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Original article

Development and Validation of the Organ Donation Attitudes Scale in Kazakhstan

Aidos Bolatov [1], Aruzhan Asanova [2], Gulnur Daniyarova [3], Vitaliy Sazonov [4], Aigerim Abdiorazova [5], Yuriy Pya [6]

[1] *PhD-student at Shenzhen University, Shenzhen, China; Researcher at University Medical Center, Astana, Kazakhstan. E-mail: bolatovaidos@gmail.com*
[2] *General manager of the Department of Science, University Medical Center, Astana, Kazakhstan. E-mail: asanova.aruzhan@umc.org.kz*
[3] *Academic secretary of the University Medical Center, Astana, Kazakhstan. E-mail: daniyarova.g@umc.org.kz*
[4] *Researcher at University Medical Center, Astana, Kazakhstan. E-mail: dr.sazonov@gmail.com*
[5] *Deputy Chairman of the Board, University Medical Center, Astana, Kazakhstan. E-mail: a.aigerim@umc.org.kz*
[7] *Chairman of the Board, University Medical Center, Astana, Kazakhstan. E-mail: yuriy.pya@umc.org.kz*

Abstract

Objective: *The Organ Donation Attitudes Scale (ODAS) was developed to assess public attitudes toward organ donation in Kazakhstan. Given the bilingual nature of the country, the aim of the study was to design and validate ODAS in both Kazakh and Russian languages.*

Methods. *The study employed a cross-sectional design, with participants recruited from various regions of Kazakhstan. The scale was developed through a combination of literature review, expert consultation, and cognitive interviewing. The psychometric properties of the ODAS were evaluated through Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) to confirm the factor structure. Internal consistency, test-retest reliability, and criterion-related validity were also assessed. ROC curve analysis was used to evaluate the predictive validity of the scale with regard to participants' willingness to donate organs.*

Results. *The EFA revealed a two-factor structure for both the Kazakh (K-ODAS) and Russian (R-ODAS) versions, which was confirmed by CFA. The KMO values were 0.928 for K-ODAS and 0.904 for R-ODAS, with Bartlett's test of sphericity significant at $p<0.001$ for both versions. Cronbach's alpha indicated high internal consistency for both K-ODAS (0.924) and R-ODAS (0.900) after adjustments. Test-retest reliability showed an ICC of 0.907, indicating stability over time. Criterion-related validity was supported by significant correlations between ODAS scores and external variables such as knowledge and willingness to donate organs. The ROC curve analysis further demonstrated the scale's predictive validity.*

Conclusion. *The ODAS is a reliable and valid tool for assessing attitudes toward organ donation in Kazakhstan. Its development in both Kazakh and Russian languages ensures its applicability across the country's diverse population. The scale's robust psychometric properties make it a valuable resource for healthcare professionals and policymakers aiming to promote organ donation.*

Keywords: *organ donation, attitudes, scale development, scale validation, Kazakhstan.*

Corresponding author: Aidos Bolatov, researcher, University Medical Center, Astana, Kazakhstan
Postal code: Z05P3Y4
Address: Kazakhstan, Astana, Kerey-Zhanibek khandar str, 5/1
Phone: +77776000096
E-mail: bolatovaidos@gmail.com

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Introduction

Organ donation is a critical component of modern healthcare systems, offering a lifeline to individuals with end-stage organ failure. As of May 10, 2024, the national waiting list for organ transplants in Kazakhstan comprises a total of 4,099 patients, reflecting the growing demand for life-saving organs. The majority of these patients are awaiting kidney transplants, with 3,661 adults and 85 children on the list. The need for liver transplants is also substantial, with 179 adults and 10 children awaiting a suitable donor. Additionally, there are 18 adults on the waiting list for lung transplants, although no children are currently listed. For heart transplants, 136 adults and 5 children are in need, while the heart-lung transplant list includes 2 adults and 3 children [1].

Organ donation represents a unique intersection of medical science, ethics, and cultural beliefs, where individual decisions can significantly impact broader societal outcomes [2]. Despite its life-saving potential, organ donation often encounters barriers rooted in personal, cultural, and religious beliefs, as well as concerns about the fairness and ethics of the medical system [3].

In Kazakhstan, a country with a rich cultural and religious diversity, these factors are particularly relevant. Understanding public attitudes toward organ donation is essential for developing strategies to increase donor rates and improve the overall effectiveness of the transplantation system [4]. Previous research indicates that positive attitudes towards organ donation are strongly associated with a higher likelihood of consenting to donation [5]. However, attitudes are influenced by a variety of factors, including beliefs about the sanctity of the body, trust in the medical system, and the perceived social value of donation [6].

The Organ Donation Attitudes Scale (ODAS) was developed to capture the complex and multifaceted perspectives on organ donation in Kazakhstan. This scale encompasses a broad range of factors that influence attitudes, including personal beliefs, societal values, and ethical considerations. It reflects the importance of recognizing organ donation as a life-saving act, which aligns with the widely supported notion that organ donation is a vital contribution to society [7].

Cultural and religious beliefs are also integral to shaping these attitudes, highlighting the need to consider how these influences can affect individuals' willingness to donate [8-10]. Trust in the medical system is another crucial factor, as confidence in ethical practices within the healthcare system is essential for fostering a supportive environment for organ donation [11, 12].

Family dynamics play a significant role in shaping organ donation attitudes, particularly in terms of comfort in discussing donation with loved ones and the likelihood of encouraging family members to consider becoming donors. These interpersonal discussions are critical in shaping donation decisions [13, 14].

Finally, concerns about the fairness of the organ allocation process are acknowledged as they significantly impact public trust and the overall willingness to participate in organ donation [15]. This scale aims to provide a comprehensive understanding of the various factors that contribute to the attitudes toward organ donation in Kazakhstan.

In summary, the ODAS aims to provide a comprehensive assessment of attitudes toward organ donation in Kazakhstan, taking into account the complex interplay of individual beliefs, cultural and religious factors, and trust in the healthcare system. By understanding these attitudes, policymakers and healthcare providers can develop targeted interventions to increase organ donation rates and improve the overall effectiveness of the transplantation system in Kazakhstan.

Material and methods

Study design. This study employed a cross-sectional design to develop and validate the Organ Donation Attitudes Scale (ODAS) in Kazakhstan. The scale was designed to measure attitudes towards organ donation among the general population, with versions available in both Kazakh and Russian languages. The study was conducted in two phases: the initial development of the scale, followed by its psychometric validation. Data were collected through self-administered questionnaires distributed to a representative sample across different regions of Kazakhstan, ensuring coverage of diverse demographic groups.

Scale development. The ODAS was developed to assess the attitudes towards organ donation among the population in Kazakhstan. The scale was designed to be applicable in both Kazakh (K-ODAS) and Russian (R-ODAS) languages to accommodate the bilingual nature of the population. The initial items for the scale were generated through a comprehensive literature review of existing organ donation attitude scales [16-20] and interviews with subject matter experts, including healthcare professionals and social psychologists. This process ensured that the items were culturally relevant and reflective of the local context. The generated items were then translated into both Kazakh and Russian, following the guidelines for cross-cultural translation and adaptation of self-report measures.

A preliminary version of the scale was pre-tested on a small sample (N=19) of bilingual participants to evaluate the clarity, cultural relevance, and understanding of the items in both languages. Cognitive interviewing techniques were used to gain insights into how respondents interpreted each item. Based on the feedback, minor revisions were made to the wording of certain items to enhance clarity and cultural appropriateness.

Sample and Data Collection. The study sample consisted of 1294 participants from different regions of Kazakhstan, representing diverse demographic backgrounds; among them 675 participants were Kazakh-speaking and 619 Russian-speaking. Data collection was conducted through self-administered questionnaires created in Google Forms platform. Participants were provided with either the Kazakh or Russian version of the ODAS, depending on their language preference.

Scale validation. The validation of the Kazakh- and Russian-language ODAS was conducted through a series of statistical analyses to ensure its reliability and validity. The process involved evaluating the test-retest reliability, internal consistency, construct validity, and criterion-related validity of the scale.

Test-retest reliability was assessed to determine the stability of the ODAS over time. A subsample of participants (N=19) was selected for this purpose. These participants completed the ODAS at two different time points, with a three-week interval between administrations. The intraclass correlation coefficient (ICC) was calculated to assess the

degree of agreement between the two sets of scores. An ICC value of 0.75 or higher was considered indicative of acceptable test-retest reliability [21].

Internal consistency of the ODAS was evaluated using Cronbach's alpha. This analysis was performed separately for the Kazakh and Russian versions of the scale to ensure that each version reliably measures the underlying construct. Cronbach's alpha values of 0.70 or higher were considered to indicate good internal consistency [22]. Additionally, item-total correlations were examined to identify any items that might reduce the overall reliability of the scale.

Construct validity was assessed through exploratory factor analysis (EFA) followed by confirmatory factor analysis (CFA). EFA was conducted using minimum residuals extraction with Promax rotation to identify the underlying factor structure of the scale. The number of factors retained was determined based on eigenvalues greater than 1.0 and the scree plot. The suitability of the data for factor analysis was assessed using the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity.

Following EFA, CFA was performed on a separate sample to confirm the factor structure identified. Model fit was evaluated using the Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA), with CFI and TLI values of 0.90 or higher and RMSEA values of 0.08 or lower indicating an acceptable fit [23].

Criterion-related validity was examined by correlating ODAS scores with external criteria that are theoretically related to attitudes towards organ donation. These criteria included measures of knowledge and willingness to organ donation. Pearson correlation coefficients were calculated to determine the strength and direction of these relationships. Significant correlations in the expected directions would support the criterion-related validity of the ODAS.

ROC curve analysis was employed to assess the predictive validity of the ODAS in relation to participants' willingness to be organ donors. Willingness was originally measured on a 5-point Likert-type agreement scale and subsequently dichotomized into two categories: "Agree" (those who expressed willingness) and "Disagree" (those who did not).

Data analysis. Data were analyzed using Jamovi software (version 2.2.5). Descriptive statistics, including means, standard deviations, and percentages, were calculated for all variables. Prior to conducting inferential analyses, the normality of the data was assessed using the Shapiro-Wilk test, and the homogeneity of variance was evaluated using Levene's test. For group comparisons, Chi-square tests were used for categorical variables, and t-tests were employed for continuous variables when the assumptions of normality and homogeneity of variance were met. In cases where these assumptions were violated, appropriate non-parametric alternatives, such as the Mann-Whitney U test, were utilized. The level of statistical significance adopted was 5% ($p<0.05$).

Ethical Considerations. The study was approved by the Local Bioethics Commission of the "University Medical Center" Corporate Fund (Protocol No. 3 dated July 14, 2023). Informed consent was obtained from all participants before data collection, and they were assured of the confidentiality and anonymity of their responses.

Results

The study included two sets of participants: those who primarily speak Kazakh and those who primarily speak Russian. A total of 1294 participants were recruited, with 675 Kazakh-speaking participants and 619 Russian-speaking participants. The Kazakh-speaking group consisted of 20.6% males, while the Russian-speaking group included 22.9%. The overall gender distribution across both groups was relatively balanced, with 21.7% males and 78.3% females. Participants' ages ranged from [insert age range] years, with a mean age of 36.8±11.5 years. Study participants' socio-demographic data is presented in Table 1.

Table 1- Study population

Variable	Kazakh-speaking (N=675)	Russian-speaking (N=619)	X^2/U-test, p
	n (%) / M±SD		
Gender			
Male	139 (20.6%)	142 (22.9)	1.05, p=0.306
Female	536 (79.4%)	477 (77.1)	
Age	37.5±11.7	36.1±11.2	193818, p=0.025
Occupation			
Student	68 (10.1%)	93 (15.0%)	22.5, p<0.001
Employed	553 (81.9%)	445 (71.9%)	
Self-employed	27 (4.0%)	49 (7.9%)	
Unemployed	13 (1.9%)	22 (3.6%)	
Pensioner	14 (2.1%)	10 (1.6%)	
Profession			
Non-medical	119 (17.6%)	265 (42.8%)	98.1, p<0.001
Medical	556 (82.4%)	354 (57.2%)	
Residence			
Rural	202 (29.9%)	65 (10.5%)	74.4, p<0.001
Urban	473 (70.1%)	554 (89.5%)	

The analysis revealed an ICC of 0.907, with a 95% confidence interval (CI) ranging from 0.764 to 0.964. The F-value was 10.804, with a significance level of $p < 0.001$.

These results indicate a high level of reliability, suggesting that the ODAS produces stable and consistent results over time.

The internal consistency of the Organ Donation Attitudes Scale (ODAS) was evaluated separately for the

Kazakh (K-ODAS) and Russian (R-ODAS) versions of the scale using Cronbach's alpha. The initial analysis revealed that one item (item 8) showed a low item-rest correlation and resulted in a higher value of Cronbach's alpha if the item was dropped (Table 2). For the Kazakh version (K-ODAS), Cronbach's alpha was initially 0.916. After removing the item 8 with low item-rest correlation, the adjusted Cronbach's alpha increased to 0.924, indicating a very high level of internal consistency. Similarly, for the Russian version (R-ODAS), the initial Cronbach's alpha was 0.860. After the removal of the problematic item 8, the adjusted Cronbach's alpha increased to 0.900, reflecting an improvement in the scale's internal consistency. These results suggest that both the K-ODAS and R-ODAS have strong internal consistency, particularly after the adjustment for the identified item. The high Cronbach's alpha values support the reliability of the scale for assessing attitudes toward organ donation in both language groups.

Table 2 - K-ODAS and R-ODAS internal consistency

#	Item	M±SD	IRC	Cronbach's α if item dropped
Kazakh-Organ Donation Attitude Scale				
1	Мен орган донорлығын адам өмірін сақтап қалудың маңызды амалы деп есептеймін *Men organ donorlygyn adam omirin saktap qaludyn manyzdy amaly dep eseptejmin*	3.75±1.05	0.736	0.905
2	Мен қайтыс болғаннан кейін өз органдарымды донорлыққа беру идеясына оң көзқараспен қараймын	3.00±1.38	0.763	0.903
3	Орган донорлығы – қоғам өмірі үшін құнды үлес болып табылады *Men kajtys bolgannan kejin oz organdarymdy donorlykka beru idejasyna on kozkaraspen karajmyn*	3.54±1.13	0.812	0.898
4	Менің діни немесе мәдени сенімдерім бойынша орган донорлығы құпталады *Menin dini nemese madeni senimderim bojynsha organ donorlygy kuptalady*	3.21±1.12	0.767	0.902
5	Мен өз отбасымның мүшелеріне орган донорлығы туралы ойлануды кеңес етер едім *Men oz otbasymnyn myshelerine organ donorlygy turaly ojlanudy kenes eter edim*	3.04±1.18	0.789	0.900
6	Қазақстанның медициналық жүйесінде органдар донорлығы этикалық нормаларға сай қаралатынына сенімдімін *Kazakstannyn medicinalyk zhuesinde organdar donorlygy etikalyk normalarga saj karalatynyna senimdimin*	3.30±1.12	0.748	0.903
7	Мен үшін отбасыммен, достарыммен орган донорлығы тақырыбын талқылау ыңғайлы *Men ushin otbasymmen, dostarymmen organ donorlygy takyrybyn talkylau yngajly*	3.05±1.15	0.724	0.905
8*	Мені Қазақстандағы донорлық органдарды үлестіру әдісінің қаншалықты әділетті екендігі алаңдатады *Meni Kazakstandagy donorlyk organdardy uylestiru ədisinin kanshalykty adiletty ekendigi alandatady*	3.37±1.07	0.469	0.924
Russian-Organ Donation Attitude Scale				
1	Я считаю, что донорство органов – важный способ спасти жизни *Ja schitaju, chto donorstvo organov – vazhnyj sposob spasti zhizni*	4.16±1.00	0.680	0.835
2	Я отношусь положительно к идее пожертвования своих органов после смерти *Ja otnoshus' polozhitel'no k idee pozhertvovanija svoih organov posle smerti*	3.90±1.21	0.794	0.819
3	Донорство органов – ценный вклад в жизнь общества *Donorstvo organov – cennyj vklad v zhizn' obshhestva*	4.16±0.96	0.784	0.825
4	Мои религиозные или культурные убеждения поддерживают донорство органов *Moi religioznye ili kul'turnye ubezhdenija podderzhivajut donorstvo organov*	3.69±1.10	0.702	0.832
5	Я бы посоветовал членам моей семьи подумать о донорстве органов *Ja by posovetoval chlenam moej sem'i podumat' o donorstve organov*	3.51±1.15	0.791	0.820
6	Я верю, что медицинская система Казахстана будет этично относиться к донорству органов *Ja verju, chto medicinskaja sistema Kazahstana budet jetichno otnosit'sja k donorstvu organov*	3.52±1.16	0.587	0.846
7	Мне комфортно обсуждать тему донорства органов со своей семьей и друзьями *Mne komfortno obsuzhdat' temu donorstva organov so svoej sem'ej i druz'jami*	3.53±1.09	0.548	0.850
8*	Меня беспокоит справедливость распределения и распространения органов для донорства в Казахстане *Menja bespokoit spravedlivost' raspredelenija i rasprostranenija organov dlja donorstva v Kazahstane*	3.72±0.99	0.014	0.900
* item was removed from final scale IRC – item-rest correlation				

Exploratory Factor Analysis was conducted to examine the underlying factor structure of the ODAS. The EFA revealed a two-factor structure for both versions of the scale, suggesting that the ODAS captures two distinct dimensions of attitudes towards organ donation (items 1-3 for factor 1 and items 4-7 for factor 2). For the K-ODAS, Bartlett's test of sphericity was highly significant ($p < 0.001$), indicating that the data were suitable for factor analysis. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.928, demonstrating that the sample size was adequate for the factor analysis. Similarly, for the R-ODAS, Bartlett's test of sphericity was also highly significant ($p < 0.001$), with a KMO value of 0.904. These results confirm that the factor structure identified by the EFA is robust and that the data are appropriate for this type of analysis. The two-factor structure identified through EFA underscores the validity of the ODAS in capturing the key components of attitudes towards organ donation across both language groups.

The two-factor structure identified by EFA was further examined using Confirmatory Factor Analysis (CFA). The CFA results confirmed the two-factor model, demonstrating that it provided a better goodness of fit for both the K-ODAS and R-ODAS compared to alternative models (Table 3 and Figure 1). The goodness-of-fit indices indicated that the two-factor structure is robust across both language groups, thus validating the factor structure of the ODAS.

Table 3 - CFA Model Fit Indices

Scale	Model	Exact fit	CFI	TLI	RMSEA	RMSEA 90% CI	
						Lower	Upper
K-ODAS	1-factor	<0.001	0.974	0.962	0.093	0.08	0.11
	2-factor	<0.001	0.988	0.981	0.065	0.05	0.08
R-ODAS	1-factor	<0.001	0.956	0.934	0.114	0.10	0.13
	2-factor	<0.001	0.980	0.968	0.079	0.06	0.10

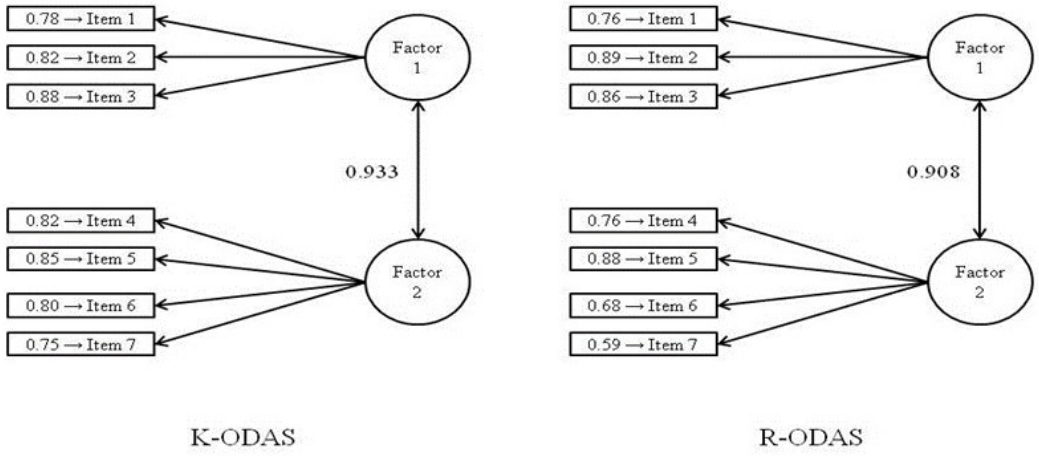

Figure 1 - CFA Model of the K-ODAS and R-ODAS

The criterion-related validity of the scale was assessed by examining its correlation with two key external variables: knowledge of organ donation and willingness to donate organs. These variables were chosen based on their theoretical relevance to attitudes towards organ donation. For both K-ODAS and R-ODAS, significant positive correlations were observed between ODAS scores and participants' knowledge of organ donation. This suggests that individuals with higher knowledge levels tend to have more favorable attitudes towards organ donation. Similarly, significant correlations were found between ODAS scores and participants' willingness to donate organs, indicating that those with more favorable attitudes as measured by the ODAS are more likely to express a willingness to donate (Table 4). These findings support the criterion-related validity of both the K-ODAS and R-ODAS, demonstrating that the scale is effective in predicting related constructs such as knowledge and willingness in the context of organ donation.

Table 4 - Criterion-related validity and ROC-curve analysis

Scale	M±SD	Knowledge on organ donation	Willingness to organ donation	Sensitivity (%)	Specificity (%)	AUC
		Correlation Spearman's rho (p)				
K-ODAS	3.27±0.965	0.529 (<0.001)	0.787 (<0.001)	87.74	80.35	0.910
R-ODAS	3.78±0.869	0.460 (<0.001)	0.831 (<0.001)	82.84	84.34	0.915

The area under the ROC curve (AUC) was calculated to determine the ability of the ODAS to distinguish between participants who were willing and those who were not willing to donate organs. The AUC for the Kazakh version was 0.910, while the AUC for the Russian version was 0.915, indicating good level of accuracy (Table 4, Figure 2). These results suggest that the ODAS is an effective tool for predicting organ donation willingness across both language groups.

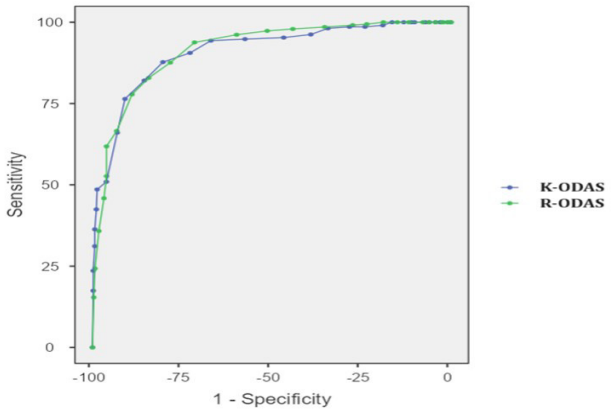

Figure 2 - ROC-curve analysis

Discussion

The development and validation of the Organ Donation Attitudes Scale (ODAS) in both Kazakh (K-ODAS) and Russian (R-ODAS) versions represent a significant step forward in understanding public attitudes towards organ donation in Kazakhstan. The findings of this study provide valuable insights into the psychometric properties of the ODAS and its utility in assessing organ donation attitudes in a culturally diverse population.

The results of the exploratory and confirmatory factor analyses indicate that the ODAS is a robust measure with a stable two-factor structure across both language groups. The high values of the Kaiser-Meyer-Olkin (KMO) measure and the significance of Bartlett's test of sphericity confirm the suitability of the data for factor analysis, with KMO values of 0.928 for K-ODAS and 0.904 for R-ODAS. The confirmation of the two-factor model by CFA suggests that the scale accurately captures the key dimensions of attitudes toward organ donation in both Kazakh and Russian-speaking populations.

