Venrooij GE, Boon TA et al. Symptoms and quality of life versus age, prostate volume and urodynamic parameters in 565 strictly selected men with LUTS suggestive of benign prostatic hyperplasia. Urology 2001; 57: 695-700.*

36. *Watanabe H. Natural History of benign prostatic hypertrophy. Ultrasound Med Biol 1986; 12: 567-71.*

37. *Boyle P, Napakov P. Epidemiology of benign prostatic hyperplasia: current perspectives. Eur Urol 1996; 29(Suppl 1): 7-11.*

38. *Abrams P. New words for old: lower urinary tract symptoms for"prostatism". Br Med J 1994; 308: 929-30.*

39. *Abrams P. evalueting lower urinary tract symptoms suggestive of benign prostatic obstruction. Scand J Urol Nephrol Suppl 1999; 203: 1-7.*

40. *Richardson TD, Oesterling JE. Age specific reference ranges for serum prostate-specific antigen. Urol Clin North Am 1997; 24: 339-51.*

41. *Hedelin H, Johansson N, Stroberg P. Uneven quality of referrals for lower urinary tract symptoms in men. Lakartidningen 2003; 100: 1435-7.*

42. *Lepor H, Machi G. Comparison of the AUA symptom index in unselected males and females between 55 and 79 years of age. Urology 1993; 42: 36-40.*

43. *Nickel JC, Effective office management of chronic prostatitis. Urol Clin North Am 1998; 25: 667-84.*

44. *Mehik A, Hellstrom P, Lukkarinen A et al. Epidemiology of prostatitis in Finish Men. BJU Int 2000; 86: 443-8.*

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Carpal tunnel syndrome: A retrospective analysis of 109 patients

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Abstract

Carpal tunnel syndrome occurs as a result of compression of median nerve in wrist. The primary complaints are numbness and pain in hands and fingers. The golden standard method in diagnosing this syndrome, seen more frequent in women, is EMG. Conservative and surgery methods are used in its treatment.

Key words: Carpal Tunnel, Median Nerve, Surgery.

Introduction

Carpal tunnel syndrome (CTS), is a term used to define various findings and symptoms resulting from compression of median nerve in wrist through carpal tunnel. It is the most common entrapment neuropathy of high-field extremity (1, 2). CTS is more common among women doing manual/home related work (3). However, in some studies, the reason of this gap is defined as genetic factors (4). The prevalence of the disease is not exactly known in Turkey, but it is reported that it is about %10 on average in US (5). The diagnosis of CTS can easily be detected through patient's story, results of neurological and electromyography (EMG) (6, 7). In the treatment of the patient, conservative methods such as non-steroid anti-inflammatory drugs and steroid injection into the area of carpal tunnel have been used (8, 9). In surgical treatment, surgical techniques providing compression in median nerve are being used as a result of cut of carpal ligament (10)

In this study, 109 patients operated with CTS diagnosis in our clinic were evaluated retrospectively.

Anatomy

Median nerve consists of the combination of two roots coming out unilateral brachial plexus and medial fasciculus. On the medial side of biceps of arm, it lies down of the arm together with brachial artery and ulnar nerve. Median nerve lies down between palmaris longus muscle beneath the forearm and the tendons of flexor carpi radialis muscle (11, 12). From there, it reaches to wrist by passing into carpal tunnel beneath the retinaculum musculorum flexorum and here it is divided into skin-muscle roots.

Carpal Tunnel is the canal between medial hamate and pisiform bones, and lateral scaphoid and trapezoid bones. Through the canal surrounded by retinaculum musculorum flexorum, median nerve, tendons of flexor pollicis longus and tendons of flexor digitorum superficialis and profundus muscle pass (13, 14). Median nerve provides skin innervation of egde side of the 4th finger and the first 3 fingers close to palm. As a result of decompression loss of sense is observed in these areas. It is typical that loss of sense is not experienced in the middle of the hand in CTS. Because the innervation of this area is provided with palmarkutanos root separated from proximal of retinaculum musculorum flexorum (Figure 1).