The reliability of the ODAS was further supported by strong internal consistency and high test-retest reliability. The Cronbach's alpha values for both K-ODAS (0.916, adjusted to 0.924) and R-ODAS (0.860, adjusted to 0.900) indicate that the scale is consistent and reliable. The test-retest reliability, with an intraclass correlation (ICC) of 0.907, underscores the scale's stability over time.

The criterion-related validity of the ODAS was supported by significant correlations with knowledge of organ donation and willingness to donate organs. These findings are consistent with existing literature, which suggests that individuals who are more knowledgeable about organ donation are also more likely to have favorable attitudes and a higher willingness to donate [24, 25]. The strong correlations observed for both K-ODAS and R-ODAS versions further validate the scale's effectiveness in predicting related constructs, underscoring its utility in assessing organ donation attitudes across different cultural and linguistic groups.

Implications for Practice and Research. The validated ODAS can serve as a valuable tool for healthcare professionals, policymakers, and researchers in Kazakhstan to better understand and address public attitudes towards organ donation. The scale's ability to reliably measure attitudes in both Kazakh and Russian languages ensures its applicability across the diverse population of Kazakhstan. This is particularly important in a multicultural context where language and cultural differences may influence health-related attitudes and behaviors.

Future research could focus on longitudinal studies to assess changes in attitudes over time and the impact of targeted educational interventions. Additionally, exploring the applicability of the ODAS in other Central Asian countries with similar cultural and linguistic contexts could further enhance the generalizability of the findings.

Study limitation. While the findings of this study are promising, there are several limitations that should be acknowledged. The study sample, though representative, may not fully capture the attitudes of all subgroups within the population, particularly those in more remote or underserved areas. Additionally, while the scale demonstrated strong psychometric properties, further validation in different contexts and settings is necessary to fully establish its reliability and validity.

Conclusion

In conclusion, the ODAS is a reliable and valid tool for assessing attitudes towards organ donation in Kazakhstan. Its development and validation in both Kazakh and Russian languages ensure that it can be effectively used across the country's diverse population. The scale's robust psychometric properties, coupled with its strong criterion-related validity, make it a valuable resource for promoting organ donation awareness and understanding public attitudes in Kazakhstan.

Conflict of interest. The authors declare that they have no confict of interest.

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Қазақстандағы орган донорлығына көзқарас шкаласын әзірлеу және валидациялау

Болатов А.К. [1], Асанова А.А. [2], Даниярова Г.Д. [3], Сазонов В.Г. [4], Абдиоразова А.А. [5], Пя Ю.В. [6]

[1] Шэньчжэнь университетінің PhD-студенті, Шэньчжэнь, Қытай; University Medical Center ғылыми қызметкері, Астана, Қазақстан. E-mail: bolatovaidos@gmail.com

[2] Ғылым департаментінің бас менеджері, University Medical Center, Астана, Қазақстан. E-mail: asanova.aruzhan@umc.org.kz

[3] University Medical Center ғылыми хатшысы, Астана, Қазақстан. E-mail: daniyarova.g@umc.org.kz

[4] University Medical Center ғылыми қызметкері, Астана, Қазақстан. E-mail: dr.sazonov@gmail.com

[5] Басқарма төрағасының орынбасары, University Medical Center, Астана, Қазақстан. E-mail: a.aigerim@umc.org.kz

[6] Басқарма төрағасы, University Medical Center, Астана, Қазақстан. E-mail: yuriy.pya@umc.org.kz

Түйіндеме

Зерттеудің мақсаты: Орган Донорлығына Көзқарас Шкаласы (ODAS) Қазақстандағы орган донорлығына деген қоғамдық көзқарасты бағалау үшін әзірленген. Елдің екі тілді сипатын ескере отырып, зерттеудің мақсаты қазақ және орыс тілдерінде ODAS шкаласын әзірлеу және валидациялау болды.

Әдістері. Зерттеу барысында көлденең қима дизайны қолданылды, оған қатысушылар Қазақстанның әртүрлі аймақтарынан қатысты. Шкала әдебиетке шолу, сараптамалық кеңес және танымдық сұхбаттардың жиынтығы арқылы

әзірленді. ODAS шкаласының психометриялық қасиеттері факторлық құрылымды валидтілігін анықтау үшін барлау факторлық талдау (EFA) және растау факторлық талдау (CFA) арқылы бағаланды. Сондай-ақ, ішкі жүйелілік, қайта тестілеудің сенімділігі және критерийлерге байланысты валидтілік бағаланды. ROC қисық сызығын талдау қатысушылардың органдарды донорлыққа беруге дайындығына қатысты шкаланың болжамды негізділігін бағалау үшін пайдаланылды.

Нәтижесі. EFA шкаланың қазақ (K-ODAS) және орыс (R-ODAS) нұсқалары үшін екі факторлы құрылымды анықтады, ол CFA арқылы расталды. KMO мәндері K-ODAS үшін 0,928 және R-ODAS үшін 0,904 болды, Бартлеттің сфералық сынағы екі нұсқа үшін де p<0,001 деңгейінде болды. Кронбахтың альфасы түзетулерден кейін K-ODAS (0,924) және R-ODAS (0,900) үшін де жоғары ішкі құрылымды көрсетті. Тест-қайта тестілеудің сенімділігі ICC 0,907 мәнін көрсетті, бұл шкаланың уақыт өте келе тұрақтылығын көрсетеді. Критерийлерге байланысты валидтілік ODAS ұпайлары мен білім және органдарды донорлыққа даярлығы сияқты сыртқы айнымалылар арасындағы маңызды корреляциялармен расталды. ROC қисығын талдау шкаланың болжамды валидтілігін дәлелдеді.

Қорытынды. ODAS - бұл Қазақстандағы орган донорлығына деген көзқарасты бағалаудың сенімді және жарамды құралы. Оның қазақ және орыс тілдерінде дайындалуы оның елдің әр түрлі тұрғындарына қолданылуын қамтамасыз етеді. Шкаланың сенімді психометриялық қасиеттері оны денсаулық сақтау мамандары мен орган донорлығын ілгерілетуге ұмтылатын саясаткерлер үшін құнды ресурсқа айналдырады.

Түйін сөздер: орган донорлығы, көзқарас, шкала әзірлеу, шкала валидациясы, Қазақстан.

Разработка и валидация шкалы отношения к донорству органов в Казахстане

Болатов А.К. [1], Асанова А.А. [2], Даниярова Г.Д. [3], Сазонов В.Г. [4], Абдиоразова А.А. [5], Пя Ю.В. [6]

[1] PhD-студент Шэньчжэньского университета, Шэньчжэнь, Китай; научный сотрудник University Medical Center, Астана, Казахстан. E-mail: bolatovaidos@gmail.com

[2] Главный менеджер Департамента науки, University Medical Center, Астана, Казахстан. E-mail: asanova.aruzhan@umc.org.kz

[3] Ученый секретарь University Medical Center, Астана, Казахстан. E-mail: daniyarova.g@umc.org.kz

[4] Научный сотрудник University Medical Center, Астана, Казахстан. E-mail: dr.sazonov@gmail.com

[5] Заместитель Председателя Правления University Medical Center, Астана, Казахстан. E-mail: a.aigerim@umc.org.kz

[6] Председатель Правления University Medical Center, Астана, Казахстан. E-mail: yuriy.pya@umc.org.kz

Резюме

Цель исследования: Шкала отношения к донорству органов (ODAS) была разработана для оценки отношения общества к донорству органов в Казахстане. Учитывая двуязычный характер страны, целью исследования было разработать и валидизировать ODAS как на казахском, так и на русском языках.

Методы. В исследовании использовался перекрестный подход, участники были набраны из различных регионов Казахстана. Шкала была разработана на основе анализа литературы, консультаций с экспертами и когнитивного интервью. Психометрические свойства ODAS были оценены с помощью исследовательского факторного анализа (EFA) и подтверждающего факторного анализа (CFA) для подтверждения факторной структуры шкалы. Также были оценены внутренняя согласованность, надежность повторного тестирования и критериальная валидность. Анализ ROC-кривой был использован для оценки прогностической достоверности шкалы в отношении готовности участников пожертвовать органы.

Результаты. EFA выявило двухфакторную структуру как для казахской (K-ODAS), так и для русской (R-ODAS) версий, что было подтверждено CFA. Значения KMO составили 0,928 для K-ODAS и 0,904 для R-ODAS, при этом критерий сферичности по Бартлетту был достоверным при p<0,001 для обоих версий. Альфа Кронбаха после корректировки показала высокую внутреннюю согласованность как для K-ODAS (0,924), так и для R-ODAS (0,900). Коэффициент надежности при повторном тестировании составил 0,907, что указывает на стабильность во времени. Критериальная валидность была подтверждена значительными корреляциями между показателями ODAS и внешними переменными, такими как знания и готовность к донорству органов. Анализ кривой ROC дополнительно продемонстрировал прогностическую валидность шкалы.

Выводы. ODAS - это надежный и валидизированный инструмент для оценки отношения к донорству органов в Казахстане. Его разработка как на казахском, так и на русском языках обеспечивает применимость к различным слоям населения страны. Надежные психометрические свойства шкал делают их ценным ресурсом для медицинских работников и политиков, стремящихся продвигать донорство органов.

Ключевые слова: донорство органов, отношение, разработка шкалы, валидация шкалы, Казахстан.

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Review article

Prognostic Significance of Structural and Functional Indicators of Myocardial Dysfunction in Postmenopausal Women: Current Perspectives

Gulmira Derbissalina [1], Ayagyoz Umbetzhanova [2], Zhanar Balmukhamedova [3], Natalya Zemlyanskaya [4], Dariga Blyalova [5], Germanas Marinskis [6]

[1] *Head of the Department of General practice with a course of evidence-based medicine, Astana Medical University, Astana, Kazakhstan. E-mail: derbissalina.g@amu.kz*

[2] *Associate Professor of the department of General practice with a course of evidence-based medicine, Astana Medical University, Astana, Kazakhstan. E-mail: umbetzhanova.a@amu.kz*

[3] *Cardiologist, functional diagnostics doctor of the city polyclinic No.6 of the Akimat of Astana, Astana, Kazakhstan. E-mail: balmukhamedova.zhanar@gmail.com*

[4] *Assistant of the Department of General practice with a course of evidence-based medicine, Astana Medical University, Astana, Kazakhstan. E-mail: zemlyanskaya.n@amu.kz*

[5] *Assistant of the Department of Internal Medicine with a course of nephrology, hematology, allergology and immunology, Astana Medical University, Astana, Kazakhstan. E-mail: daka_2015b@gmail.com*

[6] *Professor of the Vilnius University, Institute of Clinical Medicine, Clinic of Cardiovascular Diseases, Vilnius, Lithuania. E-mail: germanas@me.com*

Abstract

Menopause represents a significant period in a woman's life, marked by substantial hormonal changes that significantly impact various bodily systems, particularly the cardiovascular system. The cessation of estrogen production increases the risk of cardiovascular diseases, including myocardial dysfunction. Myocardial dysfunction during menopause may lead to heart failure, particularly in postmenopausal women, where cardiovascular events become more frequent. This condition poses a serious health concern as structural and functional heart changes may remain undetected until advanced stages, complicating diagnosis and treatment. The relevance of studying myocardial dysfunction in menopausal women lies in the profound hormonal and physiological changes occurring during this period. Loss of estrogen's protective effect contributes to increased risks of hypertension, myocardial hypertrophy, and diastolic dysfunction, even with preserved ejection fraction, complicating diagnosis and management.

The pathophysiology of myocardial dysfunction involves endothelial dysfunction, exacerbated by reduced nitric oxide synthesis and lipid metabolism disruptions, further promoting myocardial hypertrophy and fibrosis. Epidemiological data reveal a higher incidence of heart failure with preserved ejection fraction (HFpEF) in postmenopausal women, linked to more pronounced diastolic dysfunction compared to men.

Diagnostic methods like echocardiography and advanced imaging techniques such as MRI play a crucial role in identifying early structural myocardial changes, including left ventricular hypertrophy and fibrosis. Understanding the prognostic significance of these structural and functional myocardial indicators is critical for preventing cardiovascular diseases and improving patient outcomes in menopausal women.

Keywords: *menopause, myocardial dysfunction, cardiovascular disease, estrogen, heart failure, echocardiography, diastolic dysfunction, myocardial hypertrophy.*

Corresponding author: Derbissalina Gulmira, Head of the department of General practice with a course of evidence-based medicine, Astana Medical University, Astana, Kazakhstan
Postal code: Z10K8Y7
Address: Kazakhstan, Astana, Beibitshilik str, 49A
Phone: +77013469331
E-mail: derbissalina.g@amu.kz

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Introduction

Menopause represents a critical phase in a woman's life, characterized by significant hormonal changes that substantially affect various body systems, particularly the cardiovascular system. Following menopause, women lose the protective effects of estrogen, leading to an increased risk of cardiovascular diseases, including myocardial dysfunction. The development of myocardial dysfunction is a precursor to heart failure, which is of particular concern for postmenopausal women, as they experience a rise in cardiovascular events. Myocardial dysfunction during menopause is a serious medical issue with potentially substantial implications for women's health. As menopause begins, women encounter various structural and functional changes in the heart, which can adversely impact prognosis and contribute to the progression of cardiovascular diseases. These changes often go unnoticed until later stages, making diagnosis and management challenging [1,2].

Relevance of the topic. Research on myocardial dysfunction in postmenopausal women is crucial due to the profound hormonal and physiological changes occurring during this period. The loss of estrogen's protective effects significantly increases the risk of developing hypertension, myocardial hypertrophy, and diastolic dysfunction. These changes may occur even with preserved ejection fraction, complicating diagnosis and treatment and necessitating heightened clinical attention [3, 4].

Review objective. The purpose of this review is to systematically analyze and assess the prognostic significance of structural and functional indicators of myocardial dysfunction in postmenopausal women. Emphasis is placed on cardiovascular changes related to hormonal shifts and their role in the development of heart failure. The review also explores diagnostic and predictive methods using modern tools, such as echocardiography, cardiac MRI, and other cardiovascular imaging techniques.

Review methodology

1. **Literature search:** The review is based on a systematic search of scientific literature across databases including PubMed, Scopus, Web of Science, and Google Scholar. Studies were selected based on their relevance to structural and functional myocardial changes in postmenopausal women.

2. **Inclusion criteria:**

-Articles published between 2014 and 2024 to ensure the relevance of data.

-Studies focusing on myocardial dysfunction and cardiovascular risks in postmenopausal women.

-Research including analysis of structural indicators such as left atrial volume index, myocardial mass, left ventricular volumes, and systolic and diastolic function parameters.

3. **Exclusion criteria:**

-Articles published more than 10 years ago.

-Studies unrelated to postmenopausal women.

-Research lacking quantitative or qualitative indicators of structural or functional myocardial changes.

4. **Data analysis:** All selected studies were analyzed for design, methodology, and outcomes. The key focus areas included:

- Evaluation of diastolic function changes.

- Assessment of cardiac volumes and their prognostic significance.

- Impact of hormonal changes on cardiac structure.

- Analysis of prognostic indicators for cardiovascular risks.

5. **Synthesis of results:** The findings from the studies were synthesized to identify the most significant markers of myocardial dysfunction used to predict heart failure in postmenopausal women. Additionally, the review highlights the potential application of modern diagnostic tools in assessing the prognostic value of these markers.

Epidemiology and Pathophysiology of Myocardial Dysfunction

The incidence of cardiovascular diseases in postmenopausal women significantly increases. Research shows that women in this period have a higher risk of both systolic and diastolic myocardial dysfunction. This is associated with hormonal imbalances affecting vascular tone, lipid metabolism, and inflammatory processes, leading to impaired cardiac function [5,6]. The menopausal period is characterized by a sharp decline in estrogen levels, which impacts the cardiovascular system. Estrogens have a cardioprotective effect by improving endothelial function, increasing antioxidant levels, and reducing inflammatory processes. The loss of this protective effect contributes to increased vascular stiffness, elevated blood pressure, and atherogenesis. One of the key mechanisms underlying myocardial dysfunction in the postmenopausal period is endothelial dysfunction. Decreased estrogen levels lead to reduced nitric oxide synthesis, impairing vascular relaxation and promoting vasoconstriction. This increases myocardial workload and contributes to the development of left ventricular hypertrophy, an early manifestation of myocardial structural changes [5].

Estrogens also influence lipid and carbohydrate metabolism, maintaining a favorable lipid profile in premenopausal women. After menopause, there is an increase in total cholesterol and low-density lipoprotein levels, which contributes to atherogenic changes in the vessels and exacerbates cardiovascular risks [6]. These changes can lead to increased myocardial mass, development of fibrosis, and impaired cardiac contractility. Studies show that postmenopausal women have a significantly higher incidence of heart failure with preserved ejection fraction compared to men. This is due to more pronounced diastolic dysfunction, highlighting the importance of timely diagnosis of diastolic dysfunction and structural changes in the myocardium [7].

An important aspect of the pathogenesis of heart disease in menopausal women is also the activation of the renin-angiotensin-aldosterone system, leading to sodium and water retention, increased vascular stiffness, and myocardial hypertrophy. These factors also increase the risk of cardiovascular events [8].

During menopause, decreased estrogen levels directly affect the cardiovascular system, leading to changes in endothelial function and increased vascular stiffness.

These changes result in impaired diastolic function of the left ventricle, which can lead to heart failure with preserved ejection fraction.

Diastolic dysfunction may not manifest until it reaches clinically significant levels, complicating early-stage diagnosis [7, 8].

Structural changes in the myocardium and diagnostic methods for assessment

Structural changes in the myocardium in menopausal women include myocardial hypertrophy, increased wall thickness, and fibrosis. Myocardial hypertrophy is an early sign of increased cardiac workload caused by elevated blood pressure and changes in vascular tone resulting from the loss of estrogenic protection [9]. These changes are particularly pronounced in women with hypertension and obesity, confirming their prognostic significance in the development of heart failure [10]. Structural and functional changes in the myocardium play a crucial role in the progression of heart failure. Assessing these changes is an important prognostic indicator for identifying cardiovascular complications in postmenopausal women. Recent studies focus on the relationship between structural-functional indicators and cardiovascular disease prognosis, emphasizing the importance of early diagnosis and timely intervention. Structural changes in the myocardium, such as left ventricular hypertrophy, enlargement of the left atrium, and increased myocardial mass, may contribute to the development of myocardial fibrosis and impaired myocardial function. These changes have significant prognostic value as they may precede clinical manifestations of cardiovascular disease in postmenopausal women. For example, left ventricular hypertrophy and left atrial enlargement are often associated with an increased risk of heart failure and arrhythmias [9, 10].

The menopausal period is characterized by a sharp decline in estrogen levels, affecting the cardiovascular system. Estrogens have a cardioprotective effect by improving endothelial function, increasing antioxidant levels, and reducing inflammatory processes. The loss of this protective effect contributes to increased vascular stiffness, elevated blood pressure, and atherogenesis [9].

One of the key mechanisms underlying myocardial dysfunction in the postmenopausal period is endothelial dysfunction. Decreased estrogen levels lead to reduced nitric oxide synthesis, impairing vascular relaxation and promoting vasoconstriction. This increases myocardial workload and contributes to left ventricular hypertrophy, an early manifestation of myocardial structural changes [10]. Estrogens also influence lipid and carbohydrate metabolism, maintaining a favorable lipid profile in premenopausal women. After menopause, there is an increase in total cholesterol and low-density lipoprotein levels, which contributes to atherogenic changes in the vessels and exacerbates cardiovascular risks [10]. These changes can lead to increased myocardial mass, development of fibrosis, and impaired cardiac contractility. Studies show that postmenopausal women have a significantly higher incidence of heart failure with preserved ejection fraction compared to men. This is due to more pronounced diastolic dysfunction, highlighting the importance of timely diagnosis of diastolic dysfunction and structural changes in the myocardium [9]. An important aspect of the pathogenesis of heart disease in menopausal women is also the activation of the renin-angiotensin-aldosterone system, leading to sodium and water retention, increased vascular stiffness, and myocardial hypertrophy. These factors also increase the risk of cardiovascular events [8].

Understanding the prognostic significance of structural and functional myocardial changes in postmenopausal women is critical for preventing cardiovascular diseases and improving patient quality of life.

Functional indicators of myocardial dysfunction

Functional changes in the myocardium in postmenopausal women are most often expressed as diastolic dysfunction, although systolic function issues may also arise. Diastolic dysfunction is a condition where the heart loses its ability to fully relax between contractions, leading to increased pressure in the chambers and reduced capacity to fill with blood effectively [15]. Assessment of diastolic function is traditionally performed using Doppler echocardiography, which allows for the measurement of early and late diastolic filling velocities of the left ventricle. This method can also be used to assess left ventricular filling pressures, which are key prognostic indicators [16].

Other functional changes, such as reduced global longitudinal strain (GLS), can be detected using tissue Doppler imaging and speckle tracking techniques. These methods allow for the assessment of subtle changes in myocardial deformation that may precede clinically significant impairments in cardiac contractility [17]. Studies show that reduced GLS correlates with an increased risk of cardiovascular complications and worsened prognosis in menopausal women [18].

It is also important to note that preserved ejection fraction does not always indicate the absence of cardiac dysfunction. A significant number of menopausal women develop heart failure with preserved ejection fraction (HFpEF), characterized by normal systolic function with significant diastolic dysfunction [19]. HFpEF is more common in older women and is closely associated with hypertension, obesity, and diabetes, highlighting the importance of a comprehensive assessment of both structural and functional changes for predicting cardiovascular outcomes.

Structural and functional changes in the myocardium in menopausal women are closely interrelated and significantly impact cardiovascular disease prediction. Early detection of these changes using modern imaging techniques and functional tests is crucial for preventing and managing heart failure in this patient group.

Diagnostic methods for assessing myocardial dysfunction

The role of echocardiography and other imaging methods. Echocardiography (Echo) is the primary imaging method for diagnosing and monitoring myocardial dysfunction. It allows for the assessment of both structural and functional changes in the heart, such as myocardial hypertrophy, chamber enlargement, valve dysfunction, and diastolic dysfunction [11, 12].

Additional imaging methods, such as cardiac magnetic resonance imaging (MRI) and computed tomography (CT), provide more detailed information

about the structure and function of the myocardium. These methods are especially useful for evaluating myocardial fibrosis, chamber sizes, and cardiac function. MRI allows for more accurate visualization of the myocardium and its changes, which can be crucial in complex clinical cases where standard imaging methods do not provide a complete picture of the patient's condition [13,14].

Evaluation of functional parameters. Functional assessment of the myocardium includes measuring ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), as well as other parameters such as cardiac output (CO) and stroke volume (SV) [15,16]. These indicators are essential for determining the degree of heart failure and assessing the impact of structural changes on cardiac function. Functional evaluation also includes analysis of diastolic function parameters, such as e' (tissue Doppler relaxation velocity) and the E/e' ratio (the ratio of peak early diastolic filling to tissue relaxation velocity). These parameters are important for diagnosing diastolic dysfunction, which may be present even with preserved EF [17, 18].

Prognostic significance of structural indicators. Structural changes in the myocardium, such as left ventricular hypertrophy (LVH), left atrial enlargement (LAE), and increased myocardial mass, have prognostic significance for assessing the risk of cardiovascular events. LVH and LAE are often associated with worsening cardiac function and an increased risk of heart failure and arrhythmias [19, 20]. Indexed left atrial volume (LAVi) and left ventricular myocardial mass (LVMi) are key indicators that can help assess prognosis in menopausal women. These parameters can predict not only current functional impairments but also the risk of further deterioration and development of cardiovascular diseases [21, 22].

Prognostic indices and parameters. Key indices and parameters associated with prognosis include end-diastolic volume (EDV), end-systolic volume (ESV), myocardial mass, left atrial volume, and diastolic function parameters [23, 24]. These measures assist in determining the risk level and planning therapeutic interventions. For more precise prognosis, parameters such as the E/e' ratio and tissue Doppler relaxation velocity are also considered. Elevated values of these parameters can indicate significant diastolic dysfunction, which may require attention and possible adjustment of the therapeutic strategy [25, 26].

Assessment of diastolic and systolic function parameters. Functional parameters such as ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and cardiac output (CO) are crucial for evaluating myocardial condition and the extent of heart failure [27,28]. EF is used to assess systolic function of the heart, while EDV and ESV help evaluate volume changes associated with heart failure [29,30]. Diastolic function parameters, such as e' (tissue Doppler relaxation velocity) and the E/e' ratio (the ratio of peak early diastolic filling to tissue relaxation velocity), help assess diastolic dysfunction, which can be present even with preserved EF [31,32]. These indicators are particularly important for diagnosing early stages of heart failure and planning further treatment.

Early diagnosis and prognostic strategies. Early diagnosis of myocardial dysfunction is a key factor in reducing the risk of cardiovascular diseases in postmenopausal women. Modern diagnostic methods allow for the detection of structural and functional changes at early stages, enabling timely intervention and prognosis adjustment. One of the most informative diagnostic methods is echocardiography. Three-dimensional echocardiography provides more accurate data on myocardial morphology and function compared to traditional two-dimensional echocardiography. Technologies such as speckle tracking and tissue Doppler imaging allow for the assessment of myocardial deformation and detection of early signs of heart failure, even with normal ejection fraction [20]. This method is particularly important for identifying subclinical forms of dysfunction in women who do not exhibit obvious symptoms of heart disease [21]. Stress echocardiography is also a valuable diagnostic tool for evaluating myocardial response to physical exertion. It helps uncover latent ischemia and assess cardiac functional reserves, which is crucial for women at high risk of ischemic heart disease [22]. In addition to imaging methods, biomarkers play a significant role in early diagnosis. Natriuretic peptides (BNP and NT-proBNP) are markers of cardiac stress and are used to assess heart failure risk. Elevated levels of these peptides in menopausal women may indicate hidden myocardial dysfunction and increased risk of cardiac complications [23].

The use of a combination of imaging methods and biomarker analysis allows for a comprehensive approach to diagnosis and improves prognosis for women with early signs of myocardial dysfunction during menopause.

Clinical significance and prognostic optimization

Clinical significance of structural and functional changes. Effective assessment of functional parameters not only aids in diagnosing heart failure but also in predicting its progression. Understanding the significance of parameters such as e' and E/e' can help in the early detection of diastolic dysfunction and improve patient prognosis [33,34]. The clinical significance of structural and functional myocardial changes in postmenopausal women lies in their ability to predict cardiovascular outcomes. Research indicates that structural changes, such as left ventricular hypertrophy and myocardial fibrosis, are closely associated with an increased risk of heart failure, arrhythmias, and sudden cardiac death [24]. Diastolic dysfunction is the most common functional change in menopausal women and serves as an early indicator of heart failure with preserved ejection fraction. Women with pronounced diastolic dysfunction face significantly higher risks of hospitalization due to heart failure and increased mortality [25]. Additionally, changes in myocardial deformation, such as decreased global longitudinal strain (GLS), are potent prognostic markers. Women with reduced GLS have poorer outcomes, even when other cardiac function parameters remain normal. This underscores the importance of incorporating advanced technologies for assessing myocardial deformation in clinical practice [26]. Early diagnosis and active monitoring of structural and functional myocardial changes allow for the development of individualized treatment strategies aimed at slowing the progression of heart failure and improving the quality of life for menopausal women.

Potential strategies for prognostic improvement. To optimize prognosis in patients with myocardial dysfunction, a comprehensive approach is recommended, including regular monitoring of functional parameters and the application of therapeutic strategies to correct identified abnormalities [35,36]. For instance,

medications such as ACE inhibitors, beta-blockers, and aldosterone antagonists can improve both diastolic and systolic myocardial function [37,38]. Non-pharmacological interventions, such as lifestyle modifications, stress reduction, and physical activity, also play a crucial role in managing and predicting cardiovascular diseases [39].

Conclusions

The menopause period is a critical phase in a woman's life, marked by significant changes in the cardiovascular system. The loss of estrogen protection leads to numerous adverse effects on the myocardium, including structural changes such as hypertrophy and fibrosis, and functional impairments such as diastolic dysfunction and reduced cardiac contractility. These changes play a key role in increasing the risk of cardiovascular diseases and mortality in postmenopausal women. Early diagnosis of structural and functional myocardial changes, based on modern imaging methods and biomarker utilization, is a crucial step in preventing heart failure. It is important to note that subclinical forms of myocardial dysfunction often remain undetected with standard diagnostic approaches, highlighting the need for more sensitive methods, such as speckle tracking and tissue Doppler imaging.

The prognostic significance of these changes has already been demonstrated in several studies, indicating the need for active monitoring of menopausal women to identify early signs of cardiac abnormalities. This will help improve outcomes and prevent severe cardiovascular complications. This review emphasizes the importance of a comprehensive approach to the diagnosis and treatment of cardiovascular diseases in menopausal women. If needed, I can gather specific references for each section and prepare final text revisions.

Based on the literature analysis, the following conclusions can be drawn:

1. Effective assessment of both systolic and diastolic myocardial function is essential for accurate diagnosis and prognosis of cardiovascular diseases, especially in menopausal women [26, 27, 30].

2. Parameters such as e', E/e', LVEDV, and LVESV play a key role in predicting the risk of heart failure and other cardiovascular conditions [31, 32].

3. A comprehensive approach, including both pharmacological and non-pharmacological treatment, is important for improving prognosis and quality of life for patients [34, 35].

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Менопаузадағы әйелдердегі миокард дисфункциясының құрылымдық-функционалдық көрсеткіштерінің болжамдық маңызы: Мәселенің қазіргі жағдайы

Дербисалина Г.А. [1], Умбетжанова А.Т. [2], Бальмухамедова Ж.А. [3], Землянская Н.С. [4], Блялова Д.Б. [5], Germanas Marinskis [6]

[1] Дәлелді медицина курсы бар жалпы дәрігерлік практика кафедрасының меңгерушісі, Астана медицина университеті, Астана, Қазақстан. E-mail: derbissalina.g@amu.kz

[2] Дәлелді медицина курсымен жалпы дәрігерлік практика кафедрасының доценті, Астана медицина университеті, Астана, Қазақстан. E-mail: umbetzhanova.a@amu.kz

[3] Астана қаласы әкімдігінің №6 қалалық емханасының кардиологы, функционалдық диагностика дәрігері, Астана, Қазақстан. E-mail: balmukhamedova.zhanar@gmail.com

[4] Дәлелді медицина курсымен жалпы дәрігерлік практика кафедрасының ассистенті, Астана медицина университеті, Астана, Қазақстан. E-mail: zemlyanskaya.n@amu.kz

[5] Дәлелді медицина курсымен жалпы дәрігерлік практика кафедрасының ассистенті, Астана медицина университеті, Астана, Қазақстан. E-mail: daka_2015b@gmail.com

[6] Вильнюс университетінің профессоры, Клиникалық медицина институты, Жүрек-қан тамырлары аурулары клиникасы, Вильнюс, Литва. E-mail: germanas@me.com

Түйіндеме

Менопауза - маңызды гормоналды және физиологиялық өзгерістермен сипатталатын әйел өміріндегі маңызды өтпелі кезең. Бұл өзгерістер дененің әртүрлі жүйелеріне, соның ішінде жүрек-тамыр жүйесіне әсер етеді. Менопаузадан кейінгі кезеңде эстрогендердің қорғаныш әсерін жоғалту жүрек-тамыр ауруларының, соның ішінде миокард дисфункциясының даму қаупінің жоғарылауына әкеледі. Менопаузадағы әйелдердегі миокард дисфункциясы жүректің құрылымдық және функционалдық өзгерістерімен көрінеді, мысалы, сол жақ қарыншаның гипертрофиясы, фиброз және диастолалық функцияның бұзылуы.

Бұл өзгерістер көбінесе соңғы кезеңдерге дейін анықталмай диагнозды қиындатады және сақталған шығару фракциясымен жүрек жеткіліксіздігінің қаупін арттырады.

Миокард дисфункциясының негізінде жатқан патофизиологиялық механизмдерге эндотелий дисфункциясы, ренин-ангиотензин-альдостерон жүйесінің активтенуі, липидтер мен көмірсулар алмасуының өзгеруі жатады. Бұл факторлар қан тамырларының қаттылығына және қан қысымының жоғарылауына ықпал етеді. Бұл өз кезегінде миокардқа жүктемені арттырады және жүрек жеткіліксіздігінің өршуіне ықпал етеді. Миокард дисфункциясын диагностикалаудың маңызды аспектісі эхокардиография, магнитті-резонансты бейнелеу және компьютерлік томография сияқты бейнелеу әдістері болып табылады. Бұл әдістер миокардтың құрылымдық және функционалдық өзгерістерін бағалауға мүмкіндік береді, бұл постменопаузадағы әйелдерде жүрек-қан тамырлары қаупін ерте анықтау үшін маңызды.

Менопаузадағы әйелдердегі миокардтың құрылымдық және функционалдық өзгерістерінің болжамдық маңыздылығын түсіну жүрек-қан тамырлары ауруларының алдын алу және пациенттердің өмір сүру сапасын жақсартудың кілті болып табылады. Заманауи диагностикалық әдістер мен ерте араласу постменопаузадағы жүрек-қан тамырлары өзгерістерінің жағымсыз салдарын азайтуға көмектеседі.

Түйін сөздер: менопауза, миокард дисфункциясы, жүрек-тамыр аурулары, эстроген, жүрек жеткіліксіздігі, эхокардиография, диастолалық дисфункция, миокард гипертрофиясы.

Прогностическая значимость структурно-функциональных показателей дисфункции миокарда у женщин в менопаузальном периоде: Современное состояние проблемы

Дербисалина Г.А. [1], Умбетжанова А.Т. [2], Бальмухамедова Ж.А. [3], Землянская Н.С. [4], Блялова Д.Б. [5], Germanas Marinskis [6]

[1] Заведующая кафедрой общей врачебной практики с курсом доказательной медицины, Медицинский университет Астана, Астана, Казахстан. E-mail: derbissalina.g@amu.kz

[2] Доцент кафедры общей врачебной практики с курсом доказательной медицины, Медицинский университет Астана, Астана, Казахстан. E-mail: umbetzhanova.a@amu.kz

[3] Врач-кардиолог, врач функциональной диагностики городской поликлиники №6 Акимата города Астаны, Казахстан. E-mail: balmukhamedova.zhanar@gmail.com

[4] Ассистент кафедры общей врачебной практики с курсом доказательной медицины, Медицинский университет Астана, Астана, Казахстан. E-mail: zemlyanskaya.n@amu.kz

[5] Ассистент кафедры внутренних болезней с курсом нефрологии, гематологии, аллергологии и иммунологии, Медицинский университет Астана, Астана, Казахстан. E-mail: daka_2015b@gmail.com

[6] Профессор Вильнюсского университета, Институт клинической медицины, Клиника сердечно-сосудистых заболеваний, Вильнюс, Литва. E-mail: germanas@me.com

Резюме

Менопауза представляет собой важный переходный период в жизни женщины, который характеризуется значительными гормональными и физиологическими изменениями. Эти изменения оказывают влияние на различные системы организма, включая сердечно-сосудистую систему. В постменопаузальном периоде потеря защитного эффекта эстрогенов приводит к повышению риска развития сердечно-сосудистых заболеваний, в том числе дисфункции миокарда. Дисфункция миокарда у женщин в менопаузе проявляется как структурными, так и функциональными изменениями сердца, такими как гипертрофия левого желудочка, фиброз и нарушение диастолической функции. Эти изменения часто остаются незамеченными до поздних стадий, что усложняет диагностику и увеличивает риск сердечной недостаточности с сохраненной фракцией выброса.

Патофизиологические механизмы, лежащие в основе миокардиальной дисфункции, включают эндотелиальную дисфункцию, активацию ренин-ангиотензин-альдостероновой системы, а также изменения липидного и углеводного обмена. Эти факторы способствуют жесткости сосудов и повышению артериального давления, что увеличивает нагрузку на миокард и способствует прогрессированию сердечной недостаточности. Важным аспектом в диагностике миокардиальной дисфункции являются методы визуализации, такие как эхокардиография, магнитно-резонансная томография и компьютерная томография. Эти методы позволяют оценить структурные и функциональные изменения в миокарде, что важно для раннего выявления сердечно-сосудистых рисков у женщин в постменопаузе.

Понимание прогностической значимости структурных и функциональных изменений миокарда у женщин в менопаузе имеет ключевое значение для предотвращения сердечно-сосудистых заболеваний и улучшения качества жизни пациенток. Современные методы диагностики и раннего вмешательства могут помочь минимизировать негативные последствия сердечно-сосудистых изменений в постменопаузальном периоде.

Ключевые слова: менопауза, дисфункция миокарда, сердечно-сосудистые заболевания, эстроген, сердечная недостаточность, эхокардиография, диастолическая дисфункция, гипертрофия миокарда.

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Original article

Untangling the Path: Challenges in Autism Diagnosis for Kazakhstani Families

Karina Nukeshtayeva [1], Bauyrzhan Omarkulov [2], Marina Lyubchenko [3], Nailya Delellis [4], Aiman Mussina [5], Gaukhar Kayupova [6], Zhaniya Dauletkaliyeva [7]

[1] Assistant professor of the School of Public Health, Karaganda Medical University, Karaganda, Kazakhstan. E-mail: nukeshtaeva@qmu.kz
[2] Professor of the Department of Family Madicine, Karaganda Medical University, Karaganda, Kazakhstan. E-mail: omarkulov@qmu.kz
[3] Professor of the Department of Neurology, Psychiatry and Rehabilitation, Karaganda Medical University, Karaganda, Kazkahstan. E-mail: lyubchenko@qmu.kz
[4] Professor of the Central Michigan University, Michigan, USA. E-mail: delel1no@cmich.edu
[5] Professor of the Head of Department of Public Health and Epidemiology, Astana Medical University, Astana, Kazakhstan. E-mail: mussina.a@amu.kz
[6] Associate professor of the School of Public Health, Karaganda Medical University, Karaganda, Kazakhstan. E-mail: kayupovag@qmu.kz
[7] Dean of the School of Public Health, Karaganda Medical University, Karaganda, Kazakhstan. E-mail: dauletkalievaz@qmu.kz

Abstract

Navigating the labyrinth of Autism diagnosis in Kazakhstan can be an arduous journey for families. The scarcity of specialized professionals, coupled with limited awareness and resources, poses significant hurdles for early identification and intervention. This study aimed to offer a comprehensive examination of caregivers' experiences in navigating the process of diagnosing autism in their children within the context of Kazakhstan.

***Objective:** The overarching aim of this study is to illuminate caregivers' experiences in navigating the diagnostic journey for Autism Spectrum Disorder in Kazakhstan, shedding light on factors influencing parental decision-making and elucidating barriers faced by families seeking diagnostic support for their children.*

***Methods.** This study involved a mixed interview of caregivers of children diagnosed with childhood autism, atypical autism, about difficulties in the process from initial concern about the child's development to formal diagnosis.*

***Results.** On average, autism concerns emerged at 1.91 years, with specialist contact at 2.19 years. Median diagnosis age was 4.51 years, taking 2.45 years from concern. Comorbidities included Attention deficit hyperactivity disorder (16.98%), psycho-speech delay (15.09%), and mental retardation (9.43%). Satisfaction with diagnosis was low (9.43%), yet 41.5% were content. Caregivers struggled with timely diagnosis, facing awareness and support deficits from specialists and society, along with logistical and psychological challenges.*

***Conclusion**.The study sheds light on the challenges faced by caregivers in Kazakhstan during the diagnosis of autism in their children. It highlights the delayed age of diagnosis, the prevalence of comorbidities, and the dissatisfaction with diagnostic assistance, underscoring the urgent need for improved access to timely and effective diagnostic services, as well as enhanced support for caregivers navigating the complexities of autism diagnosis.*

***Keywords:** autism spectrum disorder, parents' experience, Kazakhstan.*

Corresponding author: Karina Nukeshtayeva, assistant professor, School of Public Health, Karaganda Medical University, Karaganda, Kazakhstan.
Postal code: M01K7G6
Address: Kazakhstan, Karaganda, Gogol street 40
Phone: +77782452740
E-mail: nukeshtaeva@qmu.kz

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Introduction

Autism spectrum disorder (ASD) is a pervasive developmental condition characterized by challenges in social interaction, communication, and repetitive behaviors, persisting across the lifespan [1]. ASD encompasses a spectrum of conditions, including autism, developmental disorders, and Asperger's syndrome [2]. Accurate diagnosis relies heavily on healthcare professionals' proficiency in identifying ASD's nuanced signs and symptoms, which typically manifest in early childhood and endure over time without remission [3]. Timely diagnosis and intervention are imperative as they facilitate early engagement in comprehensive interventions aimed at fostering social adaptation and behavioral correction, thereby enhancing the prospects for successful integration into educational, vocational, and social spheres [4,5].

While various diagnostic tools exist, delays in obtaining a definitive ASD diagnosis often hinder prompt intervention, prolonging the unmet needs of affected children [6-11].

Factors contributing to diagnostic delays include the subtlety and variability of symptoms, limited diagnostic methodologies tailored for young children, inadequate awareness among healthcare providers, comorbidities complicating assessment, dearth of specialized facilities, and socioeconomic constraints [12].

Families navigating prolonged diagnostic processes frequently report diminished trust in healthcare professionals, leading some to pursue unvalidated treatments out of desperation [13]. Moreover, a passive "wait and see" approach by healthcare providers exacerbates parental distress, amplifying feelings of uncertainty and distrust. The toll of caregiving for a child with ASD can precipitate heightened vulnerability to mental health issues such as depression and anxiety [14].

In Kazakhstan, as in many regions globally, the prevalence of ASD is rising, though discrepancies in data integrity persist due to inconsistent collaboration among governmental entities. The Ministry of Health has noted a substantial increase in reported cases of ASD, prompting initiatives for enhanced screening technologies to facilitate early identification [15]. Official figures from the Ministry of Education indicate thousands of diagnosed cases, yet unofficial estimates suggest a much higher prevalence, indicative of systemic discrepancies [16,17]. Compounding this challenge, medical reporting practices often conflate ASD with other mental health conditions, further obscuring accurate prevalence estimates [18].

Diagnosis of ASD in Kazakhstan is restricted to psychiatrists and typically occurs after the age of four, potentially delaying access to early interventions critical for optimal outcomes. Placement of children with ASD in institutions for individuals with mental or intellectual disabilities has been commonplace, underscoring historical challenges in providing appropriate care and support [19,20].

Early research underscores caregivers' observations of early warning signs in their children, often met with hesitancy to seek medical evaluation due to perceived barriers in the healthcare system [21].

The overarching aim of this study is to illuminate caregivers' experiences in navigating the diagnostic journey for ASD in Kazakhstan, shedding light on factors influencing parental decision-making and elucidating barriers faced by families seeking diagnostic support for their children.

Material and methods

Our study involved conducting mixed interviews with caregivers of children diagnosed with childhood autism or atypical autism, focusing on the challenges encountered from the initial concerns about the child's development to receiving a formal diagnosis. The study was conducted in the period October-December 2022.

An electronic registration form created in Google Forms was distributed through neuropsychiatric dispensaries and public associations related to autism. The registration form provided informed consent, a clear description of the purpose of the study, a description of the benefits and risks of participation, and assurance that the study would be published without identifying any participants. The parents who provided consent to participate in the study completed a registration form. All participants who completed the electronic registration form were additionally sent an online form, which included information such as “Caregivers age”, “Caregivers nationality”,“Child’s Age”, “Caregivers Education”, “Contact information”, “Age of the child when the warning signs were first noticed”, “Age of the child at the first seeking diagnostic help”, “Age of the child at diagnosis”, “Satisfaction with diagnostic help” (rated from 1 to 5, where 1 - “not satisfied," 5-" satisfied”), “Satisfaction with the timeliness of diagnosis” (estimated from 1 to 5, where 1 - “not satisfied”, 5 - “satisfied”), and “Comorbidities”.

The inclusion criteria mandated a diagnosis of childhood autism or atypical autism, aligning with prevailing medical practices in Kazakhstan guided by the International Classification of Diseases-10 (ICD-10), which designates child psychiatrists as the sole authority for autism diagnosis in children.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Karaganda Medical University (protocol code 2).

Fifty-three families meeting the inclusion criteria completed the electronic registration form and consented to participate. Direct participation in interviews was limited to mothers.

Following completion of the registration and online forms, interviews were scheduled at mutually convenient times. Interviews were conducted via phone, video calls, or messenger services, with consent obtained for recording. Transcription methods included manual transcription, dictaphone recording, or saving voice messages as electronic files. All audio recordings were transcribed into written text.

During the interviews, caregivers narrated their experiences from the initial observation of warning signs in their child's development to the eventual diagnosis. Researchers posed clarifying questions to elicit detailed responses. The interview text was coded using an iterative process involving group coding and thematic analysis. The research team collectively reviewed and analyzed transcripts, assigning codes to individual members. Frequent formulations were identified and grouped into categories, which were then organized into broader themes, including "Initial concerns," "Path to diagnosis," and "Difficulties during the diagnostic period" (Table 1).

Table 1 - Themes and citation examples

Themes	Theme An exemplary citation from caregivers
Initial concerns	When my son was already more than two years old, he did not respond to his name at all, as if he did not know him.
	"Despite the fact that I read about autism and was somewhat aware, for a long time I could not accept that the fact that my child is constantly obsessed with TV and jumping in front of it is not the norm"
	"Up to a year and a half, she developed, like all children, even somewhere ahead of her peers, but she didn't speak at all, and closer to 2 years, a regression began, which went so gradually that it seemed just a manifestation of character"
The way to diagnosis	"When I suspected that something was wrong with my daughter, the first thing I thought was that we need to see a neurologist"
	"When I first heard about autism on TV, I immediately began to check the information on the Internet and realized that a psychiatrist could most likely help us"
Difficulties during the diagnostic period	"At 2.5 years old, when contacting a neurologist, the doctor said that absolutely everything is fine with the child,
	as he is interested in the toys in the office. Therefore, we left completely calmed down and lost another year."
	"When a child was diagnosed with ASD, it was a blow to me, and I fell into depression"
	"Everyone around me was advised to send the child to kindergarten. It was thought that communication with other children would help the development of speech. However, the problem was that due to child did not understand the addressed speech, not a single preschool accepted us."

Descriptive statistics of the online form data were carried out.

Results

The mean age of the study participants was 36 years (SD=5.94). The national structure of the interview participants was as follows: 35 Kazakh people (66.03%), 13 Russian people (24.52%), and other nationalities, including Germans, Tajiks, and Ukrainians; there were 5 people (9.43%). Among the participants in the study, 27 people (50.94%) had higher education, 18 (33.96%) had secondary education, and 8 people (15.09%) had postgraduate education.

On average, initial concerns regarding the child's development were noted at 1.91 years of age (SD = 0.54), ranging from 1 to 3 years. The mean age at which caregivers first contacted a specialist about their child's development concerns was 2.19 years (SD=0.8). The minimum age at the first visit to the specialists was 1 year, and the maximum age was 4 years. The median age at final diagnosis was 4.51 years (SD=1.52), the maximum age was 8 years, and the minimum age was 2 years. The mean number of years that elapsed from the moment of the first visit to specialists with initial concerns until the final diagnosis was 2.45 years (SD=1.72). The minimum period was 1 month, and the maximum was 6 years.

The presence of comorbidities was observed in 22 children, 16.98% of whom had comorbidities due to attention deficit hyperactivity disorder (ADHD), 15.09% of whom had comorbidities due to psycho-speech development retardation, and 9.43% of whom had comorbidities due to mental retardation.