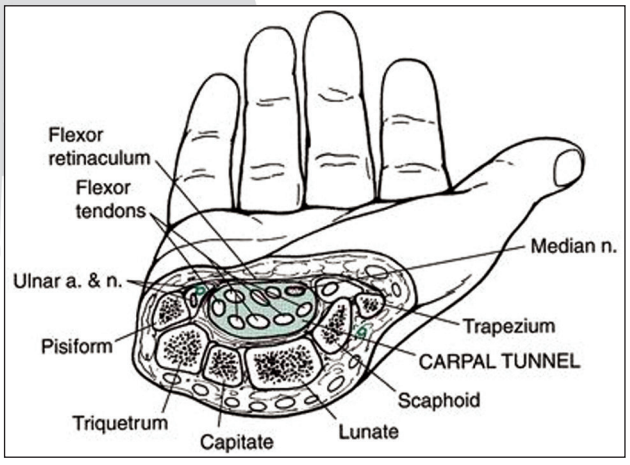

Figure 1. Anatomy of Carpal Tunnel

Materials and Methods

109 patients having been treated with diagnosis of CTS in Dr. Ersin Arslan Public Hospital between the dates 1 June 2014 and 1 June 2015 were examined retrospectively. Age, gender, complaint and neurological findings of the patients, precipitating factors that are effective at the beginning of the illness and surgical complications were evaluated. The prevalence of age, number of men and women and precipitating factors of the patients were searched. Neurologic findings, complaints and developing complications of the patients were classified by calculating the numbers and rates. After surgical operations to the patients, improvement of their complaints and surgical complications was observed about 4 month's period.

Findings

Open (classical) surgery was applied to all patients 13 of whom are male and 96 of whom are female. It was determined that the patients whose ages range from 31 and 70 have median nerve entrapment, 21 of whom are bilateral and 88 of whom are unilateral. It was noticed that median nerve entrapment is more prevalent at the ages between 41 and 60 in both sexes (Table 1). It was understood that though trauma, obesity, diabetes mellitus are among the precipitating factors, the most observed one is to use the hand for labouring works constantly and no precipitating factor was seen in 17 of the patients (Table 2). According to the incidence and prevalence rates, the most common complaints of the patients to polyclinics were subsequently nocturnal paraesthesia, numbness of hands or fingers, pain and loss of strength in fingers. During the neurological examination of the patients, it was determined that the complaints were subsequently positive Tinel's sign at the carpal, positive Phalen test, positive reverse Phalen test, motor deficiency and sense deficiency (Table 3, 4). 90 patients whose post-operation (post-op) observation time is about 4 months experienced no complication, but it was detected that 12 patients suffered from pain in wound area and 7 of them had punctured wounds. During the observation time, the complaints of 84 patients passed, and the complaints of 25 patients lessened but continued (Table 5).

Table 1. Patients' distribution as gender and age

Age	Male	Female	Total
31-40	1	3	4
41-50	5	38	43
51-60	3	25	28
61-70	4	30	34

Table 2. Precipitating factors

Condition	The Number of Patients
Usage of hand in heavy works repetitvely	49
Obesity	20
Diabetes Mellitus	17
Trauma	6
Patients with non-predispozant factor	17

Table 3. The distribution of patients' complaints

Complaint	The Number of Patients
Nocturnal paraesthesia	72
Numbness of hands and fingers	62
Pain in hands and fingers	53
Loss of Strength	49

Table 4. Neurological Examination Findings of patients

Neurological Examination Findings	The Number of Patients
Motor Deficiency	48
Sense Deficiency	36
Positive Carpal Tinel	92
Positive Phalen	85
Positive of reverse Phalen	79

Table 5. Complications occurring after surgery

Complications	The Number of Patients
Pain in wound area	12
Cut in wound area	7
No developing complication	90

Discussion

CTS is an entrapment neuropathy in which many symptoms occur and which results from the decompression of median nerve through carpal tunnel (15). In the development of CTS, there are many factors. However, in some studies carried out, it is stated that an important part of the

incidences is idiopathic or genetic factors play a crucial role (4, 16). In the CTS, the most important precipitating factor is trauma. It is shown in many studies that when the wrist exposes to repetitive traumas, this increases the risk of CTS (17-19). In many patients with CTS, connective tissue is exposed to heavy stress repetitively. It is followed by the compression of median nerve and its ischemia. Continuing ischemia leads to demyelination and axonal loss in median nerve in the final stage. Except trauma, systemic and endocrine diseases are among the precipitating factors. In our study, the most common precipitating factor was the exposure of the hand to repetitive stress with 49 patients in appropriate with the literature. However, not being any precipitating factor in 17 patients differentiates from the literature.

Generally, patients' complaints such as pain, numbness and nocturnal paraesthesia are seen in the areas where median nerve innerves. However, in some studies, it was shown that these complaints exist in the areas where ulnar nerve innerves (20). As to our study, no complaint is detected in the areas where ulnar nerve innerves. Venous stasis in synovium is shown as the reason of nocturnal paraesthesia that is the most prevalence symptom in CTS. Increasing of venous stasis increases nerve compression as well and a pain could occur in a degree which could lead patients to wake up at night.