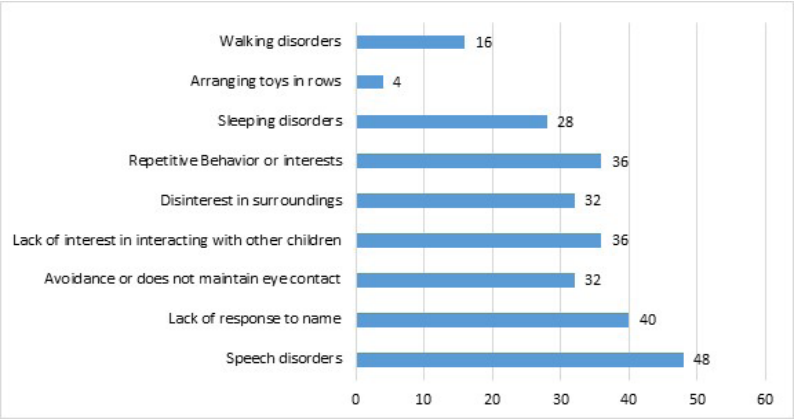

Figure 1 - Prevalence of warning signs as reported by study participants

11 study participants (20.75%) were not satisfied with the impact of diagnostic assistance, and only 5 people (9.43%) were satisfied with it. Most of the participants (22 people, 41.5%) were satisfied with the diagnosis of their children; only 2 (3.77%) were satisfied, while 16 (30.19%) of the participants were not satisfied.

Figure 1 depicts the frequency of warning signs that alerted caregivers to potential development issues with the child. Primarily, caregivers reported speech disorders, wherein the child either exhibited delayed speech development or lacked speech entirely: "The first thing that made me think that something was wrong was when I saw the child, who was younger than my son for more than half a year, carry out such commands as, for example, "take off your hat." While my son didn't understand me at all." Moreover, in the majority of cases, caregivers expressed concern over the child's lack of response when called by name.

All warning signs observed in the children were identified by their caregivers, who subsequently confided their concerns with relatives and friends. This sharing of apprehensions served to seek support and solicit advice on how to proceed. Remarkably, within the social circles of these families, similar unsettling symptoms were noted, notably speech delays or complete absence thereof.

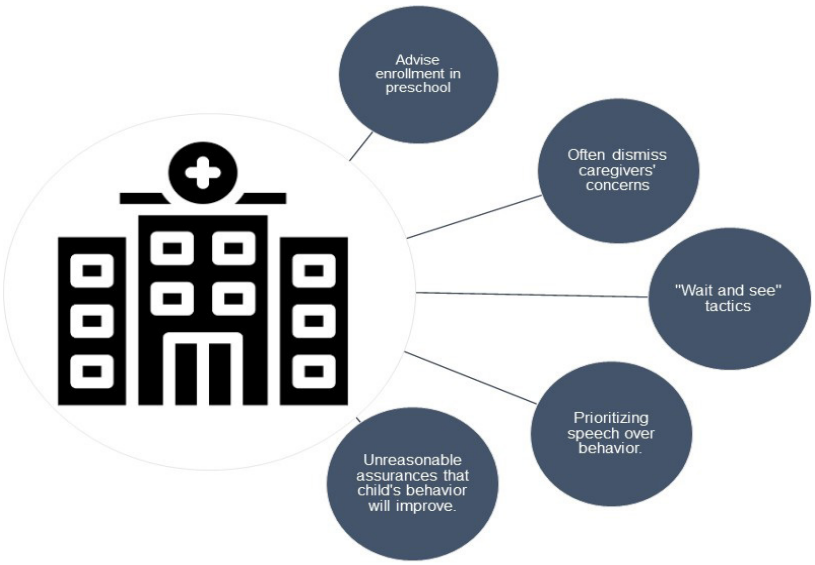

Figure 2 - Health providers' response to parents' concerns about the child's development

Nonetheless, caregivers uniformly recounted receiving reassurance and counsel advising against further action, often rationalized with statements such as, "Why label the child when everything seems fine? Perhaps he's just being a bit spoiled." The individuals around the caregivers commonly advised them to enroll the child in preschool, suggesting that exposure to other children would encourage speech development and instill discipline. Within the study cohort, caregivers perceived the child's anxious behavior as typical, while preschool staff highlighted potential developmental disorders. Despite initial advice to "Wait and See," parents proactively sought specialist input at the first inkling of concern. In determining whether their child's behavior and development were typical, parents predominantly relied on internet resources and discussions with other parents of children with developmental disorders via various messenger platforms.

Caregivers noted that despite their children undergoing routine psychophysical development screenings required for preschool enrollment, healthcare providers did not identify any alarming signs.

Caregivers primarily sought consultations from private pediatric neurologists, expressing a lack of confidence in neurologists at public primary care facilities. As one caregiver recounted, "When we visited the neurologist at our local clinic when our child was 3 years old, we were told it was premature and that the child was too young." Instead, we were advised to enroll the child in preschool." Another caregiver shared, "We were prescribed sedatives and reassured that our child, exhibiting self-harming behavior, was simply hyperactive and would outgrow it by age 7."

Children were frequently diagnosed with language delay, with the focus primarily on speech initiation and development, while behavioral issues were often dismissed as a transient phase the child would eventually overcome. Ultimately, child psychiatrists were responsible for final diagnoses, despite caregivers harboring significant biases and concerns about psychiatry. As one caregiver expressed, "I was apprehensive about the potential impact on his future, such as employability," and another admitted, "I feared the possibility of my child being prescribed psychotropic medications."

However, in Kazakhstan, obtaining disability benefits, which could offset some expenses for costly interventions, necessitated a psychiatrist's evaluation, prompting caregivers to engage with them. Despite initial reservations, most caregivers found solace in receiving a definitive diagnosis, providing clarity and understanding of their child's condition. Yet, when evaluating satisfaction with the diagnostic journey and the timeliness of diagnosis, the majority of caregivers expressed dissatisfaction or remained neutral.

Figure 2 illustrates the primary challenges encountered by participants in our study while seeking diagnostic care." The primary challenge faced by caregivers was the perceived lack of acknowledgment of the severity of their situation by specialists. As one caregiver lamented, "I believe the worst mistake is to placate a mother when diligent action is required." Many specialists were found to be unaware of autism spectrum disorder (ASD), hindering their ability to provide appropriate guidance, thereby exacerbating caregivers' mistrust of the medical system. "We sought assistance, but it was not forthcoming," one caregiver expressed, reflecting on their frustration. Concerns about potential adverse effects of medications further fueled caregivers' withdrawal from seeking help.

Furthermore, parents reported a lack of support from their social circles and family members, who often dismissed their child's condition due to outward appearances of health. Additionally, the accessibility of diagnostic services was impeded by challenges associated with the child's behavior. Some caregivers found it daunting to venture outside with their children, let alone endure long waits to see healthcare providers. Private specialists were also overwhelmed, resulting in lengthy waiting lists extending for months.

The psychological well-being of caregivers emerged as a paramount concern. "My peers blame me for spoiling him, while doctors accuse me of neglecting my child and realizing the issue too late. I'm at a loss," one caregiver expressed, highlighting the emotional turmoil experienced. "It appears that parents require psychological support foremost, followed by assistance for the child. By delaying recognition of the problem, we rob the child of valuable time," another caregiver emphasized, underscoring the urgent need for holistic support.

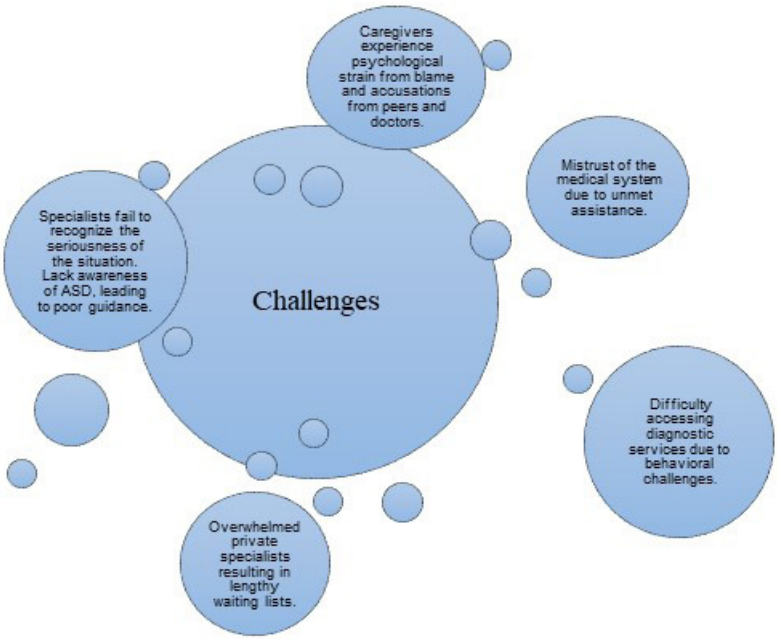

Figure 3 - Primary challenges encountered by caregivers while seeking diagnostics

Discussion

This study investigated the journey of caregivers towards the diagnosis of Autism Spectrum Disorder (ASD) in Kazakhstan and the challenges encountered. The primary issues were examined from the perspective of parents.

Our findings indicate that the mean age at final diagnosis was 54.12 months, aligning closely with the global average age at ASD diagnosis reported in a meta-analysis of 35 studies from 35 countries (50.12–70.83 months) [22].

The average duration between the initial referral to a specialist due to concerns and the ultimate diagnosis was 29.4 months, with some studies reporting periods exceeding 2 years [23]. The average age at which parents recognize their child's warning signs (1.91 years) is very close to the 1.7 years reported in a large study of parental experience in diagnosing autism in children in the United Kingdom [24].

Every fifth participant in our study was absolutely dissatisfied with the diagnostic care provided to them, and approximately 30% of participants were not satisfied with the age of diagnosis. Reducing the time that passes from the time parents first express concerns about their child's development to the time they are diagnosed with ASD is an important step toward improving the parenting experience. It is important to recognize that in some cases, clinicians are simply unable to give the child an accurate diagnostic assessment at an early stage; therefore, reassessment at regular intervals is necessary. Further research is needed to better understand how services are structured and organized to quickly and timely assess children with suspected ASD.

In our study, Attention Deficit Hyperactivity Disorder (ADHD) emerged as the most common comorbidity in children with ASD, contributing to diagnostic delays. Symptoms of ADHD may divert attention from ASD, delaying diagnosis, as anxiety symptoms are often attributed to ADHD [25].

As in other studies, parents pay the most attention to the development of the child's speech [26]. There is evidence that speech development disorders in children are a marker of increased vulnerability to the development of ASD, which suggests that both parents and medical workers should always pay attention to these kinds of complaints and not waste time waiting for the child to speak on the way to kindergarten [27].

In our study, we found that parents first turn to pediatric neurologists. Another study that presented the results of a survey of parents of children with autism in Kazakhstan reported that 73% of parents first turned to neurologists [28]. The final diagnosis was made by psychiatrists, as parents turned to them to obtain the right recommendations and conclusions for disability registration. However, research recommends a multidisciplinary approach for diagnosing ASD. It is important that these multifaceted assessments be performed by clinicians who have extensive experience in standardized testing of children and who have specific knowledge of ASD assessment [29].

Additionally, an extremely important point is to increase awareness of ASD among health providers who conduct routine screening of the psychophysical development of young children in Kazakhstan. After all, according to the results, most parents reported that no alarming symptoms were noticed during routine screenings.

When parents express their concerns during a child's examination, healthcare professionals should listen to and act on this information using ASD-specific screening rather than reassuring parents [30]. At the very least, if a waiting period is determined to be the best course of action, practitioners should establish a "wait and see" in which parents are given a certain amount of time to observe under the clear direction of the provider. If there is no improvement in development after this period, it is very important to refer such children for a comprehensive examination. Given the public health emergency posed by ASD and the long period between the first parental problems and a diagnosis of autism, there is an urgent need to improve methods for the early detection of ASD in Kazakhstan.

The small number of participants who volunteered to participate in the study is a limitation of this study. An examination of the demographics of the participants revealed that the views presented in this survey mostly reflected those of mothers with mostly college degrees. Another limitation of the sample was the small number of parents who participated in the study from various regions

of Kazakhstan, preventing the reliable assessment of regional differences. Furthermore, with any self-sampling, it is impossible to determine whether the experience of those who completed the interview differed from that of nonrespondents. Those who had a particularly excellent or negative experience looking for a diagnosis for their child were more likely to complete this interview.

Conclusion

In conclusion, this study provides valuable insights into the diagnostic journey of caregivers of children with autism in Kazakhstan. It reveals significant delays in diagnosis, with caregivers encountering numerous challenges, including comorbidities, dissatisfaction with diagnostic assistance, and a lack of awareness among specialists.

Addressing these systemic challenges requires a multifaceted approach, including expanding training programs for diagnosticians, enhancing public awareness campaigns, and improving the availability of affordable services nationwide. By fostering a more inclusive and supportive environment, Kazakhstan can strive towards ensuring that every child receives the timely diagnosis and support they deserve.

Conflict of interests. The authors declare no conflicts of interest.

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Author contribution. Conceptualization, investigation, original draft preparation, visualization – K.N.; Methodology, data curation, supervision, project administration – B.O.; writing—review and editing, supervision – M.L.; writing—review and editing, supervision, project administration – N.D.; writing—review and editing – M.A.; investigation, original draft preparation – G.K; original draft preparation – Zh.D.

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Жолды ашу: Қазақстандағы отбасылар үшін аутизм диагностикасының қиындықтары

Нукештаева К.Е. [1], Омаркулов Б. К. [2], Любченко М.Ю. [3], Nailya Delellis [4], Мусина А.А. [5], Каюпова Г. С. [6], Даулеткалиева Ж.А.[7]

[1] Қоғамдық денсаулық мектебінің ассистент-профессоры, Қарағанды медицина университеті, Қарағанды, Қазақстан. E-mail: nukeshtaeva@qmu.kz

[2] Отбасылық медицина кафедрасының профессоры, Қарағанды медицина университеті, Қарағанды, Қазақстан. E-mail: omarkulov@qmu.kz

[3] Неврология, психиатрия және реабилитология кафедрасының профессоры, Қарағанды медицина университеті, Қарағанды, Қазақстан. E-mail: lyubchenko@qmu.kz

[4] Орталық Мичиган университетінің профессоры, Маунт Плезант, Мичиган, АҚШ. E-mail: delel1no@cmich.edu

[5] Қоғамдық денсаулық және эпидемиология кафедрасы меңгерушісі, Астана медицина университеті, Астана, Қазақстан. E-mail: mussina.a@amu.kz;

[6] Қоғамдық денсаулық мектебінің қауымдастырылған профессоры, Қарағанды медицина университеті, Қарағанды, Қазақстан. E-mail: kayupovag@qmu.kz

[7] Қоғамдық денсаулық мектебінің деканы, Қарағанды медицина университеті, Қарағанды, Қазақстан. E-mail: dauletkalievaz@qmu.kz

Түйіндеме

Қазақстандағы аутизмді диагностикалау лабиринтінде шарлау отбасылар үшін қиын жол болуы мүмкін. Арнайы дайындалған мамандардың аздығы, науқастардың хабардарлық деңгейінің төмендігі, ерте анықтау және араласу үшін айтарлықтай кедергілер тудырады.

Бұл зерттеудің негізгі мақсаты – Қазақстандағы аутизм спектрінің бұзылуының диагностикалық жолы туралы ата-аналардың тәжірибесіне жарық түсіру, ата-аналардың шешім қабылдауына әсер ететін факторларға ден қою және диагностикалық қолдау іздеген отбасылар және балалары үшін кездесетін кедергілерді түсіну.

Әдістері. Бұл зерттеу балалық шақтағы аутизм, атипті аутизм диагнозы қойылған балалардың ата-аналарымен баланың дамуы туралы бастапқы алаңдаушылықтардан ресми диагнозға дейінгі үдерістегі қиындықтар туралы аралас әдіспен анықтауға бағытталған сұхбаттарды қамтыды.

Нәтижесі. Зерттеу тобында аутизм проблемалары орташа алғанда 1,91 жаста, ал маманға жолдама 2,19 жаста пайда болғаны белгілі болды. Диагноз қойылғанда орташа жас 4,51 жасты құрады. Қосымша ауруларға зейін тапшылығының гиперактивтілігінің бұзылуы (16,98%), ақыл-ойдың артта қалуы (15,09%) және ақыл-ойдың артта қалуы (9,43%) жатады. Диагнозға қанағаттанушылық деңгейі біршама төмен (9,43%), дегенмен респонденттердің 41,5% диагноз қою сапасына қанағаттанған екені анықталды. Қамқоршылар мамандар мен әлеуметтік ортаның хабардарлығы мен қолдауының жетіспеушілігіне, сондай-ақ логистикалық және психологиялық қиындықтарға тап болып, дер кезінде диагноз қоюдың кешігуімен күресуде.

Қорытынды. Зерттеу Қазақстандағы заңды өкілдердің өз балаларындағы аутизмді диагностикалау кезінде қандай қиындықтарға тап болатынын көрсетеді. Қиындықтар диагностиканың кешіктірілуін, қосымша аурулардың таралуын және диагностикалық көмекке қанағаттану деңгейінің төмендігі секілді тұстарды қамтыды. Дер кезінде жүргізілген және тиімді диагностикалық қызметтерге қолжетімділікті жақсартудың өзекті қажеттілігін көрсетеді. Сондай-ақ аутизм диагностикасының күрделі мәселелерін зерттейтін қамқоршыларға қолдауды күшейтеді.

Түйін сөздер: аутизм спектрінің бұзылуы, ата-ана тәжірибесі, Қазақстан.

Распутывая путь: трудности диагностики аутизма для семей в Казахстане

Нукештаева К.Е. [1], Омаркулов Б. К. [2], Любченко М.Ю. [3], Nailya Delellis [4], Мусина А.А. [5], Каюпова Г. С. [6], Даулеткалиева Ж.А. [7]

[1] *Ассистент-профессор Школы общественного здоровья, Медицинский университет Караганды, Караганды, Казахстан. E-mail: nukeshtaeva@qmu.kz*

[2] *Профессор кафедры семейной медицины, Медицинский университет Караганды, Караганды, Казахстан. E-mail: omarkulov@qmu.kz*

[3] *Профессор кафедры неврологии, психиатрии и реабилитации, Медицинский университет Караганды, Караганды, Казахстан. E-mail: lyubchenko@qmu.kz*

[4] *Профессор Центрального университета Мичигана, Маунт Плезант, Мичиган, США. E-mail: delel1no@cmich.edu*

[5] *Заведующая кафедрой общественного здоровья и эпидемиологии, Медицинский университет Астана, Астана, Казахстан. E-mail: mussina.a@amu.kz*

[6] *Ассоциированный профессор Школы общественного здоровья, Медицинский университет Караганды, Казахстан. E-mail: kayupovag@qmu.kz*

[7] *Декан Школы общественного здоровья, Медицинский университет Караганды, Караганды, Казахстан. E-mail: dauletkalievaz@qmu.kz*

Резюме

Преодоление сложностей диагностики аутизма в Казахстане представляет собой значительное испытание для семей. Недостаток квалифицированных специалистов, ограниченная осведомленность и нехватка ресурсов создают серьезные препятствия для своевременного выявления расстройства и начала вмешательства.

Цель исследования: изучить опыт родителей, проходящих процесс диагностики расстройства аутистического спектра в Казахстане, определить факторы, влияющие на принятие решений семьями, и выявить основные барьеры, с которыми они сталкиваются в поиске диагностической помощи для своих детей.

Методы. Исследование включало проведение полуструктурированных интервью с родителями детей, которым были поставлены диагнозы детский аутизм и атипичный аутизм. Интервью касались трудностей, которые родители испытывали от момента возникновения первых подозрений относительно развития ребенка до получения формального диагноза.

Результаты. Средний возраст, когда родители впервые начали беспокоиться о развитии своих детей, составил 1,91 года, а обращение за профессиональной помощью происходило в 2,19 года. Диагноз же ставился в среднем в возрасте 4,51 года. Среди сопутствующих заболеваний были выявлены синдром дефицита внимания и гиперактивности (16,98%), задержка психоречевого развития (15,09%) и умственная отсталость (9,43%). Только 9,43% родителей выразили удовлетворенность процессом постановки диагноза, в то время как 41,5% остались довольны полученной помощью. Родители сталкивались с множеством препятствий, среди которых были недостаточная осведомленность и поддержка со стороны специалистов и общества, а также логистические и психологические трудности.

Выводы. Данное исследование подчеркивает серьезные проблемы, с которыми сталкиваются семьи в Казахстане при диагностике аутизма у своих детей, включая поздний возраст постановки диагноза и высокую распространенность сопутствующих расстройств. Оно также акцентирует внимание на неудовлетворенности родителей качеством диагностической помощи и необходимости улучшения доступа к своевременным и эффективным услугам, а также усиления поддержки родителей в процессе диагностики.

Ключевые слова: расстройства аутистического спектра, родительский опыт, Казахстан.

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Original article

Insurance Management in Clinical Trials (International and Domestic Experience

Gulnara Kulkayeva [1], Margarita Graf [2], Valentina Tarassova [3], Adlet Tabarov [4]

[1] Chairman of the Board, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan, E-mail: gulnara1412@mail.ru

[2] Head of Clinical Development Center, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan. E-mail: m.graf@nrchd.kz

[3] Clinical Development Center Project Manager, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan. E-mail: v.tarasova@nrchd.kz

[4] Vice chairman of the Board, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan. E-mail: a.tabarov@nrchd.kz

Abstract

The issue of insurance for clinical trial participants is one of the important factors in creating a "safe" research ecosystem. Clinical trials may encounter adverse outcomes, and researchers are focused on maintaining a balance between the safety of study participants and the bureaucratic obstacles in the legal aspect of the path to scientific discoveries

Objective. Develop recommendations for improving Kazakhstan's clinical trials insurance system based on the analysis of best practices conducted.

Methods. Analysis of the experience of 14 countries on issues of insurance of clinical trials according to 3 parameters: stability of the insurance institution; regulation of the insurance issue; mechanism for reimbursement of insurance payments; and tariff policy.

Results. Each country has its own standardized protocols and requirements for clinical trial insurance. Some countries make insurance "mandatory" by enshrining it in law (most European countries), while others make it advisory (USA, UK). Two forms of research insurance are practiced: "liability" of initiators and "accident" insurance for participants. Approaches to determining insurance limits also differ - some cover only insurance payments upon completion, while others set minimum coverage for an insured event. In Kazakhstan, a norm is regulated that obliges participants in clinical trials to be insured, but there is no mechanism, rules, or requirements for the process. The lack of clear requirements for the content of the document on life and health insurance for research participants is a barrier for sponsors.

Conclusion. Based on the experience of international practices, it is necessary to consolidate a national model of insurance for clinical trials in Kazakhstan. The key aspects for promoting the clinical trials insurance system at the political level in Kazakhstan are the definition of insurance, insurance event, amount of insurance payments, insurance rates, the procedure for paying the insurance premium, the procedure for concluding the contract and its term, rights, and obligations of the parties to the contract and insured persons, the procedure for making insurance payments.

Keywords: clinical research, subject insurance system.

Corresponding author: Graf Margarita, Head of Clinical Development Center, National Research Center for Health Development named after Salidat Kairbekova, Astana, Kazakhstan.
Postal code: Z05K5M0
Address: Kazakhstan, Astana, Mangelik El Avenue, 20
Phone: +7 7172 570-951 (1060), +7 701 915 9222
E-mail: m.graf@nrchd.kz

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Introduction

Insurance is a critical component in clinical research, serving both as a regulatory requirement and a safeguard for participants. According to the Declaration of Helsinki, established by the World Medical Association, the welfare of participants in research involving human subjects is paramount. This principle mandates that researchers take all necessary measures to minimize potential adverse effects on participants' physical, mental, and social well-being [1].

In today's global environment, with the observed growth of clinical trials (from 2,408 trials in 1999 to 54,952 in 2022), insurance plays a pivotal role in establishing a "safe" research ecosystem. This growth underscores the necessity of ensuring that the principle of benefit outweighs risk for study participants [2]. Clinical trials may encounter adverse outcomes, as, for example, in studies with fialuridine drugs (NIH, USA, 1993), TGN1412 (TeGenero, UK, 2006), the results have significantly influenced changes in the rules and procedures governing clinical trials [3-4].

Countries are focused on developing affordable clinical research insurance systems that balance participant safety with legal and bureaucratic challenges in pursuing scientific discoveries. Sustainable insurance, which ensures the protection of research subjects' rights in cases of harm, has been shown to impact patient recruitment and boost interest in participation positively. The approach to clinical research insurance; the level of regulation of the issue; the amount of insurance payments, premiums; the judicial mechanism, and the claim process differ from country to country. On the one hand, countries implementing a national insurance system demonstrate a commitment to the development of the clinical research market, on the other hand, this is a barrier to international research, leading to financial costs on the part of the sponsor.

For Kazakhstan, the clinical research insurance system is not fully regulated, and today sets an important task for the country's politicians – to create sustainable conditions for the promotion of clinical research, including international ones. While Kazakhstan's legislation mandates life and health insurance for participants in clinical research, the mechanisms for implementing this requirement remain underdeveloped. This gap hinders the creation of a robust environment for clinical research and limits the country's ability to attract and facilitate international studies.

The objective of the review is to develop recommendations for improving the clinical trials insurance system in Kazakhstan based on the analysis of best practices.

Methodology

The clinical trials insurance systems of the USA, European countries (Germany, Sweden, Switzerland, Sweden, France, etc.), Russia and others (n=14) were analyzed. The assessment was carried out following the analytical scheme based on a set of relevant (significant) parameters: sustainability of the clinical trials insurance institute; regulation of the clinical trials insurance issue; mechanism for reimbursement of insurance payments with the establishment of presentation periods; and tariff policy in terms of determining the amount of insurance payments. The study materials were national regulatory legal acts, industry standardizing documents, and original articles on the issue under study over the past 3 years.

International practice of clinical trial insurance

In alignment with the standards of good clinical practice (GCP) in conducting clinical trials, countries adhere to the implementation of insurance policies at the national level. Each country has its standardized procedures for insurance and liability coverage related to clinical trials (Table 1). Some countries give insurance a "mandatory" ("permitted") character, securing it at the legislative level, as in most European countries, other countries – a recommendatory ("non-admission") (USA, UK). Two forms are practiced: – insurance of "liability" of the initiators of the study (sponsor, research team) and "from accidents" of the participants in the study. Approaches to determining insurance limits also vary – some require the initiators of the study to cover only insurance payments upon the fact, while others establish minimum coverage levels for insured events.

1/3 of the clinical trials market is in the United States and remains one of the main sources of global research [5-6]. In the United States, clinical trials insurance is not mandatory ("non-admitted") and is provided within the framework of the existing health insurance system (Affordable Care Act), and covers routine costs of medical care (visits to health workers, standard treatments, laboratory tests, supportive therapy, etc.) [7]. Since 2020, the Clinical Treatment Act (H.R. 913) has been passed in the United States, which requires all federal programs to cover routine costs associated with qualifying clinical trials (Phase I, II, III, or IV) that are conducted in connection with the prevention, detection, or treatment of cancer or other life-threatening conditions [8].

According to experts (D. Brettler et al., 2022), clinical trials conducted in the United States have a certain flexibility in the development of insurance programs. [9]. Typically, insurance policies are issued for 12 months, covering the anticipated activities of the sponsor within that timeframe. US companies conducting clinical trials involving humans outside the country face several problems: differences in insurance regulations, insurance payment mechanisms, and other processes in countries with their insurance systems. An important problem for the US insurance system is the lack of national standards for compensation for damage associated with clinical trials, which leads to denials of insurance for clinical trial subjects because the service "clearly does not meet the established standard of care."

Some U.S. states (including Pennsylvania and New Jersey) have "comparative negligence" statutes that 1) limit the amount of damages a research subject can recover if the research subject is partially responsible for the damages; and 2) allow a research subject to sue a party that is only minimally responsible for the damages [10].

The European experience of insuring subjects of clinical trials is related to the adoption in 2014 of the European Union Regulation on Clinical Trials No. 536/2014, which notes the responsibility of EU Member States (Article 76) for compensation for any harm caused to a subject as a result of his participation in a clinical trial conducted on their territory [11]. Along with this Regulation, individual national standards for insurance systems have been defined in the EU Member States. Approaches to ensuring participants in clinical trials vary, despite the general principles. This variation can be a barrier to conducting international clinical trials, as the lack of a unified insurance mechanism increases bureaucracy and extends the time

required to obtain necessary permits. Characteristic features of the insurance system in the EU Member States are the mandatory availability of insurance coverage for study participants [12]. Insurance is intended to provide compensation for any harm caused to the subject's health as a result of his or her participation in a clinical trial, and in practice insurance companies pay compensation only for specific damages incurred – the cost of treatment and loss of ability to work. Exclusions include worsening of pre-existing health problems unrelated to participation in a clinical trial; intentional harm to health caused by participants or the research team; and the event of withdrawal from the trial.

The insurance must cover the period from the inclusion of the first patient (screening) to the last visit, and also take into account the extended reporting period – the period during which the insurance company can be notified of harm caused to the research subject (in Germany – up to 10 years, in other countries - from 3 months to 10 years, and for studies involving children – more than 10 years).

The cost of clinical trial insurance is not set at a flat rate but varies based on several factors: risk (studies using non-invasive medical devices have lower costs than studies involving surgical interventions); duration of the clinical trial; number of study subjects; cohort of subjects (children and subjects with severe pre-existing diseases increase the cost). The cost of insurance is estimated from 5 to 30 thousand euros per clinical trial (average value – 17.5 thousand euros).

In Germany, Austria, and the Netherlands, participants in clinical trials are subject to compulsory accident insurance, while the systems of the Czech Republic, France, Greece, Portugal, Spain, and Poland are based on compulsory "liability" insurance for those conducting the trial, although the amount of insurance is often not fixed by law. In the UK, the insurance mechanism is voluntary, but in practice accident insurance is always required regardless of fault.

One of the first countries in the European Union to introduce insurance in clinical trials is Germany (since 1978), compared to all EU countries (since 1985). Insurance in Germany is issued in favor of the participant in the clinical trial with an insurance company authorized to operate in an EU member state. Insurance issues are regulated by the German Pharmaceutical Products Act (AMG) for medicinal products and the German Medical Devices Act (MPG) for medical devices [13]. Many sponsors also issue insurance for cases for which insurance is not required by law, for example, for new methods of examination and treatment [14]. A mandatory condition is a reasonable proportionality of the volume with the risks associated with the clinical trial (in the event of physical injury, deterioration in health, and death), and the minimum insured amount is 500 thousand euros per subject and at least 5 million euros per study protocol. Germany is also one of the EU countries that provides insurance for research using radioactive materials. The amount of the insurance premium is determined taking into account the medicinal product, the phase of the clinical trial, the number of study subjects, and the amount of the insurance sum, and ranges from 30 to 400 euros per volunteer [15].

Since the adoption of the Federal Law on Research Involving Human Participants (HRA) in Switzerland in 2014, the minimum insurance amount is set depending on the categorization of research projects involving humans depending on the degree of expected risk to the participants (A, B and C): for risk class A (registered medicinal products, bioequivalence) no payments are made, for class B the amount for an accident (bodily injury) is 250 thousand euros (3 million euros per protocol), and for class C (for unregistered medicinal products) - 1 million euros (per protocol - 10 million euros) [16,17]. Damage that occurs during the term of the insurance policy is subject to insurance, and the extended coverage period is 120 months after the termination of the clinical trial. The amount of insurance premiums in Switzerland varies and depends on the number of participants, in the study, while the minimum value always remains reserved [18,19].

The Austrian clinical trial insurance system is regulated according to the industry standard Medicines Australia Guidelines for Compensation for Injury Resulting from Participation. This system, akin to practices in other countries, determines the amount of insurance compensation based on the nature, severity, and persistence of the harm sustained. The minimum insured amount for an accident under the protocol is 3.5 million euros per study protocol or 500 thousand euros for study participants [20].

The insurance system in Spain (Art Royal Decrece 561/1993) makes the sponsor responsible for taking out civil liability insurance, according to which, in the event of failure to fully cover damages, all participants in the study (the clinical trial organizer, the principal investigator, and the head of the clinical site) are jointly and severally liable, regardless of fault, for damage caused to the health of the clinical trial subject (during the study and for one year after its completion), as well as for economic damage directly arising from such damage [21,22]. Limitations on compensation are noted in relation to harm caused to the health of the subject if it is inherent in the pathology being studied or is part of the side effects of the drug prescribed for the specified pathology, as well as the development of the disease itself as a result of the ineffectiveness of the treatment. The minimum insured amount of civil liability in Spain is 30 million monetary units of the local currency (equivalent to 1,775.0 thousand dollars) for each study subject, in the form of a one-time compensation [23]. In the event that such compensation is established as a permanent or increasing annual income, the coverage limit of such insurance will be no less than 3 million monetary units of the country's currency per year (177.5 thousand dollars) per subject of the clinical trial.

A difference is the Swedish experience, where there is no statutory regulation on insurance, but the Swedish Medicines Association provides sponsors with insurance through a group mechanism [24]. This mechanism provides insurance limits on a group basis, so that companies share the limits within the pooling agreement, rather than having a specific limit for their specific trial. With this approach, insurance payments depend on an adequate policy for setting limits available at the time of the claim. This approach may result in claims against the sponsor of one clinical trial leaving other sponsors without sufficient protection.

In the UK, clinical trial insurance policies are optional and are available in two ways: Fault Policies – legal costs, expenses, and compensation awarded to litigants as a result of negligence or lack of due care; and Non-Negligent Harm – compensation is paid following guidelines to participants who have suffered harm [25]. This insurance must demonstrate a causal relationship to the harm. The Association of the British Pharmaceutical Industry (ABPI) has published guidance setting out the distinction between compensation for Phase I (healthy volunteers) clinical trials and Phases II, III, and IV.

These guidelines apply to all clinical trials since 2015. For Phase I clinical trials that do not involve direct therapeutic benefit to the subjects (healthy volunteers and patient volunteers not suffering from the target disease), warranties and legal obligations to pay compensation in the event of harm arising from participation in the clinical trial are required. Compensation is provided for personal injury arising from negligence on the part of the research team, defect in service (failure to meet safety expectations), and other causal relationships. The amount of compensation is calculated based on the amount of damages normally awarded for similar harm by an English court if liability is accepted. Compensation may be reduced to the extent that the volunteer is partly responsible for the harm (or if the volunteer has received equivalent payment for such harm under any insurance policy taken out by the company in favor of the volunteer). The recommended minimum level of insurance cover (since 2012) is set at £5 million in total per protocol for first-in-human studies, reducing this to a minimum of £2,5 million in total per protocol for other types of studies [26]. The standard for the duration of insurance coverage (recommended) is up to 3 years after completion of the study.

For Phase II, III, and IV trials, the Association of the British Pharmaceutical Industry advocates a simple and expeditious procedure for the provision of compensation for harm arising from participation in clinical trials [276]. Although there is no legal obligation, compensation should be paid to trial subjects who suffer physical injury (including death). Compensation should be paid if, on the balance of probabilities, the harm was attributable to the administration of the investigational medicinal product (except in Phase IV) or to any clinical intervention or procedure covered by the trial protocol, and only for the more serious harm of a long-term and disabling nature (including exacerbation of existing disease), and not for temporary pain or discomfort or less serious or treatable complaints. Compensation should also be paid to a child who suffers harm in utero when the subject's mother participates in a clinical trial. It is stipulated that compensation should not be paid (or should be reduced) where there are significant departures from the trial protocol; in the event of a wrongful act or default by a third party, including the failure of a physician to adequately respond to adverse reactions; as well as due to the negligent behavior of the patient himself. The mechanism for determining the amount of compensation is flexible, which can be reduced or excluded taking into account the seriousness of the disease, the degree of likelihood of adverse reactions, etc.; as well as taking into account the risks and benefits of the established treatment compared with known or investigational drugs, and requires taking into account the circumstances of the individual patient.

The Brazilian experience in terms of compensation for damages resulting from clinical trials, which is also enshrined in law, is interesting. As specified in PANDRH-GCP, the sponsor is responsible for providing insurance coverage for any unforeseen damage to study participants [28]. Normative documents do not limit liability and compensation for damages, even in cases where this is provided for in the Clinical Trial Agreement (CTA) [29]. Insurance provides for two types of compensation: free comprehensive medical care (immediate and deferred, with the term for the latter not regulated), as well as compensation for damages (for physical and psychological injuries). The investigator, sponsor, and clinical site are fully responsible for medical services during the study, while liability for compensation for damages is not defined [30]. Brazilian legislation does not establish economic losses, the mechanism for receiving insurance payments, or the amount of compensation. The insurance system does not distinguish between “no-fault” compensation. It also defines the possibility and participation of subjects in the study without insurance coverage or by determining an alternative insurance option. But in this case, the research subject bears a double burden - the risk of participating in the study and insurance against possible economic losses.

Despite the rapid growth of the clinical research industry in India (7-10 thousand annually), which is also associated with the possibility of recruiting a large number of research subjects (16% of the world's population lives in this country), the clinical research insurance system is poorly developed [31]. Professional liability insurance for researchers is a common practice, but it does not protect health workers from compensation for claims related to participation in a clinical trial. The system sets minimum and maximum limits, and the insured amount averages from 1 to 20 million, and both the costs of protection and claims are paid under the policy within the policy limits. The insured amount, as in the EU countries, depends on a number of factors, including the size of the study, the phase of the study, the financial stability of the organization conducting the study, the type of drug or device being studied, and the demographic characteristics of the subjects on whom the studies will be conducted [32].

In the report by K. Sridharan et al. (2016), the results of the assessment of insurance documentation by the Ethics Committees of India were presented, in which many shortcomings were found - lack of coverage for the entire duration of clinical trials; the presence of provisions that make it difficult to pay compensation to study participants, etc., identifying these areas as priority areas for improvement in these issues [33].

According to Chinese law, clinical trial insurance is mandatory to cover treatment costs and provide appropriate compensation for subjects harmed by the study drug. However, there is no requirement for local insurance for this purpose (Chinese companies have not offered such services until recently), and it is carried out within the framework of global clinical trial insurance, which includes China [34-35]. This approach to the insurance system has expanded the horizons of clinical trials, with 27,7% of global clinical trial activity in 2022 occurring in China [36].

In Latin America, clinical trial insurance is also not mandatory, but many bioethics committees, especially in Argentina, occasionally request proof of insurance as part of their document review when approving clinical trials. The increased demand for insurance has led to an increase in clinical trial insurance in local markets.

In Australia (eg NSW Public Health Organisations), insurers must be approved by the Australian Prudential Regulation Authority, or an overseas insurer with a minimum Standard and Poor's (or equivalent) credit rating of A- or above. The policy must provide coverage for study subjects for at least A$20 million per occurrence and in aggregate per year [37, 38]. The policy must not include a deductible or self-insurance amount exceeding A$25,000 for each claim or series of claims arising from the same underlying cause.

Russia has taken the path of building a system of compulsory insurance for clinical research. The Law on the Circulation of Medicines defines the object of insurance as the property interest of the insured person associated with harm to his life or health as a result of clinical trials of a medicinal product [39].

Insured events are the death of the insured person or deterioration of his health, including those leading to the establishment of disability, if there is a causal relationship between the occurrence of this event and the participation of the said person in the clinical trial. When researching a biomedical cell product, the initiators of the research refer to the relevant law [40].

The standard rules establish the amount of insurance payments - in the event of the death of the insured person - 2 million rubles (22.5 thousand US dollars), in the event of deterioration of health resulting in the establishment of disability from 500 thousand to 1.5 million tenge (3.5 - 17 thousand US dollars) depending on the disability group, and also in the event of deterioration of health, but not resulting in the establishment of disability - no more than 300 thousand rubles (3.5 thousand US dollars) [41]. The amount of the insurance tariff is determined depending on the purposes of the clinical trial, for example, to establish the safety of a drug for patients from among healthy volunteers - 9.811 rubles (US), to select optimal dosages and course of treatment - 3.804 rubles (US), etc. The rules also regulate insurance coefficients, which differ depending on the number of patients and are built on the principle - the higher the number of patients, the lower the coefficients, for example, when insuring up to 50 patients - 1.0, and when insuring over 800 patients - 0.7. The insurance premium is determined depending on the insurance tariff.

The insurance payment under the contract is made regardless of payments due under other types of insurance, including compulsory insurance, as well as in the order of social security and compensation for damage (patients' demands for compensation for damage in the form of a property claim following the civil legislation of the Russian Federation).

Kazakhstan's realities in building an insurance system for conducting clinical trials

In Kazakhstan, the insurance of subjects of clinical trials is carried out in practice within the framework of general insurance activities; there are no rules regulating the insurance of subjects of clinical trials [42]. The Code of the Republic of Kazakhstan "On Public Health and the Healthcare System" defines the mandatory condition for conducting interventional clinical trials as the execution of documents on the life and health insurance of the research participant (civil liability insurance contract, Insurance Policy). Responsibility for the insurance of research subjects is determined by the GCP Rules, which also guarantee legal and financial support from the sponsor to researchers or a medical organization in the event of claims related to the study, except for those claims that arose as a result of intent or negligence on the part of the researcher or members of the research team [43]. The formation of a policy on insurance activities in the field of clinical trials does not lie within the competence of the authorized representative in the field of health.

The Rules for Conducting Clinical Trials regulate the provision of a Standard for the Activities of Bioethics Commissions, which defines the content of a document on life and health insurance for a research participant - but this document has not yet been developed [44]. The lack of clear requirements for the content of a document on life and health insurance for research subjects is a barrier for sponsors (especially when conducting international clinical trials). The industry needs to develop requirements for the process of insuring research subjects - from determining the size of the insurance rate and the insurance amount in the event of death, deterioration of health, resulting in disability, etc.; to a mechanism for determining cause-and-effect relationships and rules for compensation by insurance companies.

The imputed system of professional liability insurance for healthcare professionals does not include the issue of "insurance of the liability of researchers and protection of their interests." This regulatory document specifies responsibility for failure to perform, improper performance of professional duties of healthcare professionals, resulting in varying degrees of severity of health and death, as well as mechanisms for protecting their interests, without taking into account the specifics of research activities [45].

The clinical research system of Kazakhstan requires regulation of the issue of insurance (of participants in clinical research), in the construction of which it is rational to refer to the experience of countries with stable systems in the global community.

The key areas for creating a clinical research insurance system in Kazakhstan are as follows. It is rational to create it within the framework of the existing research infrastructure of the country through regulation by national rules. Countries are given the competence to establish national rules for insurance conditions - definition of the concept of "insurance" and "insured event", the number of insurance payments, insurance rates, the procedure for paying the insurance premium, the procedure for concluding the contract and its term, the rights and obligations of the parties to the contract and the insured persons, the procedure for making insurance payments.

Today, the definition of "clinical research insurance" is understood as "a risk transfer instrument in which one organization (the policyholder) transfers its risks (with exceptions) to another entity (the insurer) through an agreed payment and contractual agreement." In turn, an exception is understood as "an instrument by which the insurer limits the amount of risk that the policyholder can transfer to it." The essence of this insurance is to provide the policyholder with a reserve against claims from patients who suffered during a clinical trial.

This conceptual apparatus defines all the components of the process that must be included when building an insurance system and includes:

- Defining the vector to which the insurance coverage will be directed - insurance of damage suffered by the subject of a clinical trial and/or insurance of the professional liability of the researcher. Several countries adhere to the second type, implying that it covers all the risks of a clinical trial.

- Defining the type of compensation to which the subject of a clinical trial is entitled - medical care in the event of adverse effects (except for short-term ones) or financial compensation for psychological, social, and economic damage.

- Setting the limit of coverage of an insurance event in the current practice can be based on the approach of "legal liability" (as in the USA) or "no-fault" (some EU countries). It is necessary to set these limits by the risks, as well as the criteria for setting the limits of these amounts (standard compensation amounts). A number of insurance systems have developed a special fair approach, according to which the amount of payments is calculated depending

on risk factors (age of the patient, his health condition at inclusion and the phase of the study, etc.). When determining the compensation mechanism, stakeholders often rank financial costs based on the phase of the clinical study - the amount of insurance payments for the early phases of the study is often higher. It is believed that subjects of phases 3 and 4 studies are exposed to less risk.

- Establishment of the insurance period - an extended reporting period, which determines the period after the expiration of the policy, during which the cause-and-effect relationships of damage as a result of the clinical study can be identified, and insurance payments are covered. In many countries, the definition of the extended insurance period is regulated by law, and in practice ranges from 3 months to 10 years (on average for the countries analyzed in this article up to 3 years).

- A list of the standard package of documents required to settle claims.

One of the important factors in building a clinical research insurance system is the overregulation of judicial practice - the mechanism for establishing causal relationships between the resulting harm or death (which may be caused by the natural progression of a disease) as a consequence of the actions of a medicinal product and medical device, or the negligent attitude of the research team when implementing the research protocol. It is rational to also provide for a "no-fault" compensation option when it is impossible to establish the fact of negligence/error on the part of the research team.

For the effective implementation of the clinical research insurance system, it is necessary to create a stable institutional basis - insurance companies operating in this area (registered or licensed in the country). Insurance companies must not only guarantee that the policies they provide are broad and comply with local and national rules (for international ones), but also be able to protect the interests of participants in the research process. Following international practice, several external factors are of great importance for insurance companies - a qualified research environment (researchers, medical organizations), the responsibility of study participants, a well-established legislative system, a legal basis for regulating activities, and requirements for insurers.

The system of compensation (payments) to subjects of clinical trials in court proceedings in many countries is considered through tort liability. In practice, this legal procedure, especially in cases of negligence on the part of health professionals, has disadvantages: high legal costs and labor-intensive process; compliance of the amount of compensation with the level of damage caused; high transaction costs; unknown level of risks and uncertainty in conducting research, etc.

The tendency of sponsors to attract multi-center, international clinical trials dictates the need to create a flexible legal framework for the formation of insurance conditions during clinical trials. Historically, the practice aimed at securing insurance issues following national regulations has become a certain obstacle to the conduct of international multi-center trials.

Conclusions

By adhering to the standards of good clinical practice (GCP), countries guarantee insurance for participants in clinical trials. Each country has its standardized protocols and requirements for how insurance is carried out and for covering liability associated with the conduct of clinical trials.

Based on the experience of international practices, Kazakhstan needs to establish a national insurance model for clinical trials. Key aspects to address in developing and promoting this system at the political level include the definition of insurance, insurance event, amount of insurance payments, insurance rates, the procedure for paying the insurance premium, the procedure for concluding an agreement and its terms, rights, and obligations of the parties to the agreement and insured persons, the procedure for making an insurance payment.

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Клиникалық зерттеулер жүргізу кезінде сақтандыру мәселелерін басқару (халықаралық және отандық тәжірибе)

Кулкаева Г.У. [1], Граф М.А. [2], Тарасова В.М. [3], Табаров А.Б. [4]

Түйіндеме

Клиникалық зерттеулерге қатысушыларды сақтандыру мәселесі «қауіпсіз» зерттеу экожүйесін қалыптастырудағы маңызды факторлардың бірі болып табылады. Клиникалық зерттеулер қолайсыз нәтижелерге тап болуы мүмкін және зерттеушілер зерттеуге қатысушылардың қауіпсіздігі мен ғылыми жаңалықтар жолындағы құқықтық аспектідегі бюрократиялық кедергілер арасындағы тепе-теңдікті сақтауға бағытталған.