While patients' neurological examination is performed, positive results of Phalen, reverse Phalen and carpal tinel tests assist for the diagnosis. However, the golden standard method to diagnose CTS is electromyography (EMG). The earliest and the most crucial finding in EMG is that the period of emotional latency lengthens. Abnormality of motor latency appears in later periods (13, 15). Since Cervical Radiculopathy is the most confusing pathology with CTS, it must primarily be remembered in determining diagnosis. In Cervical Radiculopathy, the decrease of pain while resting, being dermatome in loss of pain and sense help to distinguish itself from CTS. Except Radiculopathy, it should be considered that there are pathology of the peripheral nerve system, first carpometacarpal joint osteoarthritis, trigger finger and De Quervain tenosynovitis (16, 21).

CTS treatment is divided into two groups as conservative and surgical. In conservative treatment, non-steroid anti-inflammatory drugs, hand-wrist split and steroid injections have been used. Surgical treatment is more prevalent in the incidences where median nerve denervation findings exists or conservative treatment failed to treat (22). Surgical treatment could be performed as endoscopic and open surgery (23). In both surgical methods, the aim is to eliminate the compression on median nerve by cutting transverse carpal ligament (13). However, open surgery method is still acknowledged as a golden standard. In our study, open surgery operation was performed in all patients. We think one of the reasons of finishing the complaints of 84 patients and decreasing complaints of 25 patients is that open surgery is chosen by us.

Result

We explained our experiences about the post-op complications, precipitating factors, neurological examination, complaint, gender and age of 109 patients with CTS. We are of the opinion that CTS patients would be beneficial to assess the treatment methods and diagnosis.

References

1. *Jablecki CK, Andary MT, So YT, Wilkins DE, Williams FH. Literature review of the usefulness of nerve conduction studies and electromyography for the evaluation of patients with carpal tunnel syndrome. AAEM Quality Assurance Committee. Muscle Nerve, 1993; 16: 1392-414.*

2. *Beek AL. Management of Nerve Compression Syndromes and Painful Neuromas. InMcCarthy JG (ed). PlasticSurgery. Philadelphia: W.B. SaundresCompany, 1990; 4817-46.*

3. *Palmer KT, Harris EC, Coggon D. Carpal tunnel syndrome and its relation to occupation: a systematic literature review. Occup Med, 2007; 57: 57-66.*

4. *Hakim AJ, Cherkas L, El Zayat S, Mac Gregor AJ, Spector TD. The genetic contribution to carpal tunnel syndrome in women: At win study. Arthritis Rheum, 2002; 47: 275-9.*

5. *Nordstorm DL, Vierkant RA, DeStefano F, Layde PM. Risk factors for carpal tunnel syndrome in a general population. Occup Environ Med, 1997; 54(10): 734-40.*

6. *Shapiro S. Microsurgical carpal tunnel release. Neurosurgery, 1995; 37: 66-70.*

7. *Phalen GS. Spontaneous compression of the median nerve at the wrist. JAMA, 1951; 145: 1128-1133*

8. *Burke DT, Burke MM, Stewart GW, Cambre A. Splinting for carpal tunnel syndrome: Insearch of the optimal angle. Arch Phys Med Rehabil, 1994; 75: 1241-1244.*

9. *Harter BT, Mckierman JE, Kirzinger SS, Archer FW, Peters CK, Harter KC. Carpal tunnel syndrome: surgical and nonsurgical treatment. J Hand Surg, 1993; 18A: 734-739.*

10. *Phalen GS. The Carpal-tunnel syndrome: clinical evaluation of 598 hand. Clin Orthop, 1972; 83: 29-40.*

11. *Kline DG, Hudson AR, Kim DH. Atlas of Peripheral Nerve Surgery. W.B. Sunders Company, 2001.*

12. *Moore KL, Agur AMR, Elhan A. (Translation Editor) Basic Clinical Anatomy. Second Edition. Ankara, 2006.*

13. *Greenberg MS. Handbook of Neurosurgery; 3rd ed. Florida: Greenberg Graphics, 1994.*

14. *Frank H. Netter. Atlas of Human Anatomy, Paperback2nd ed. 1997.*

15. *Werner RA, Andary M. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. Clin Neurophysiol, 2002; 113: 1370-81.*

16. *Preston DC, Shaprio BE. Median neuropathy. Electromyography and Neuromuscular Disorders Clinical Electrophysiologic Correlations. Boston: Butterworth-Heinemann, 1998; 235-64.*

17. *Pelmear PL, Taylor W. Hand-arm vibration syndrome. J Fam Pract, 1994; 38: 180-8.*

18. *Franzblau A, et al. Medical screening of office workers for upper extremity cumulative disorders. Arch of Environ Health, 1993; 48: 164-72.*

19. *Bekkelund SI, Pierre-Jerome C, Torbergsen T, Ingerbirigtsen T. Impact of occupational variables in carpal tunnel syndrome. Acta Neurol Scand, 2001; 103: 193-7.*

20. *Stevens JC, et al. Symptoms of 100 patients with electromyographicaly verified carpal tunnel syndrome. Muscle Nerve, 1999; 22: 1448-56.*

21. *Chuinard RG. The upper extremity: elbow, forearm, wrist and hand. In: D'Ambrosia RD (eds). Musculoskeletal Disorders. Philadelphia: Lippincot, 1986; 395-446.*

22. *Szabo RM. Entrapment and Compression Neuropathies. In: Green DP, Hotchkiss RN, Pederson WC (eds). Green's Operative Hand Surgery. Philadelphia: Churchill Livingstone Company, 1999; 1404-22.*

23. *Cokluk C, Senel A, Iyigun O, Celik F, Rakunt C. Open median nerve release using double mini skin incision in patients with carpal tunnel syndrome: technique and clinical results. Neurol Med Chir (Tokyo), 2003; 43: 465-8.*

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Extracerebral And Spinal Cord Relapses of Lymphomatosis Cerebri: A Case Report

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Abstract

Background: Primary central nervous system lymphoma (PCNSL) is a rare malignant tumor. Extracerebral and Spinal Cord relapses of PCNSL is extremely rare and no one report the clinical features of the disease to date.

Case presentation: A 46-year-old woman presented with a 5-days history of progressive weakness of lower limbs and 1-day history of repeated seizures. Based on clinical manifestations and the results of computed tomography (CT), magnetic resonance imaging (MRI), and cytology examination, a clinical diagnosis of primary central nervous system lymphoma was made. After radiotherapy, the tumor partial disappearance was noted on repeat brain MRI. Two month later, a relapse of tumor at brain and spinal cord was diagnosed by brain biopsy and fludeoxyglucose F 18 positron emission tomography/computed tomography (18-FDG PET/CT) .Six months later, the second relapse of tumor at left chest wall was noted on chest CT examination, which completely disappeared after chemotherapy. Two years later, the third relapse of tumor in the left shoulder was confirmed by cytology and 18-FDG PET/CT examination. A final differential diagnosis of diffuse large B-cell lymphoma was made. The patient again received chemotherapy and she has been alive for 42 months, and she is still alive.

Conclusion: The sites of relapse of PCNSL can be central nervous system(CNS) and extracerebral, and extracerebral relapse may be caused by cerebrospinal fluid.

Keywords: Extracerebral Relapse, Lymphomatosis Cerebri, Spinal Cord, Primary central nervous system lymphoma.

Introduction

Primary central nervous system (CNS) lymphoma (PCNSL) is an aggressive brain tumor, representing 4% of intracranial neoplasms and 4-6% of extranodal lymphomas with an yearly incidence of 0-5 cases per 100,000 people [1, 2]. Its outcome remains unsatisfactory with a survival of less than 20–30% at 5years and a median survival of 10–20 months[3]. PCNSL exclusively occurs in the CNS. It typically manifests as an intracranial mass lesion with generalized symptoms such as headache, confusion, lethargy, and hemiparesis. B symptoms are rarely reported [4]. About 60% of the patients with PCNSL are found to have a single lesion and it can be located in the hemispheres (38%), thalamus/basal ganglia (16%), corpus callosum (14%), periventricular region (12%), and cerebellum (9%)[5]. PCNSL tends to infiltrate the subependymal tissues and disseminates through the cerebrospinal fluid (CSF) to the meninges. However, only a few literature reports are concerned with the spinal cord and extracerebral relapse of PCNSL. In this case report, a primary CNS lymphoma relapsed in these sites of a female patient was described.