Зерттеудің мақсаты: үздік тәжірибелерді талдау негізінде Қазақстанның клиникалық зерттеулерін сақтандыру жүйесін жетілдіру бойынша ұсынымдар әзірлеу.

Әдістері. Клиникалық зерттеулерді сақтандыру мәселелері бойынша 14 елдің тәжірибесін 3 параметр бойынша талдау: сақтандыру институтының тұрақтылығы; сақтандыру мәселесін реттеу; сақтандыру төлемдерін өтеу тетігі; және тарифтік саясат.

Нәтижесі. Әр елдің өзінің стандартталған хаттамалары мен клиникалық зерттеулерді сақтандыру талаптары бар. Бірқатар елдер сақтандыруға «міндетті» сипат беріп, оны заңнамалық деңгейде (Еуропа елдерінің көпшілігі), ал басқа елдер ұсыным бекітеді (АҚШ, Ұлыбритания). Зерттеуді сақтандырудың екі түрі қолданылады: бастамашылардың «жауапкершілігі» және қатысушылардың «жазатайым оқиғалардан» сақтандыру. Сақтандыру лимиттерін анықтаудағы тәсілдер де ерекшеленеді - кейбіреулері тек сақтандыру төлемдерін жабады, ал басқалары сақтандыру жағдайының минималды қамтуын белгілейді. Қазақстанда клиникалық зерттеулерге қатысушыларды сақтандыруды жүргізуді міндеттейтін норма реттелген. Алайда процесске тетік, ережелер мен талаптар бүгінгі таңда әлі де қарастырылмаған. Зерттеуге қатысушылардың өмірі мен денсаулығын сақтандыру құжатының мазмұнына нақты талаптардың болмауы демеушілер үшін кедергі болып табылады.

Қорытынды. Халықаралық тәжірибеге назар аудара отырып, Қазақстанда клиникалық зерттеулер жүргізу кезінде сақтандырудың ұлттық моделін бекіту қажет. Қазақстанда клиникалық зерттеулерді сақтандыру жүйесін саяси деңгейде ілгерілетудің негізгі аспектілері: сақтандыруды, сақтандыру жағдайын, сақтандыру төлемдерінің мөлшерін, сақтандыру тарифтерін, сақтандыру сыйақысын төлеу тәртібін, шартты жасасу тәртібін және оның қолданылу мерзімін, шарт тараптары мен сақтандырылған тұлғалардың құқықтары мен міндеттерін, сақтандыру төлемін жүзеге асыру тәртібін айқындайды.

Түйін сөздер: клиникалық зерттеулер, субъектілерді сақтандыру жүйесі.

Управление вопросами страхования при проведении клинических исследований (международный и отечественный опыт)

Кулкаева Г.У. [1], Граф М.А. [2], Тарасова В.М. [3], Табаров А.Б. [4]

Резюме

Вопрос страхования участников клинических исследований является одним из важных факторов при формировании «безопасной» исследовательской экосистемы. Клинические исследования могут сталкиваться с неблагоприятными исходами, и исследователи ориентированы соблюдать баланс между безопасностью участников исследования и бюрократическими препятствиями в правовом аспекте на пути научных открытий.

Цель исследования: Выработка рекомендаций по совершенствованию системы страхования клинических исследований Казахстана на основе проведенного анализа лучших практик.

Методы. Анализ опыта 14 стран по вопросам страхования клинических исследований по 3 параметрам: устойчивость института страхования; регуляция вопроса страхования; механизм возмещения страховых выплат; и тарифная политика.

Результаты. Каждая страна имеет собственные стандартизированные протоколы и требования к страхованию клинических исследований. Ряд стран придают страхованию «обязательный» характер, закрепляя его на законодательном уровне (большинство стран Европы), другие страны - рекомендательный (США, Великобритания). Практикуется две формы страхования исследования: «ответственности» инициаторов и «от несчастных случаев» участников. Различаются и подходы при определении страховых лимитов – одни покрывают только страховых выплаты по факту, другие - устанавливают минимальное покрытие страхового случая. В Казахстане зарегулирована норма обязывающая проводить страхование участников клинических исследования, но отсутствует механизм, правила и требования к процессу. Отсутствие четких требований к содержанию документа о страховании жизнь и здоровью участников исследования является барьером для спонсоров.

Выводы. Ориентируясь на опыт международных практик, в Казахстане необходимо закрепить национальную модель страхования при проведении клинических исследований. Ключевыми аспектами для продвижения на политическом уровне системы страхования клинических исследований в Казахстане выделяется: определение страхования, страхового случая, размера страховых выплат, страховые тарифы, порядок выплаты страховой премии, порядок заключения договора и срока его действия, права и обязанности сторон договора и застрахованных лиц, порядок осуществления страховой выплаты.

Ключевые слова: клинические исследование, система страхования субъектов.

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Letter to the Editor

Prospects and Relevance of Studying Craniofacial Changes in Anencephaly

Anar Abdullayev

Head of Department of Human Anatomy and Medical terminology, Azerbaijan Medical University, Baku, Azerbaijan.
E-mail: anarabdullaev72@mail.ru

Abstract

Anencephaly, being a rather severe malformation, represents an extensive field for studying such relationships as the brain-skull (brain-base of the skull, brain-vault of the skull, brain-facial skull), brain-endocrine system; not only the theoretical, but also the absolutely complete clinical significance of this kind of research is very great. Of course, first of all, the study of anencephaly covers problems of occurrence (genetic, racial predisposition, diet, metabolic relationships) and diagnosis. However, the cranial changes associated with anencephaly, although primarily described due to the close proximity and relatively easy access, are unfortunately less addressed in the relevant literature. Intensive growth in the technology of plastic and reconstructive operations on the face, orthodontic interventions require thorough knowledge of the formation of skull structures; this formation is impossible without correct relationships with the brain.

The aim of the research was to study the state of research on craniofacial changes in anencephaly. Anencephaly causes significant changes not only in the cranial vault but also in its base and facial part.

A distinctive feature of these changes, first of all, is their extreme variability. The whole variety of developmental processes occurring at the contact between the brain and the skull, with anencephaly, turns into a rather complex malformation picture; studying this picture requires the attention of both clinicians and morphologists. Naturally, all attention is focused on solving etiological and diagnostic issues; in addition, it is necessary to take into account the growing needs of transplantation. But with all this, the anatomical picture of all cases of anencephaly must be clearly clarified, taking into account the cause-and-effect relationships of what is happening, from which it follows that the development of the problem of defects of the primary neural tube in general and anencephaly in particular should be carried out initially from a morphological point of view.

Defects in the central nervous system associated with defects in the formation of the primary neural tube have extremely serious consequences. Anencephaly is the most severe of these developmental defects. Diagnosis at the earliest stages of pregnancy is difficult due to objective circumstances. Even diagnosis within the time limits indicated in the literature, i.e., acceptable for the same objective reasons, requires special preparedness specialists. Considering these associated factors, the study of cranial changes in anencephaly is of particular importance. This concerns both the establishment of certain standards for the development of the skull and the determination of the special properties of the anencephalic skull to improve diagnosis.

Key words: anencephaly, fetus, skull, neural tube defects.

Corresponding author: Abdullayev Anar Sardar oglu, Head of Department of Human Anatomy and Medical terminology, Azerbaijan Medical University, Baku, Azerbaijan
Postal code: AZ 1010
Address: Azerbaijan, Baku, Academician Mirali Kashkay Str. 24/83
Phone: +994516820871
E-mail: anarabdullaev72@mail.ru

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Introduction

Absence of the brain (anencephaly) results in acrania (absence of the skull), acalvaria (roofless skull), or cranioschisis (fissured cranium), with variable effects on the face. These fetuses have a minimal survival rate. Ossification of the intramembranous calvarial bones depends on the presence of the brain; in its absence (anencephaly), no bony calvaria forms. In anencephaly, the absence of the calvaria results in cranioschisis, characterized by a short, narrow, lordotic chondrocranium, with notochordal anomalies in many cases; the absence of the brain results in the cranial base remaining unflattened, allowing the facial bones to occupy anomalous positions. Macroglossia typifies anencephaly; trisomy 21 syndrome; Crouzon syndrome; and the association of coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies (CHARGE syndrome) [1].

Among the neural tube defects, the reported prevalence of anencephaly was highest at 2.1 per 1000 births (95% CI, 1.6–2.8), followed by spina bifida at 1.9 per 1000 births (95% CI, 1.4–2.7). Anencephaly is a neural tube defect that occurs due to the failure of normal tube closure at the cranial end of the 4-week old embryo, resulting in the absence of a major portion of the brain, skull, and scalp. Anencephaly (a Greek word meaning "no brain") is the end stage of a neural tube defect, starting with the (partial) absence of the cranial vault (acrania) (Figure 1). Anencephaly is characterized as the most severe form of neural tube defect (NTD), and the role of folic acid deficiency in its development is discussed. Hispanics are indicated as a population at greater risk in terms of anencephaly development. Also, when discussing other risk factors, attention is paid to defects in folic acid metabolism, obesity and diabetes, dieting, etc. [2–5]. General interest in the topic of anencephaly has increased due to the possible use of anencephaly organs for transplantation and the ethical and scientific issues raised by this possibility [6].

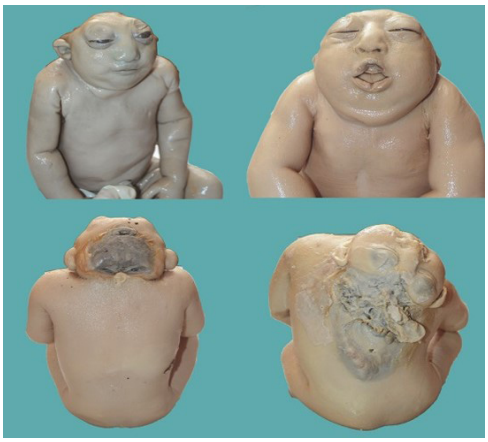

Figure 1 - Anencephaly (from the museum of the Department of Human Anatomy and Medical Terminology of the Azerbaijan Medical University).
*The draft of this manuscript has been approved by the Bioethics Committee of the Azerbaijan Medical University**

The worldwide prevalence of anencephaly is high; therefore, clinicians and specialists need to emphasize the importance of prevention strategies as well as control and treatment strategies [7].

Naturally, the strengthening of the diagnostic component of the problem of anencephaly and neural tube defects in general is associated with ultrasound examinations of the developing fetus. However, until certain stages of pregnancy, due to objective reasons, such a study cannot give clear results [4, 8–10].

Fleurke-Rozema J.H. et al. [4] showed that in a country where first trimester ultrasound at 11 to 14 weeks' gestation is not performed routinely, many cases of anencephaly remain undetected until the midtrimester scan. Anencephaly and exencephaly can be diagnosed in the first trimester, when the skull is not visible due to the absence of the cranial vault, but the face itself, including the orbits, can be visualized. When the brain remnants appear flat, the term anencephaly is used. When brain remnants appear as an irregular, bulging structure, the term exencephaly is usually preferred. Prenatal diagnosis is obvious in the second trimester. In the first trimester, the rounded structure corresponding to the exposed brain can be misleading if an ultrasound is done too early, at 8–10 weeks. This emphasizes the need to perform ultrasounds in the first trimester of pregnancy, at 12–13 weeks, when it becomes possible to analyze the anatomical structures of interest [8].

Exencephaly, anencephaly, meningoencephalocele, and alobar holoprosencephaly were fully detected on scans in the first trimester. Several types of central nervous system malformations may be partially detected on scans in the first trimester, including posterior fossa (PFA) anomalies, open spina bifida, semilobar holoprosencephaly, and severe ventriculomegaly [9]. Anencephaly occurs when the head of the neural tube does not close, resulting in the absence of the fetal skull and brain. By the end of the first - beginning of the second trimester, a normal fetal head should be visible on a prenatal ultrasound. Anencephaly is diagnosed when no calvarial vault or normal brain tissue is visible above the orbits. Careful knowledge of normal intracranial anatomy and the use of a logical sonographic approach can improve the description of abnormalities, leading to a more accurate differential diagnosis in early pregnancy [10].

According to Thomas J.A. et al. [6], for the neuroendocrinologist, the tragedy of the human fetus with the congenital absence of the brain provides at least the opportunity to obtain information about the role of the hypothalamus and its hypophysiotropic hormones in the development of the human anterior pituitary gland and its endocrine target glands. Another issue is the growing evidence that folic acid supplementation around the time of conception reduces the incidence of neural tube defects.

Thus, anencephaly, being a rather severe malformation, represents an extensive field for studying such relationships as the brain-skull (brain-base of the skull, brain-vault of the skull, brain-facial skull), and brain-endocrine system; not only the theoretical, but also the absolutely complete clinical significance of this kind of research is very great. Of course, first of all, the study of anencephaly covers problems of occurrence (genetic, racial predisposition, diet, metabolic relationships) and diagnosis. However, the cranial changes associated with anencephaly, although primarily described due to the close proximity and relatively easy access, are unfortunately less addressed in the relevant literature. Intensive growth in the technology of plastic and reconstructive operations on the face, orthodontic interventions require thorough knowledge of the formation of skull structures; this formation is impossible without correct relationships with the brain.

Based on the above, we set a goal to study the state of research on craniofacial changes in anencephaly.

Craniofacial changes in anencephaly

According to Trenouth M.J. [11], anencephaly has great importance because it acts as a natural experiment for studying normal and abnormal skull growth. Normal craniofacial growth can be explained as a multifactorial process; in this process, all components are balanced and interact in a coordinated manner. This is largely consistent with research [12], which states that comprehensive studies of different bone groups according to their discrete evolutionary precursors, combined with facial analysis, are a vital prerequisite for understanding the interdependence of the development of various tissue components as well as for determining pathogenesis.

Until the studies are compiled, it is difficult to assess which defects are primary and which are secondary.

The specimens in the study of Garol J.D. et al. [13] were classified and grouped as follows: meroacrania, a cranial defect not involving the foramen magnum; holoacrania, a cranial defect involving the foramen magnum; and holoacrania with rachischisis, a cranial defect involving the foramen magnum and extending into the vertebral column. The size of the calvarial defect in fetuses with meroacrania ranged from about one centimeter to several centimeters in diameter, the latter exposing the entire floor of the skull. The opening in the skull was successively limited in front by the frontal bone, laterally by the parietal or squamosal temporal bones, and behind by the parietal or occipital bones, depending on the size of the defect. As the size of the vault defect increased, the size, shape, and spatial orientation of the bones of the calvarium changed more strongly than normal.

Kjaer I. et al. [14] indicated that cases of anencephaly without cervical rachischisis differ markedly from cases with cervical rachischisis. Morphological characteristics, such as bilateral narrowing of the basilar part of the occipital bone combined with normal craniocaudal dimensions, are found in cases without cervical rachischisis. In these cases, frontal clefting of the vertebral bodies was observed. Caudocranial shortening of the basilar part of the occipital bone was found in cervical rachischisis, in which there was also complete median splitting of the vertebral bodies. The study found that when initial closure of the neural groove failed, skeletal abnormalities were more extensive. The study supports the hypothesis that the notochord is an important clue to understanding the pathogenesis of anencephaly.

The cranial floor in cases with meroacrania changed shape from ovoid to trapezoidal, with a narrow end located in the front. This configuration is caused by a decrease in the width of the anterior fossa and the adjacent part of the middle fossa, as well as an increase in the width of the posterior fossa. The middle fossa in front was shallow, and in front of its posterior border, the bottom was not concave but convex. The border between the middle and posterior fossas ran almost perpendicular to the midline. The posterior fossa maintained the same width as the middle fossa instead of tapering posteriorly. In the lateral projection, the bottoms of the anterior and middle fossae were at the same level [15].

Lomholt J.F. et al. [16] noted the importance of the connection between bone compartments and their neural contents. Authors pointed out that neuro-osteologically, the space for the cerebellum is smaller in fetuses with anencephaly than in normal fetuses of the same age, and that there is a difference in size reduction. Examining the development of the cerebellum and brainstem in anencephaly in relation to skull base development may help clarify whether the smaller posterior fossa volume is a developmental error or simply secondary to a calvarial defect. The study revealed two morphological types of the posterior cranial fossa. In one type, the morphology of the cranial fossa was close to normal, whereas in the other type, the posterior cranial fossa was deformed and significantly smaller in size. The latter condition is hypothesized to be due to a primary error in chondral and cranial development.

Because desmal ossification of the neurocranium is induced by the presence of soft tissue (the brain), bone does not develop as a direct consequence of the absence of the brain. The base of the skull, on the contrary, is formed by chondral ossification, which is genetically determined and is therefore also present in anencephaly [17]. The authors indicated that the temporal bone was also one of the bones found in skulls with anencephaly and was positioned vertically in skulls with the foramen magnum and more horizontally in all other skulls without it. From a dorsal point of view, the temporal bones were located at different angles; in skulls without a foramen magnum, their petrous part was located significantly below the horizontal. In addition, the seven skulls had a rather acute angle from a dorsal point of view and less than 150° in the location of the temporal bones, while the two skulls had a rather obtuse angle. Despite the altered arrangement of the temporal bones and the base of the skull, all foramina for nerves and vessels were present, but their position and the direction of the foramina changed. For example, in three skulls, the internal acoustic pore was directed cranially, and in eight skulls, dorsally.

The jugular foramen extended far laterally to the internal acoustic pore. Metzner L. et al. [18] pointed out that in anencephaly, the frontal bone is severely affected. In a normal fetus, the frontal bone forms an angle of 122.3 ± 14.2° with the nasal bone. In the anencephalic skull, there was a marked increase in this angle since the frontal bone does not have an eminence. In anencephalics with meroacrania, the glabellar part of the frontal bone formed an angle of 162 ± 8.7° with the nasal bone and then almost immediately lay flat at an angle of 210 ± 9.8° with the nasal bone. In cases of holoacrania and holoacrania with rachischisis, the angles were 199 ± 4° and 192 ± 7.5°, respectively, for the glabellar part of the frontal bone, and in both groups, the frontal eminence was absent. Morphologically, the most affected facial bone was the zygomatic bone. In the lateral

projection, it usually had a rhomboid shape, but normally it had a "⊥" shape.

The frontal process of the zygomatic bone had a posterosuperior slope, while normally it was directed upward. Consequently, the frontozygomatic suture was located more posteriorly than normal.

As indicated by Trenouth M.J. [11], the nasomaxillary segment in anencephaly was significantly smaller, and the intermaxillary space and mandible were significantly larger than normal. The squamous occipital bone was underdeveloped compared to the norm and had a more vertical slope. During normal growth, the squamous occipital bone rotates from a vertical to a horizontal position as the brain grows. The basilar occipital bone was at a much higher level than normal, and the back of the skull was greatly shortened. The base of the skull was also relatively shorter and at a higher level than the normal standard. This discrepancy was most pronounced posteriorly and decreased anteriorly.

The cranial and facial structures of fetuses with anencephaly were affected in various locations. The most significant changes were observed in measurements related to the transverse plane. All measurements except maxillary length, mandibular body length, and mandibular plane angle differed significantly between anencephaly cases and controls. It turned out that during prenatal development, brain growth prevailed over facial growth. These results indicate that cephalic tissue affected not only the base of the skull but also all facial structures [19]. According to Friedmann I. et al. [20], the anencephalic temporal bones provide an excellent source of comparative anatomy for studying the pathology of Meniere's disease and neurosensory lesions.

The strong association between the cleft palate and the male fetus should be considered during the diagnosis. The presence of associated abnormalities like spina bifida, cleft palate, clubbed foot, clubbed hands, and gastroschisis points to the fact that anenchepaly consists of more than one an etiological entity [21].

As follows from the above studies, anencephaly causes significant changes not only in the cranial vault but also in its base and facial part. A distinctive feature of these changes, first of all, is their extreme variability. The whole variety of developmental processes occurring at the contact between the brain and the skull, with anencephaly, turns into a rather complex malformation picture; studying this picture requires the attention of both clinicians and morphologists. Naturally, all attention is focused on solving etiological and diagnostic issues; in addition, it is necessary to take into account the growing needs of transplantation. But with all this, the anatomical picture of all cases of anencephaly must be clearly clarified, taking into account the cause-and-effect relationships of what is happening, from which it follows that the development of the problem of defects of the primary neural tube in general and anencephaly in particular should be carried out initially from a morphological point of view.

Conclusions

Defects in the central nervous system associated with defects in the formation of the primary neural tube have extremely serious consequences. Anencephaly is the most severe of these developmental defects. Diagnosis at the earliest stages of pregnancy is difficult due to objective circumstances. Even diagnosis within the time limits indicated in the literature, i.e., acceptable for the same objective reasons, requires special preparedness specialists. Considering these associated factors, the study of cranial changes in anencephaly is of particular importance. This concerns both the establishment of certain standards for the development of the skull and the determination of the special properties of the anencephalic skull to improve diagnosis.

Conflict of interest. Not declared

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Анэнцефалия кезіндегі краниофациалды өзгерістерді зерттеудің өзектілігі мен келешегі

Абдуллаев А.С.

Адам анатомиясы және медициналық терминология кафедрасының меңгерушісі, Әзірбайжан медицина университеті, Баку, Әзірбайжан. E-mail: anarabdullaev72@mail.ru

Түйіндеме

Анэнцефалия дамудың айтарлықтай ауыр кемістігі бола отырып, ми - бас сүйегі (ми-бас сүйегінің негізі, бас сүйегі, ми-бет бас сүйегі), ми - эндокриндік жүйе сияқты қатынастарды зерттеу үшін кең өрісті білдіреді. Мұндай зерттеулердің тек теориялық емес, сонымен қатар толық клиникалық маңызы өте зор. Әрине, ең алдымен анэнцефалияны зерттеу оның себебін (генетикалық, нәсілдік бейімділік, диета, метаболикалық байланыстар) және диагностика мәселелерін қамтиды. Дегенмен, анэнцефалиямен байланысты бас сүйегінің өзгерістері, ең алдымен, жақындық пен салыстырмалы түрде оңай қол жеткізуге байланысты сипатталғанымен, өкінішке орай, тиісті әдебиеттерде аз қамтылған. Бетке пластикалық және қалпына келтіру операциялары технологиясының қарқынды өсуі, ортодонтиялық араласулар бас сүйек құрылымдарының қалыптасуын терең білімді талап етеді. Бұл қалыптасу мимен дұрыс қатынассыз мүмкін емес.

Зерттеудің мақсаты анэнцефалия кезіндегі бас сүйек - бет әлпетіндегі өзгерістерді зерттеудің жағдайын зерттеу болды.

Анэнцефалия бас сүйегінің қоймасында ғана емес, оның негізі мен бет бөлігінде де елеулі өзгерістер тудырады. Бұл өзгерістердің айрықша белгісі, ең алдымен, олардың шектен тыс өзгергіштігі. Ми мен бас сүйегінің жанасуында болатын даму процестерінің барлық алуан түрі (ми-бас сүйегінің негізі, бас миы, бас миы-бет сүйегі), анэнцефалиямен өте күрделі даму ақаулық көрінісіне айналады. Бұл суретті зерттеу клиниктердің де, морфологтардың да назарын қажет етеді. Әрине, барлық назар этиологиялық және диагностикалық мәселелерді шешуге бағытталған. Сонымен қатар, трансплантацияның өсіп келе жатқан қажеттіліктерін ескеру қажет. Бірақ мұның бәрімен анэнцефалияның барлық жағдайларының анатомиялық бейнесі болып жатқан оқиғаның себеп-салдарлық байланыстарын ескере отырып, нақты анықталуы керек. Осыдан жалпы бастапқы жүйке түтігінің ақаулары мәселесін, атап айтқанда анэнцефалияны дамытуды морфологиялық тұрғыдан бастапқыда жүргізу керек деген қорытынды шығады.

Біріншілік жүйке түтігінің қалыптасу ақауларымен байланысты орталық жүйке жүйесінің ақаулары өте ауыр зардаптарға әкеледі. Анэнцефалия - даму ақауларының ішіндегі ең ауыры. Жүктіліктің ең ерте кезеңдерінде диагноз қою объективті жағдайларға байланысты қиын. Тіпті әдебиетте көрсетілген мерзімде диагноз қою, объективті себептермен, арнайы дайындықты мамандардың қатысуын талап етеді. Осы байланысты факторларды ескере отырып, анэнцефалиядағы бас сүйек өзгерістерін зерттеу ерекше маңызға ие. Бұл бас сүйегінің дамуының белгілі бір стандарттарын белгілеуге де, диагнозды жақсарту үшін анэнцефалиялық бас сүйегінің ерекше қасиеттерін анықтауға да қатысты.

Түйін сөздер: анэнцефалия, ұрық, бас сүйек, жүйке түтігі ақаулары.

Перспективы и актуальность изучения черепно-лицевых изменений при анэнцефалии

Абдуллаев А.С.

Заведующий кафедрой анатомии человека и медицинской терминологии, Азербайджанский медицинский университет, Баку, Азербайджан. E-mail: anarabdullaev72@mail.ru

Резюме

Анэнцефалия, являясь достаточно тяжелым пороком развития, представляет обширное поле для изучения таких взаимоотношений, как мозг-череп (мозг-основание черепа, мозговой свод черепа, мозг-лицевой череп), мозг-эндокринная система; не только теоретическое, но и абсолютно полное клиническое значение такого рода исследований очень велико. Конечно, в первую очередь, изучение анэнцефалии охватывает проблемы причины возникновения (генетическая, расовая предрасположенность, диета, метаболические связи) и диагностики. Однако черепные изменения, связанные с анэнцефалией, хотя и описаны, в первую очередь, из-за непосредственной близости и относительно легкого доступа, к сожалению, менее освещены в соответствующей литературе. Интенсивный рост технологии пластических и реконструктивных операций на лице, ортодонтических вмешательств требуют глубоких знаний формирования структур черепа. Это формирование невозможно без четких взаимоотношений с мозгом.

Целью исследования было изучение состояния исследований черепно-лицевых изменений при анэнцефалии.

Анэнцефалия вызывает значительные изменения не только на своде черепа, но и на его основании и лицевой части. Отличительной чертой этих изменений, в первую очередь, является их чрезвычайная вариабельность. Все многообразие

происходящих процессов развития на соприкосновении мозг - череп (мозг - основание черепа, мозговой свод черепа, мозг - лицевой череп), при анэнцефалии превращается в достаточно сложную мальформационную картину. Изучение этой картины, требует внимания как клиницистов, так и морфологов. Естественно, все внимание сконцентрировано на решении этиологических и диагностических вопросов. Кроме того, надо учитывать растущие потребности и трансплантологии. При всем этом анатомическая картина всех случаев анэнцефалии должна быть четко выяснена, учитывая причинно-следственные связи происходящего, из чего следует, что разработка проблемы дефектов первичной нервной трубки в целом, и анэнцефалии в частности, должна вестись изначально с морфологических позиций. Пороки центральной нервной системы, связанные с дефектами формирования первичной нервной трубки, имеют чрезвычайно тяжелые последствия. Анэнцефалия представляет собой самую тяжелую из этих пороков развития. Диагностика на самых ранних этапах беременности затруднена ввиду объективных обстоятельств. Даже диагностика в сроки, указанные в литературе, т.е. допустимые по этим же объективным причинам требуют специалистов особой подготовленности. Учитывая данные сопутствующие факторы, изучение черепных изменений при анэнцефалии приобретает особую значимость. Это касается как установления определенных нормативов развития черепа, так и определения особых свойств анэнцефалического черепа для улучшения диагностики.

Ключевые слова: анэнцефалия, плод, череп, дефекты нервной трубки.

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Original article

An Analysis of the Adult Population's Opinion in the Republic of Kazakhstan on Satisfaction with the Free Medicine Supply System

Gulzira Zhussupova [1] , Vitaliy Koikov [2]

[1] *Chief Specialist of the Center for the Development of Scientific and Research Activities, Astana Medical University; Researcher at the "SANAT" National Education Development Science Center, Astana, Kazakhstan. E-mail: zhussupova.gu@amu.kz*

[2] *Vice-Rector for Research of the Astana Medical University, Astana, Kazakhstan. E-mail: koykov@inbox.ru*

Abstract

Access to medicines is a fundamental component of the full realization of the right to health. Equal access to medicines is a global priority. Alongside this, market access to innovative medicines is a crucial factor in improving the population's life expectancy and quality of life. The issue of improving the accessibility of medical services by ensuring equal access to quality healthcare is emphasized in the National Development Plan of the Republic of Kazakhstan until 2029. Market access to innovative technologies largely depends on citizens' willingness to adopt the technology. Therefore, patient participation in market access to medicines is crucial.

Research Objective: To study the subjective opinion of the population on satisfaction with the outpatient medicine supply system, offering suggestions to improve its accessibility, effectiveness, and responsiveness to patient needs.

Methods. A sociological study was conducted through a survey of the adult population using the Survey Monkey platform in an online format. The total number of respondents: adults - 1,730 people, including 710 men (41.05%) and 1,020 women (58.95%).

Results. Almost 80% of respondents reported that medicines are always available in the pharmacy, but 18% noted that they are periodically absent, and 2.5% believe that free medicines are never available in pharmacies. 78% of the listed medicines that patients purchased independently are included in the List of free medicines. 23.41% of respondents took antibiotics without a doctor's prescription. 61.12% of respondents are not ready to pay the price difference between the original drug and the generic. The overall assessment of the free drug provision system in Kazakhstan is as follows: 35.47% of participants rated it as excellent, 47.58% as good, 9.14% as satisfactory, and 5.47% of respondents consider the work of the free drug provision system unsatisfactory.

Conclusions. The survey results revealed problems in the provision of medicines guaranteed by the state. Overall, the free outpatient drug provision system in Kazakhstan is well-established, with patients receiving the necessary medicines on time for diseases managed at the outpatient level. However, there are problematic issues that require improvement in this area.

Keywords: access to medicines, free drug provision, population satisfaction with drug provision.

Corresponding author: Gulzira Zhussupova, Chief Specialist of the Center for the Development of Scientific and Research Activities, Astana Medical University, Astana, Kazakhstan.
Postal code: Z10K8Y7
Address: Kazakhstan, Astana, Beibitshilik str, 49A
Phone: +7 707 953 81 48
E-mail: zhussupova.gu@amu.kz

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Introduction

Access to medicines is a fundamental component of the full realization of the right to health. Medical care in case of illness, as well as the prevention, treatment, and control of diseases, largely depend on timely and adequate access to quality medicines [1]. Equal access to medicines is a global priority. Therefore, to achieve the United Nations Sustainable Development Goals (SDGs), particularly target 3.8, it is necessary to address issues of availability, acceptability, and affordability of guaranteed quality medicines [2]. However, about 2 billion people worldwide do not have access to essential medicines, especially in low- and middle-income countries. Recognizing health as a human right obligates states to ensure access to timely, acceptable, and affordable healthcare [3].

In addition, market access to innovative medicines is a crucial factor in improving the population's life expectancy and quality of life [4]. For instance, an analysis of the impact of pharmaceutical innovations on patient health in Belgium showed that medicines approved for sale between 1987 and 1995 reduced premature cancer mortality by 20% and added 1.52 years to relapse-free survival in 2012 [5]. Improving life expectancy and quality of life, in turn, increases labor productivity [4]. For example, a study showed that while market access to innovative hepatitis C drugs significantly increased healthcare costs, this growth was more than offset by savings from reduced use of other medicines, prevention of cirrhosis, further infections, and increased labor productivity in Belgium [6].

The issue of improving the accessibility of medical services by ensuring equal access to quality healthcare is emphasized in the National Development Plan of the Republic of Kazakhstan until 2029 [7]. This document notes the underdevelopment of the pharmaceutical sector: in 2023, the share of domestically produced medicines and medical products in the local pharmaceutical market amounted to only 14.4%, and the share of Kazakhstani products in the rapidly growing procurement volumes of medicines was only 32% [7]. As of December 31, 2022, the Single Distributor purchased 1,587 items of medicines (952) and medical products (612). Of the 952 purchased medicines, 328 items (34.4%) do not have registered analogs in the Republic of Kazakhstan (original medicines). For 2022, 97% of drugs and medical supplies from the declared need for 2022 were procured in the amount of more than 385.89 billion tenge [8].

It should be noted that the COVID-19 pandemic also taught us that market access to innovative technologies (such as new mRNA vaccines) largely depends on citizens' and patients' willingness to adopt the technology [9]. Therefore, patient participation in market access to medicines is crucial [4].

This article presents the results of a study on the subjective opinion of the population on satisfaction with the free outpatient drug provision system in light of the reforms, providing suggestions to improve its accessibility, effectiveness, and responsiveness to patient needs.

Materials and Methods

A population survey to assess satisfaction with the free outpatient drug provision system (ODPS) was conducted at the request of the Ministry of Health of the Republic of Kazakhstan from April 21 to May 16, 2022.

Focus Group: Healthcare consumers at the outpatient level, including patients (adults) under dynamic observation.

Total number of respondents: Adults – 1,730 people, including 710 men (41.05%) and 1,020 women (58.95%).

The sociological study was conducted through a survey of the adult population using the SurveyMonkey platform in an online format. SurveyMonkey is a global leader in online surveys and forms that provide people with the information they need to make quick and confident decisions. The fast and intuitive feedback management platform connects millions of users worldwide with AI-generated real-time information, enabling meaningful decisions. The service allows for quickly creating surveys, compiling very detailed and visual reports, protecting data, and integrating tools with MailChimp, GroSocial, CleverReach, and other services.

The survey was predominantly conducted among residents of regional cities (56.21%) and cities of republican significance (31.82%). A total of 6.45% and 5.52% of participants were residents of district centers and villages, respectively (Figure 1).

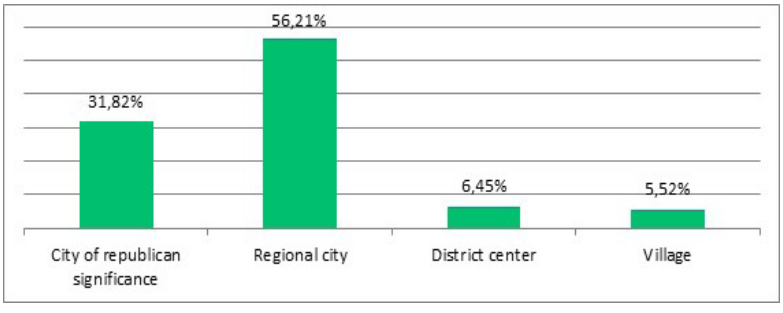

Figure 1 - Ranking of respondents by place of residence

Of the 1,721 respondents, 1,574 people (91.46%) were under dynamic observation by a general practitioner at the time of the survey (Figure 2).By gender, 710 men (41.05% of the total number of respondents) and 1,020 women (58.95%) participated in the survey (Figure 3).In terms of age distribution, the largest group of respondents was aged 18 to 60 years (63.61% of the total number) (Figure 4).

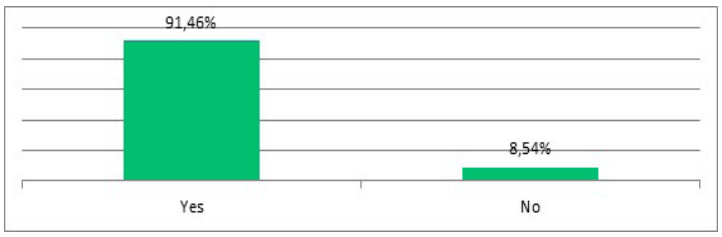

Figure 2 - Status of being under dynamic observation by a general practitioner

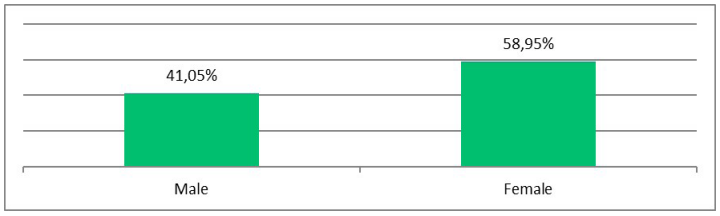

Figure 3 - Ranking by gender

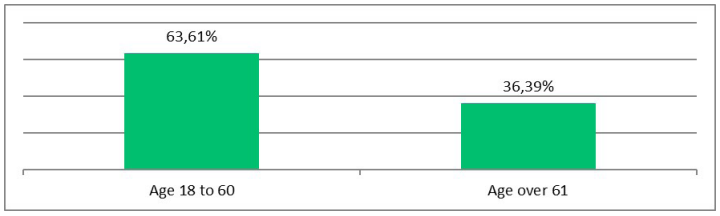

Figure 4 - Ranking by age group

The questionnaire included 17 questions, of which 14 were closed-ended and 3 were open-ended. The questionnaire was developed by the author independently (Copyright Certificate No. 26456 dated May 24, 2022).

Results

The results of the ranking of respondents under dynamic observation and receiving free treatment for diseases are presented in Table 1. A total of 1.296 respondents answered this question, with 217 skipping the response. Of the participants, 108 noted that they were healthy, and 47 did not receive free medicines.

Table 1 - Ranking of respondents under dynamic observation by a general practitioner and receiving free treatment for diseases

Nosologies	Number	% ratio
Arterial hypertension	529	40.8
Diabetes mellitus	291	22.45
Ischaemic heart disease	96	7.4
Mental disorders	59	4.55
Epilepsy	36	2.78
Rheumatoid arthritis	31	2.38
Coronavirus infection, Pneumonia	21	1.62
Chronic obstructive pulmonary disease	20	1.53
Bronchial asthma	19	1.46
Hypothyroidism, Hyperthyroidism	13	1
Angina	6	0.46
Iron deficiency anemia	5	0.39
Oncology	2	0.15
Chronic heart failure	2	0.15
Arrhythmia	1	0.08
Other	167	12.89
Total	1296	100

Out of 1.718 respondents, 1.571 people (91.44%) answered that they were prescribed free medicines. At the same time, 7.28% of respondents indicated that they were not prescribed free medicines, and 1.28% of respondents indicated various reasons (they did not know they could get medicines for free, they were not under dynamic observation) (Figure 5). Also, 80.11% of respondents noted that they receive medicines once a month (Figure 6).

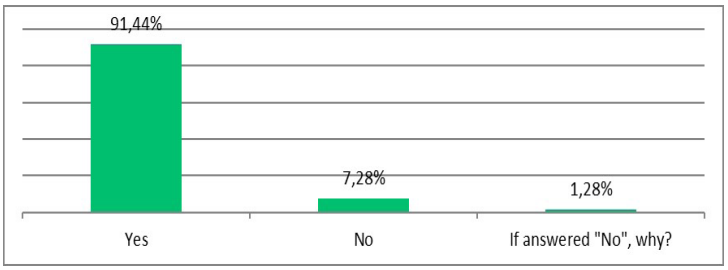

Figure 5 - Respondents' answers regarding prescription of free medicines

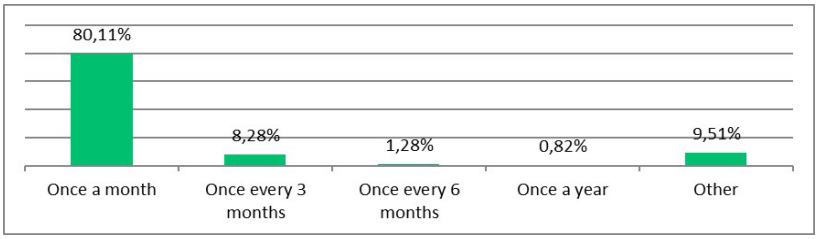

Figure 6 - Respondents' answers to the question: "How often do you receive free medicines?"

To the question: "If you had the opportunity to receive a medicine from another manufacturer that you consider to be better than the drug provided according to the outpatient drug provision system list, would you be willing to pay the price difference?" the following results were obtained: 531 (30.91%) respondents are willing to pay, 8% might pay for a drug from another manufacturer that they consider better than the drug provided according to the ODPS list. 61.12% of respondents are not ready to pay (Figure 7).

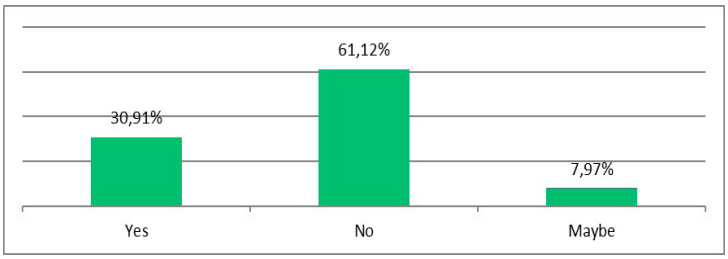

Figure 7 - Respondents' answers to the question: "If you had the opportunity to receive a medicine from another manufacturer that you consider to be better than the drug provided according to the outpatient drug provision system list, would you be willing to pay the price difference?"

When asked if the prescribed medicine is always available in the pharmacy, 1.356 respondents (79.39%) answered that it is always available, 18.15% answered that it is periodically absent, and 2.46% noted that it is never available.When asked: "Name the medicines that you purchased at your own expense for the treatment of the main disease within the last 3 months or earlier?" the following results were obtained (Table 2).

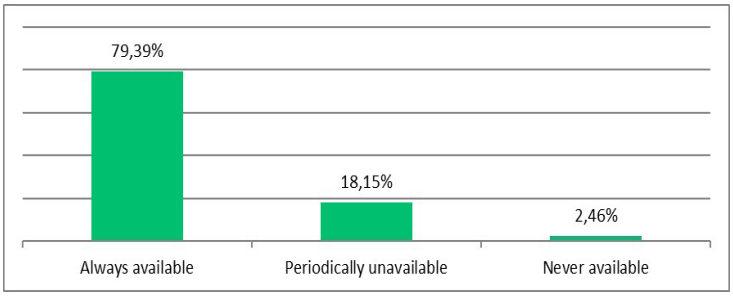

Figure 8 - Respondents' answers to the question: "Is the prescribed medicine always available in the pharmacy?"

At the same time, 78% of the listed medicines are included in the ODPS list (arterial hypertension, antiepileptic, diabetes mellitus).

1.665 respondents (98%) of the 1,699 who responded know how to correctly take the prescribed medicine, 21 people (1.24%) know approximately, and 13 people (0.77%) do not know how to take the prescribed medicine (Figure 9).

Table 2 - List of medicines/groups of medicines that respondents purchased at their own expense

№	Name of medicine/group of medicines	Number of respondents
1	Antibacterial drugs	6
2	Fenoterol and Ipratropium bromide	10
3	Levothyroxine	3
4	Pantoprazole	1
5	Iron sulfate	4
6	L-lysine escinate	1
7	Methotrexate	5
8	Nonsteroidal anti-inflammatory drugs	16
9	Antiepileptic drugs	94
10	Hypoglycemic drugs, insulin	102
11	Antianginal and antihypertensive drugs	114

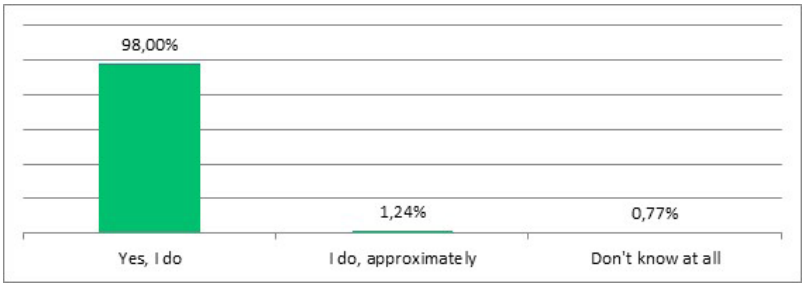

Figure 9 - Respondents' answers to the question: "Do you know how to take the prescribed medicine?"

1.612 respondents (94.05%) of the 1.714 who responded receive information on the correct use of the prescribed medicine from the doctor, 62 people (3.62%) receive information from the instructions for medical use of the medicine, 18 people (1.05%) learn from the pharmacist, 19 people (1.11%) from the internet, and the remaining 3% of respondents learn from friends, relatives, neighbors, and reference literature (Figure 10).

1.601 respondents (93.3%) learned that they have the right to free medicines from the doctor, and only 0.12% learned from the pharmacist; the rest from other sources (mass media, relatives, friends, etc.) (Figure 11).

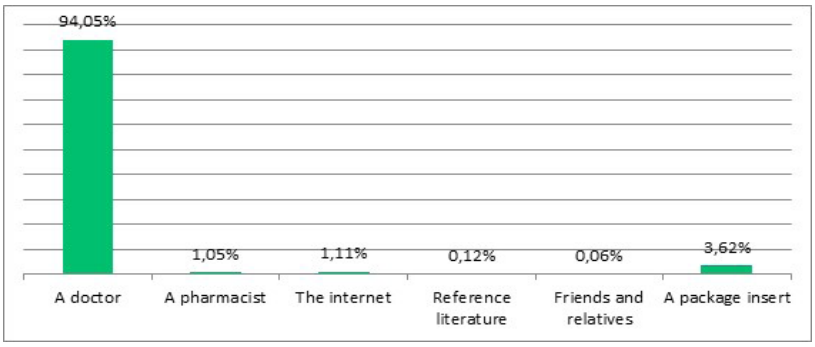

Figure 10 - Respondents' answers to the question: "Where do you get information on how to correctly take the prescribed medicine?"

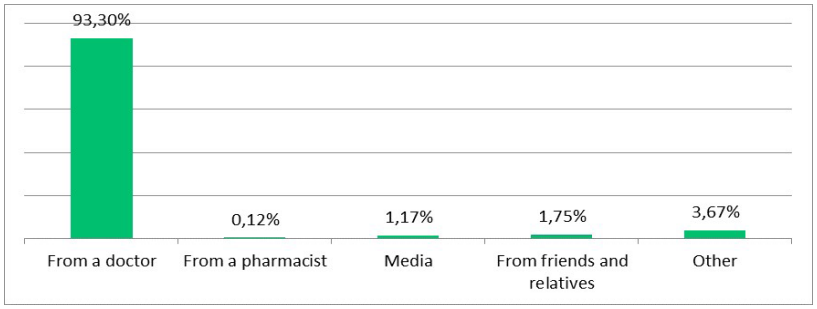

Figure 11 - Respondents' answers to the question: "From whom did you learn that you have the right to free medicine?"

Given that this study was conducted during the pandemic when there was an increase in the irrational use of antimicrobial drugs, two questions about the use of antibiotics were included in the survey. The results showed that 23.41% of respondents took antibiotics without a doctor's prescription, 51.02% did not take antibiotics without a prescription. Only 22% took antibiotics by doctor's prescription, and 1.98% received antibiotics for free.

When asked if they took antibiotics when they or their relatives were ill with COVID-19, 458 respondents (26.71%) answered that they did, but most respondents (73%) answered that they did not take antibiotics (Figure 13).

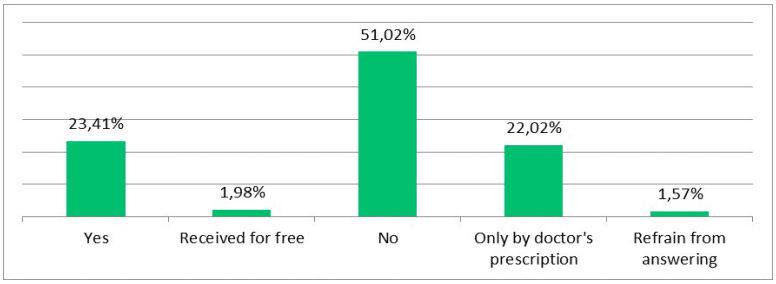

Figure 12 - Respondents' answers to the question: "Did you take antibiotics without a doctor's prescription?"