Case presentation

A 46-year-old woman was presented with a 5-day history of progressive weakness of lower limbs and 1-day history of repeated seizures on February 1, 2012. She has a good health and no chronic disease. Brain magnetic resonance imaging (MRI) scan showed diffuse hyperintense lesions in the bilateral ventricle, corpus callosum, bilateral basal ganglia, thalamus, midbrain and brainstem on fluid-attenuated inversion recovery

(FLAIR) images with gadolinium contrast enhancement, through the analysis of the magnetic resonance angiography (MRA), MR spectroscopy (MRS), prompt cerebral lesions for the possibility of a tumor (Figure 1). The patient was transferred to the intensive care unit of department of internal medicine due to worsening of illness. Large doses of steroids and diazepam were administered. The seizures were terminated; however, the patient was moved to coma. A cytology examination of CSF showed 90% lymphocytes count, however, no tumor cell was detected on repeated cytology. Chest CT, abdominal ultrasound, bone marrow cytology did not find anything abnormal. On considering the patient's illness and clinical manifestations, a suspicion of CNS lymphoma was made. A whole brain irradiation was performed, then the symptoms gradually disappeared with radiotherapy. The lesions were found partially to have disappeared with the repeat gadolinium-enhanced MRI scan. However, she subsequently developed lower limbs paralysis on both sides and urinary retention on April 13, 2012. A spinal cord MRI scan showed a hyperintense lesion on gadolinium-enhanced T2-weighted images. A repeat brain MRI scan showed little lesions compared to previous MRI scan findings (Figure 2), but MRI showed the spinal cord lesions (Figure 3a). Brain biopsy of the gadolinium-enhancing lesion around the left lateral ventricle was performed, pathology and immunohistochemistry showed B-cell lymphoma. Immunohistochemistry findings were positive for CD20, LCA, PAX5, Ki67, (40%) (Figure 3b), negative for CD3, CD43, CD68, CD53. 18-FDG PET/CT showed the brain and spinal cord lesion with high metabolism. The patient received multiple cycles of intrathecal chemotherapy with methotrexate and high dose methotrexate (3-5g) systemic chemotherapy. The function of lower limbs and voiding function recovered gradually after chemotherapy. A spinal cord MRI showed complete disappearance of the lesion (Figure 4). On November 1, 2012, the patient was presented with a left anterior chest wall swelling. A CT scan of the chest showed soft tissue mass in the left anterior chest wall subpectorally (Figure 5). A percutaneous biopsy was performed and no tumor cells were found. However, the patient received one cycle of chemotherapy with CHOP. The tumor disappeared, and then the patient subsequently received multiple cycles of chemotherapy (R-ESHAP, RHyperCVAD-B). A complete remission was achieved after one year (Figure 6), and chemotherapy was stopped in july 2013. In November 2014, a follow-up PET/CT scan showed multiple nodules and inflammatory lesions on the left shoulder (Figure 7). A pathological and immunohistochemical examination of shoulder biopsy specimen revealed diffuse large B-cell lymphoma Immunohistochemistry findings were strongly positive for CD20, CD79a, Bcl-2, Ki67(70%), weekly positive for CD3, CD45RO, CD10. (Figure 8). The nodules disappeared after one cycle of R-CHOP chemotherapy. Then the patient refused to continue chemotherapy. She was a major side effect of chemotherapy for severe bone marrow suppression and infection, and there was no obvious long-term complication. She was still alive and healthy.

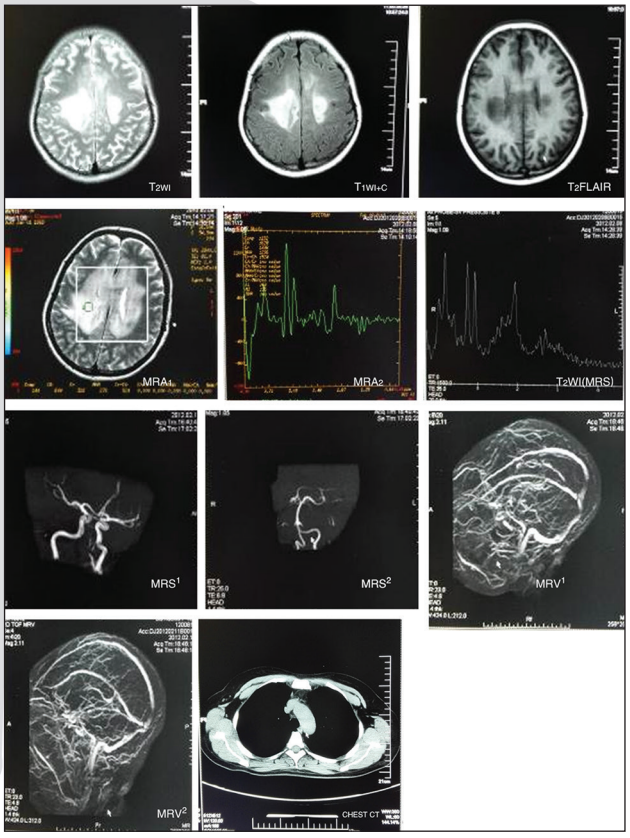

Figure 1. A magnetic resonance imaging of brain, a magnetic resonance angiography of brain blood vessels, brain wave magnetic resonance spectrum examination, and chest CT

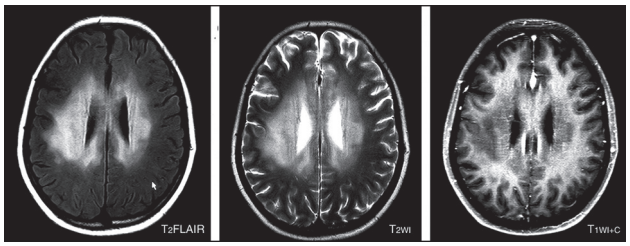

Figure 2. Disappearance of brain tumor after radiotherapy in magnetic resonance imaging

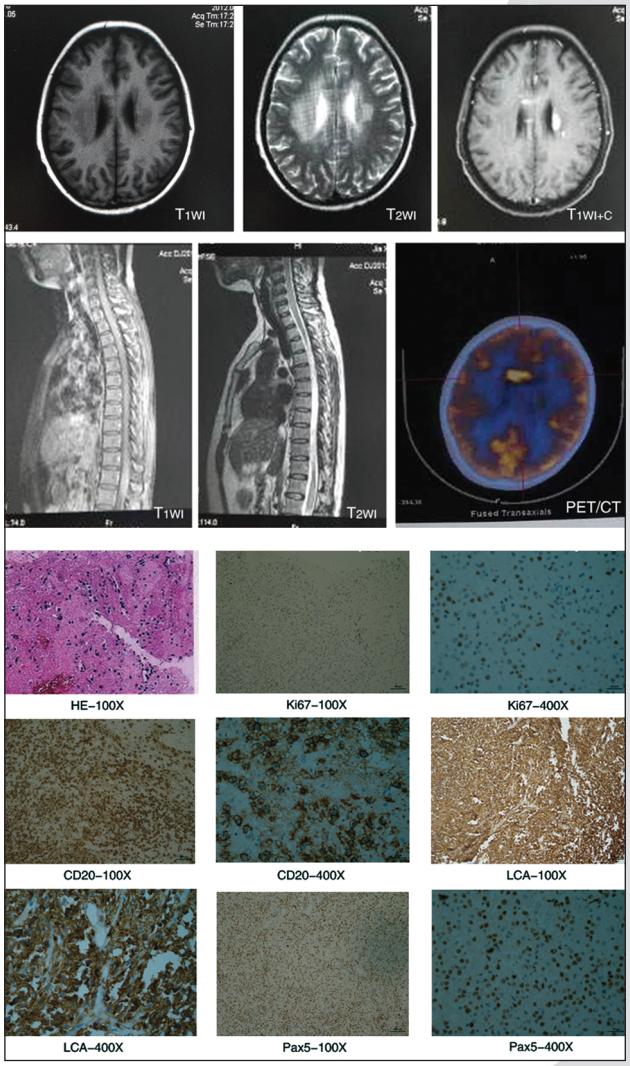

Figure 3. A spinal cord magnetic resonance imaging scan showed lesions at 12th thoracic and 1st lumbar regions and the immunohistochemical examination of brain tissues was positive for CD20, LCA, PAX5, Ki67, (40%), negative for CD3, CD43, CD68, CD53, and the diagnosis of B-cell lymphoma was made .

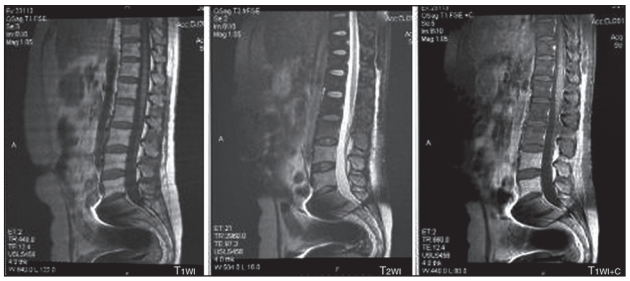

Figure 4. A spinal cord magnetic resonance imaging scan showed disappearance of thoracolumbar lesions

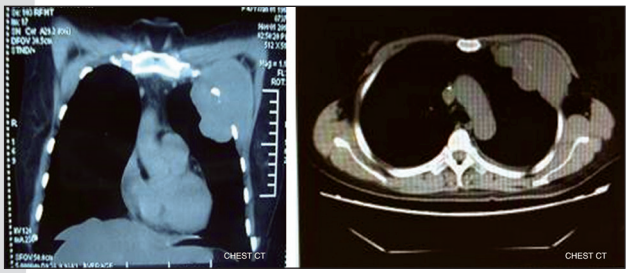

Figure 5. A chest computed tomography scan showed a soft tissue mass in the chest wall

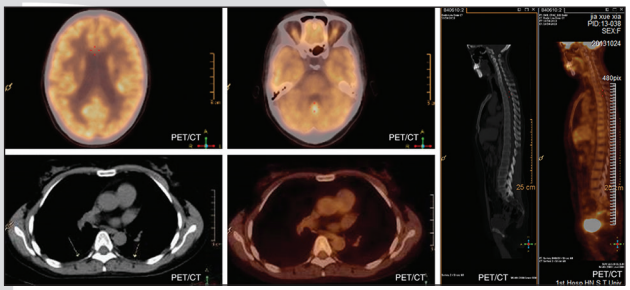

Figure 6. A positron emission tomography/computed tomography scan showed complete remission

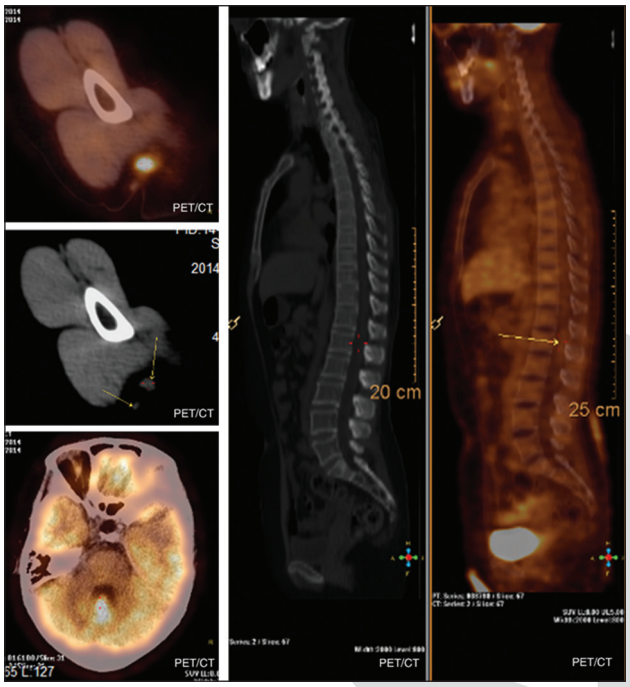

Figure 7. A positron emission tomography/computed tomography scan showed multiple nodules in the left shoulder

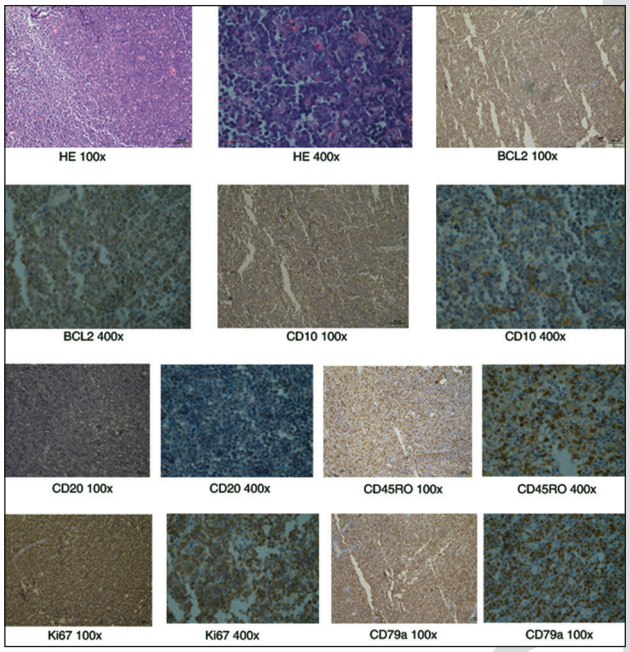

Figure 8. An immunohistochemical examination of left shoulder skin biopsy specimen showed diffuse large B-cell lymphoma, Immunohistochemistry findings were strongly positive for CD20, CD79a, Bcl-2, Ki67(70%), weekly positive for CD3, CD45RO, CD10

Conclusions

PCNSL is usually confined to the CNS at the time of diagnosis and relapse occurs mainly within the CNS. PCNSL is mostly locally relapsed with rare systemic spread. For instance, 6 out of 143 patients (4.2%) and 10 out of 209 patients with PCNSL were found to have systemic relapse from Jahnke et al. and Sawyna Provencher et al. studies, respectively [6, 7]. The primary sites of relapse included lymph nodes, musculoskeletal system, testis, bone marrow, kidney, adrenal glands, and liver. Some patients were found to have relapse in more than one site. In this case report, the patient had relapse in spinal cord, chest wall and left shoulder skin. At first, the pathological findings were negative for systemic relapse; however, the chest CT scan results and the sensitivity to chemotherapy confirmed the differential diagnosis of relapse in extracerebral. Two reasons may explain this phenomenon: 1) the pathological findings of chest wall specimen were negative for tumor cells which may be because of latent stage of the disease; 2) lymphoma cells can relapse through outward invasion in an unknown fashion. No one is yet to confirm which one is right or both, in this case, a slow, gradual invasion of lymphoma cells from the brain tissues to the spinal cord through CSF was apparent, followed by muscular tissue and skin involvement. The case confirm the second kinds of inference are correct.

Consent

The study protocol was approved by the Ethics Committees of the First Affiliated Hospital of Henan University of Science and Technology, Luoyang, and all participants provided written informed consent.

Author contributions

Dianbao Zhang and Xianfen Zhang carried out the studies, participated in collecting data, and drafted the manuscript. C and D performed the statistical analysis and participated in its design. Wengen Gao, Jubao Sun and Huanhuan Tao helped to draft the manuscript. All authors read and approved the final manuscript.

References

1. *Rubenstein J, Ferreri AJ, Pittaluga S. Primary lymphoma of the central nervous system: epidemiology, pathology and current approaches to diagnosis, prognosis and treatment. Leuk Lymphoma. 2008; 49 Suppl 1: 43-51.*

2. *Ferreri AJ, Abrey LE, Blay JY, Borisch B, Hochman J, Neuwelt EA et al. Summary statement on primary central nervous system lymphomas from the Eighth International Conference on Malignant Lymphoma, Lugano, Switzerland, June 12 to 15, 2002. J Clin Oncol. 2003; 21: 2407-14.*

3. *Rubenstein J, Ferreri AJ, Pittaluga S. Primary lymphoma of the central nervous system: epidemiology, pathology and current approaches to diagnosis, prognosis and treatment. Leuk Lymphoma 2008; 49(suppl 1): 43–51.*

4. *Ferreri AJ, Reni M, Pasini F, Calderoni A, Tirelli U, Pivnik A et al. A multicenter study of treatment of primary CNS lymphoma. Neurology. 2002; 58: 1513-20.*

5. *Andrés J.M. Ferreri, MD * , Emerenziana Marturano, MD, Primary CNS lymphoma. Best Practice & Research Clinical Haematology 25 (2012); 119–130.*

6. *Jahnke K, Thiel E, Martus P, Herrlinger U, Weller M, Fischer L et al. Relapse of primary central nervous system lymphoma: clinical features, outcome and prognostic factors. J Neurooncol. 2006; 80: 159-65.*

7. *Provencher S, Ferlay C, Alaoui-Slimani K, Devidas A, Lepretre S, de Prijck B et al. Clinical characteristics and outcome of isolated extracerebral relapses of primary central nervous system lymphoma: a case series. Hematol Oncol. 2011; 29: 10-6.*

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

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Introduction

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Instructions for the authors

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Table 1. Page layout description

Paper size	A4
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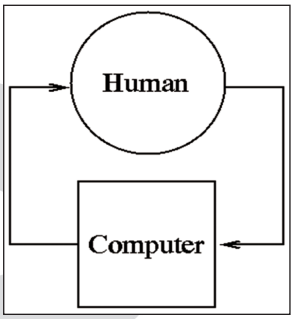

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

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References

1. *Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999; 341: 1284–1291.*
2. *Stewart SM, Lam TH, Beston CL, et al. A Prospective Analysis of Stress and Academic Performance in the first two years of Medical School. Med Educ 1999; 33(4): 243- 50.*

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