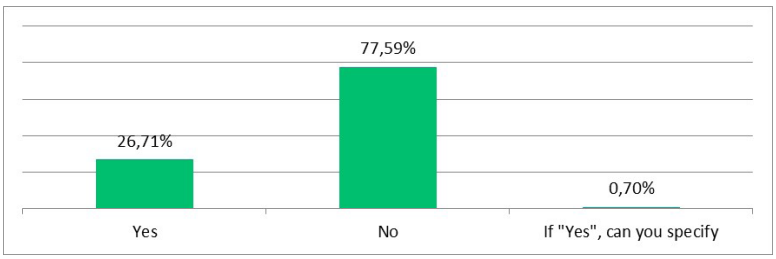

Figure 13 - Respondents' answers to the question: "Did you take antibiotics when you/your relatives were ill with COVID-19?"

Respondents were also asked to provide a general assessment of the free drug provision system in Kazakhstan, and the following results were obtained: 35.47% rated it as excellent, 47.58% as good, 9.14% as satisfactory, and 5.47% of respondents consider the work of the free drug provision system unsatisfactory (Figure 14).

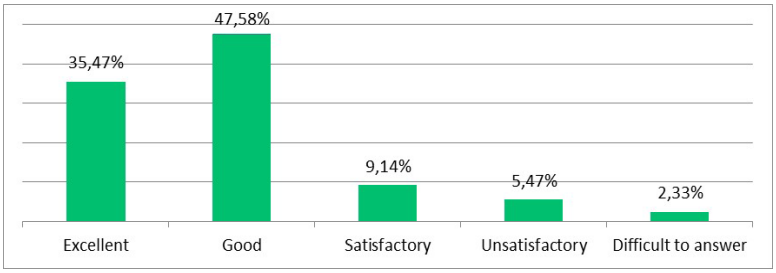

Figure 14 - General assessment of the free drug provision system in Kazakhstan by the adult population

At the end of the survey, respondents were asked to submit proposals for improving drug provision. Proposals were collected from 748 respondents (43%), while 982 (57%) respondents refrained from answering. The proposals were analyzed and grouped by direction and presented in Table 3.

Table 3 - Proposals from the population to improve the free drug provision system

№	Proposals from the population to improve the system of free drug provision
1	Free (full) provision of drugs for all categories of the population
2	Expansion of the list, financing of medicines in accordance with clinical protocols for diagnosis and treatment.
3	Switching to electronic medicine prescription
4	Free provision of medicines to pregnant women
5	Reducing the price of medicines, especially for expensive medicines
6	Do not substitute medicines prescribed by your doctor with cheap analogues. This affects the quality of treatment!
7	Issuing free medications at any pharmacy
8	When providing free medication, the patient's place of residence is not taken into account – in a village, it is necessary to go to the regional center to the pharmacy, the trip costs more than the cost of the medicine
9	Inclusion of orphan drugs in the general drug provision list
10	Expansion of the list of combination medicines for the treatment of arterial hypertension

Discussion

88% of respondents who participated in the survey were residents of regional centers and cities of republican significance. Only 12% of respondents were residents of district centers and villages. This is obviously due to the fact that the survey was conducted online. According to inbusiness.kz, citing ranking.kz, the share of internet users aged 6 years and older in Kazakhstan in 2021 was 90.9% of the total population, which is significantly higher compared

to previous years: 85.9% in 2020 and 81.9% in 2019. The share of network users in cities increased from 87.7% in 2020 to 92.2% in 2021, while in rural areas it increased from 83.4% to 88.8% [10]. Also, 63.6% of respondents were aged 18 to 60 years, with 41% men and 59% women.

According to the results of the ranking of respondents under dynamic observation and receiving free treatment for diseases, 40.8% of participants suffer from arterial hypertension and 22.5% from diabetes mellitus. It should be noted that these nosologies are among the top 10 nosologies on which 73% of the total drug provision expenditure is spent within the allocated budget funds for outpatient drug provision, for example, 19% (first place in the top 10) is spent on diabetes mellitus, and 6% (fifth place in the top 10) on arterial hypertension [8]. 91.5% of participants were prescribed free medicines, which may indicate sufficient availability of medicines, considering that 91.5% of respondents are under dynamic observation by a doctor. At the same time, 80.1% of respondents noted that they regularly receive free medicines once a month.

Although the issue of co-payment for original medicines is often discussed, 61.12% of respondents are not ready to pay the price difference between the original drug and the generic. According to a population survey in 2021, 31% of respondents are not willing to receive a medicine that is better compared to the one provided according to the ODPS list, while the majority (69%) are willing to pay for a similar medicine from another manufacturer [11]. At the same time, proposals to improve drug provision suggest providing free medicines to all categories of the population.

The survey results revealed problems in the provision of state-guaranteed medicines. Although almost 80% of respondents reported that medicines are always available in pharmacies, 18% noted that medicines are periodically absent, and 2.5% believe that free medicines are never available in pharmacies. According to a population survey in 2021, 48% of respondents reported that the prescribed medicine is periodically absent in the pharmacy [11]. Additionally, according to the Single Distributor report, only 97% of medicines were purchased, and the remaining 3% were not purchased, meaning they did not reach patients [8]. Meanwhile, the distribution of budget funds across the regions of the republic is still uneven. The largest amount of funding for ODPS is observed in Almaty, Karaganda region, Astana, East Kazakhstan, and Almaty regions. At the same time, the funding of these five regions accounts for more than 48% of the total ODPS funding by the Single Distributor for 9 months of 2021 [12].

The survey also highlighted that out-of-pocket expenses for purchasing medicines include drugs that are part of the free provision list. For instance, 78% of the medicines that respondents bought at their own expense are included in the ODPS free list. This may be due to the low awareness of the population about the medicines included in the free list.

98% of respondents stated that they know how to correctly take the prescribed medicine, but 2% know approximately or do not know how to take the prescribed medicine. It is encouraging that 94% of respondents receive information on the use of medicines from their doctor, while only 1% receive it from the pharmacist and 5% from the internet, friends, and relatives. However, self-medication remains a serious healthcare issue, which became especially prevalent during the COVID-19 pandemic, with uncontrolled use of non-steroidal anti-inflammatory and antimicrobial drugs [13,14,15]. Given that this study was conducted during the pandemic, during which there was an increase in irrational use of antimicrobial drugs, two questions regarding the use of antibiotics were included in the survey. The fact that only 23.41% of respondents took antibiotics without a doctor's prescription, i.e., self-medicated, indicates that by the second year of the pandemic, healthcare workers managed to reduce the uncontrolled use of antibiotics compared to 2021 (when 50% of respondents took antibiotics without a doctor's prescription) [11]. Only 22% of respondents took antibiotics strictly as prescribed by a doctor. Here, it is important to note the role of pharmaceutical counseling, which, unfortunately, is not well-developed in our country. More and more studies confirm that addressing medication-related issues is a critical topic for counseling, as low awareness of errors in the administration of certain dosage forms and dosages, even during repeated uses, can significantly impact the safety and effectiveness of medication therapy. For example, in one study, the effectiveness of intervention improved from 29% initially to 46% after receiving pharmaceutical counseling [16,17,18,19].

Thus, more than 90% of the adult population positively assessed the free drug provision system, which is significantly better compared to the survey results from 2021 (66%) [11]. At the same time, 5.47% of respondents consider the work of the system unsatisfactory. For comparison, in 2021, 21% of respondents rated the free drug provision system as unsatisfactory.

Conclusions

The survey results revealed issues in the provision of state-guaranteed medicines. Overall, the free outpatient drug provision system in Kazakhstan is well-established, with patients receiving the necessary medicines on time for diseases managed at the outpatient level. However, there are problematic areas that require improvement in this direction.

Conflict of Interest. None declared.

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Тегін дәрі-дәрмекпен қамтамасыз ету жүйесіне қанағаттану туралы Қазақстан Республикасының ересек тұрғындарының пікірін талдау

Жусупова Г.К. [1], Койков В.В. [2]

[1] *Ғылыми зерттеу жұмыстарын дамыту орталығының бас маманы, Астана медицина университеті; «Санат» білім беруді дамытудың Ұлттық ғылыми орталығының сарапшы маманы, Астана, Қазақстан. E-mail: zhussupova.gu@amu.kz*

[2] *Астана медицина университетінің ғылыми жұмыстар жөніндегі проректоры, Астана, Қазақстан. E-mail: koykov@inbox.ru*

Түйіндеме

Дәрі-дәрмектерге қол жеткізу мәселесі денсаулыққа құқықты толық іске асырудың негізгі құрамдас бөлігі болып табылады. Дәрі-дәрмектерге тең қол жеткізу бүкіл әлемде бірінші кезектегі міндет болып табылады. Сонымен қатар, нарыққа инновациялық дәрі-дәрмектерге қол жеткізу халықтың өмір сүру ұзақтығы мен сапасын жақсартудың шешуші факторы болып табылады. Сапалы медициналық көмекке тең қолжетімділікті қамтамасыз ету арқылы медициналық қызметтердің қолжетімділігін арттыру проблемасы Қазақстан Республикасының 2029 жылға дейінгі ұлттық даму жоспарында атап көрсетілген. Инновациялық технологиялар нарығына қол жеткізу негізінен азаматтардың технологияны қабылдауға дайындығына байланысты. Сондықтан пациенттердің дәрі-дәрмек өте нарығына кіруге қатысуы маңызды.

Зерттеудің мақсаты: пациенттердің қажеттіліктеріне қолжетімділігін, тиімділігін және жауаптылығын арттыру бойынша ұсыныстар бере отырып, амбулаториялық дәрі-дәрмекпен қамтамасыз ету жүйесіне қанағаттану туралы халықтың субъективті пікірін зерттеу.

Әдістері. Әлеуметтанулық зерттеу онлайн форматта SurveyMonkey платформасы арқылы ересек тұрғындарға сауалнама жүргізу арқылы жүргізілді. Респонденттердің жалпы саны: ересектер – 1730 адам, оның ішінде ерлер – 710 (41,05%), әйелдер – 1020 (58,95%).

Нәтижелер. Сауалнамаға қатысқандардың 80% -ға жуығы дәріханада дәрі-дәрмектер әрқашан бар екенін айтты, бірақ 18% - ы мезгіл-мезгіл жоқ екенін, ал 2,5% -ы дәріханаларда ешқашан тегін дәрі жоқ деп санайды. Пациенттер өздері сатып алған аталған препараттардың 78% - ы тегін дәрі-дәрмектер тізіміне кіреді. Респонденттердің 23,41 % -ы антибиотиктерді дәрігердің нұсқауынсыз қабылдаған. Респонденттердің 61,12% - ы бастапқы препарат пен генерик арасындағы баға айырмашылығын төлеуге дайын емес. Қазақстанда тегін дәрі-дәрмекпен қамтамасыз ету жүйесінің жалпы бағасы келесідей: қатысушылардың 35,47% -ы өте жақсы, 47,58% -ы жақсы, 9,14% -ы қанағаттанарлық және респонденттердің 5,47% -ы тегін дәрі-дәрмекпен қамтамасыз ету жүйесінің жұмысын қанағаттанарлықсыз деп санайды.

Қорытынды. Сауалнама нәтижелері Мемлекет кепілдік берген дәрі-дәрмектермен қамтамасыз етудегі проблемаларды анықтады. Жалпы, Қазақстанда тегін амбулаториялық дәрі-дәрмекпен қамтамасыз ету жүйесі жолға қойылған, пациенттер амбулаториялық деңгейде басқарылатын аурулар бойынша уақтылы қажетті дәрілік заттарды алады. Алайда, осы бағыттағы жұмысты жетілдіруді талап ететін проблемалық мәселелер бар.

Түйін сөздер: дәрі-дәрмектерге қол жеткізу, тегін дәрі-дәрмекпен қамтамасыз ету, халықтың дәрі-дәрмекпен қамтамасыз етілуіне қанағаттануы.

Анализ мнения взрослого населения Республики Казахстан об удовлетворенности системой бесплатного лекарственного обеспечения

Жусупова Г.К. [1], Койков В.В. [2]

[1] Главный специалист, Центр развития научно-исследовательской деятельности, Медицинский университет Астана; эксперт Национального научного центра развития образования "Санат", Астана, Казахстан. E-mail: zhussupova.gu@amu.kz

[2] Проректор по научной работе, Медицинский университет Астана, Астана, Казахстан. E-mail: koykov@inbox.ru

Резюме

Вопрос доступа к лекарствам является основополагающим компонентом полной реализации права на здоровье. Равный доступ к лекарствам является приоритетной задачей во всем мире. Наряду с этим, доступ на рынок инновационных лекарственных средств является решающим фактором в улучшении продолжительности и качества жизни населения. Проблема повышения доступности медицинских услуг через обеспечение равного доступа к качественной медицинской помощи подчеркивается в Национальном плане развития Республики Казахстан до 2029 года. Доступ на рынок инновационных технологий в значительной степени зависит от готовности граждан принять технологию. Поэтому участие пациентов в доступе на рынок лекарств имеет решающее значение.

Цель исследования: Изучение субъективного мнения населения об удовлетворенности системой амбулаторного лекарственного обеспечения, с предоставлением предложений по повышению ее доступности, эффективности и отзывчивости на потребности пациентов.

Методы. Социологическое исследование проведено путем анкетирования взрослого населения через платформу SurveyMonkey в онлайн формате. Общее число респондентов: взрослые – 1730 человек, из них мужчин – 710 (41,05%), женщин – 1020 (58,95%).

Результаты. Почти 80% опрошенных сообщили, что лекарственные средства всегда есть в аптеке, но 18% отметили, что периодически отсутствуют, а 2,5% считают, что бесплатных лекарств никогда нет в аптеках. 78% из перечисленных препаратов, которые пациенты покупали самостоятельно, входят в Перечень бесплатных лекарств. 23,41% респондентов принимали антибиотики без назначения врача. 61,12% респондентов не готовы оплачивать разницу в цене между оригинальным препаратом и генериком. Общая оценка системы бесплатного лекарственного обеспечения в Казахстане выглядит следующим образом: 35,47 % участников оценили на отлично, 47,58% на хорошо, 9,14 % на удовлетворительно и 5,47 % респондентов считают работу системы бесплатного лекарственного обеспечения неудовлетворительной.

Выводы. Результаты опроса выявили проблемы в обеспечении лекарственными средствами, гарантированных государством. В целом система бесплатного амбулаторного лекарственного обеспечения в Казахстане налажена, пациенты получают своевременно необходимые лекарственные средства по управляемым на амбулаторном уровне заболеваниям. Однако имеются проблемные вопросы требующие совершенствования работы в данном направлении.

Ключевые слова: доступ к лекарствам, бесплатное лекарственное обеспечение, удовлетворенность населения лекарственным обеспечением.

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Описание клинического случая

Несращение места остеотомии при поперечной укорачивающей остеотомии бедренной кости в сочетании ТЭТС. Клинический случай

Бекназаров А. [1], Ашимов К. [2], Berk Guclu [3], Октяброва Д. [4], Байдалин Т. [5], Сулейменов Б. [6], Агабеков Е. [7]

[1] *Врач травматолог-ортопед, Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова, Астана, Казахстан. E-mail: dr.askar1990@gmail.com*

[2] *Заведующий отделением ортопедии №3, Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова, Астана, Казахстан. E-mail: kairat_ashimov@mail.ru*

[3] *Заведующий кафедрой ортопедии и травматологии, Университет Уфук, Анкара, Турция. E-mail: gucluberk@yahoo.com*

[4] *PhD докторант, Медицинский университет Астана; врач травматолог-ортопед, Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова, Астана, Казахстан. E-mail: oktyabrovadana@gmail.com*

[5] *Заведующий отделением ортопедии №7, Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова, Астана, Казахстан. E-mail: t.baidalin@gmail.com*

[6] *Врач травматолог-ортопед, Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова, Астана, Казахстан. E-mail: bekjan-suleimen@mail.ru*

[7] *Врач травматолог-ортопед, Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова, Астана, Казахстан. E-mail: yerdaulet.21@mail.ru*

Резюме

Дисплазия тазобедренного сустава - это тяжелая патология опорно-двигательного аппарата, которая при несвоевременной диагностике и лечении приводит к нарушению функции тазобедренного сустава. Это приводит к остеоартрозу, который требует хирургического вмешательства. В данном отчете описан случай несращение зоны поперечной подвертельной укорачивающей остеотомии в сочетании тотальной эндопротезировании левого тазобедренного сустава.

Следует отметит что, в нашем сообщении/исследовании были некоторые ограничения, такие как: короткий период наблюдения и один пациент. Мы считаем что, для получение хороших результатов нужно дальнейшее исследование с длительным сроком наблюдения и значительной выборкой пациентов с DDH типа по Crowe. Данное наблюдение за пациентом продолжается.

Ключевые слова: дисплазии тазобедренного сустава, эндопротезирование, подвертельная укорачивающая остеотомия, несращения.

Corresponding author: Durdana Oktyabrova, PhD student at the Astana Medical University, traumatologist-orthopedist, National scientific center of traumatology and orthopedics named after academician N.D. Batpenov, Astana, Kazakhstan.
Postal code: Z10K8Y7
Address: Kazakhstan, Astana, Beibitshilik str, 49A
Phone: +7 747 989 4746
E-mail: oktyabrovadana@gmail.com

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Введение

Дисплазии тазобедренного сустава (ДТС) считаются сложной патологией которые приводят к нарушению функции сустава и опороспособности нижних конечностей, снижению качества жизни пациента из - за длительного вывиха бедра с рождения [12]. Вследствие некорректной диагностики и лечения данного заболевания со временем развивается диспластический коксартроз [4].

ДТС представляет собой актуальную проблему в современной ортопедии и требует комплексного и тщательного подхода к лечению. При лечении данного заболевания нужно учитывать анатомические особенности: недоразвитие вертлужной впадины, высокий вывих головки бедренной кости [11], контрактуру окружающих мягких тканей [10], несоответсвие длины нижних конечностей проявляющийся хромотой [6], а так же увеличением антеверсии [1]. В лечении ДТС IV типа по Crowe по литературным данным описывается применение тотального эндопротезирования тазобедренного сустава (ТЭТС) с подвертельной укорачивающей остеотомией (ПУО). При его выполнении хирурги сталкиваются с определенными техническими трудностями связанные с патологией сустава [13]. Несмотря на то что применение данной техники лечения дают удовлетворительные результаты и улучшают качество жизни пациентов, как и при любой хирургической операции возможен риск серьезных осложнений, таких как нейропатия седалищного нерва и несращение зоны остеотомии.

В представленной рукописи описывается клинический случай пациента с несращением места остеотомии при поперечной укорачивающей остеотомии бедренной кости при ТЭТС с высоким вывихом бедра.

Клинический случай

В Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпенова была госпитализирована 44-летняя пациентка с жалобами на выраженную боль и ограничение движений в левом тазобедренном суставе, сильную хромоту, прогрессирующие в последние 6 месяцев. С рождения наблюдается у ортопеда с диагнозом врожденный вывих бедра. До настоящего времени не получала специализированного лечения по коррекции ДТС. В анамнезе жизни отсутствуют какие–либо другие заболевания.

Пациент передвигается самостоятельно при помощи трости, сильно хромая на левую нижнюю конечность, отмечается утиная походка. Визуально имеется укорочение левой нижней конечности, гипотрофия мышц левого бедра и ягодицы, а также симптом Тренделенбурга положительный слева. Длина правой нижней конечности 76 см., а левой 71 см., отмечается несоответствие длины нижней конечности на 5,0 см. Объем движения в левом тазобедренном суставе ограничены и болезненны: сгибание разгибание 90º-0-180º, отведение-приведение 10º-0-15º, ротация кнаружи-кнутри 10º-0-5º. Правый тазобедренный сустав в норме. Проведен опрос по следующим шкалам: Visual Analogue Scale (VAS) – 9 баллов, Harris Hip Score (HHS) – 40 баллов, Oxford Hip Score (OHS) – 20 балла. Произведена рентгенография тазобедренных суставов в прямой проекции, где рентгенологически отмечалось: врождённый верхний вывих головки левой бедренной кости, дисплазия левого тазобедренного сустава, неоартроз на уровне гребня левой подвздошной кости, сужение суставной щели, склероз замыкательных пластин, краевые костные разрастания, кистозная перестройка около суставной зоны, уплощение вертлужной впадины, правый тазобедренный сустав не изменён (Рисунок 1). На основании клинических и рентгенологических данных выставлен диагноз: Дисплазия левого тазобедренного сустава IV типа по Crowe. Левосторонний диспластический коксартроз III-IV степени. Укорочение левой нижней конечности до 5,0 см. Смешанная контрактура левого тазобедренного сустава.

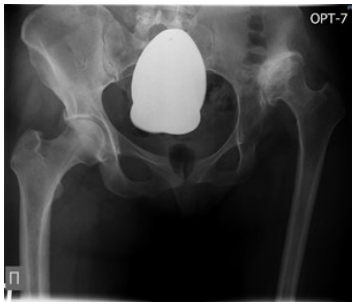


Рисунок 1 - Предоперационная рентгенография тазобедренных суставов в прямой проекции

После подготовки в плановом порядке под спинно-мозговой анестезией была выполнена: ТЭТС с поперечной подвертельной укорачивающей остеотомией. Использовали доступ Хардинга, длина разреза операционной раны составила 18 см. После обнажения вертельной области и определение истинной вертлужной впадины, произведена обработка фрезами, последний размер №44. Далее имплантировали прессфит чашу №44 мм, погружение чаши 95% с фиксацией двумя винтами, затем установили полиэтиленовый вкладыш №44/28 мм. В последующем обработка костномозгового канала бедренной кости рашпилем до №16. При попытке пробного вправления с низведением до уровня истинной вертлужной впадины было проблематично, в связи с чем проведена поперечная подвертельная укорачивающая остеотомия левой бедренной кости на 2,0 см. Установили бедренный компонент Wagner фирмы Zimmer №16 и оптимальную титановую головку №3,5/28 мм. После вправление при максимальных объемах движений самопроизвольного вывиха не происходило и отсутствовала ротационная подвижность. Рану послойно ушили наглухо с оставлением параоссально силиконового дренажа.

Кровопотеря составила 800,0 мл, время операции - 110 минут. Интраоперационно проведена рентгенография правого тазобедренного сустава в прямой проекции для исключения нестабильности компонентов эндопротеза (Рисунок 2).

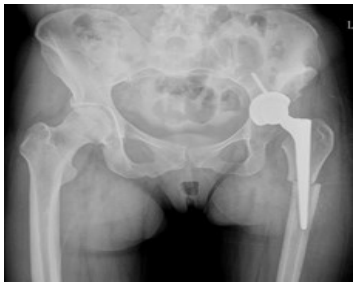
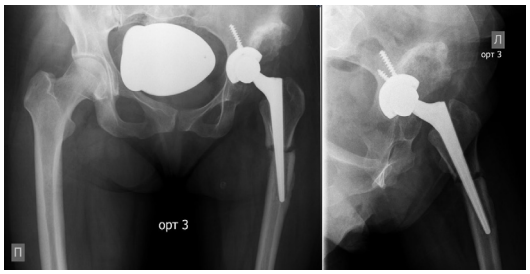


Рисунок 2 - Интраоперационная рентгенография тазобедренных суставов в прямой проекции

Ранний послеоперационный период протекал без особенностей. В послеоперационном периоде получала препараты: наркотические анальгетики однократно, нестероидные противовоспалительные препараты, антикоагулянты, гастропротекторы, антибиотик группы цефалоспоринов, а также препараты железа. После стабилизации общего состояния пациентка активизирована на вторые сутки после операции начала передвигаться с помощью костылей без опорной нагрузки на правую нижнюю конечность. Дополнительно еще получила первый этап реабилитации в объеме: активная индивидуальная кинезотерапия нижней конечности в послеоперационном периоде №5, индивидуальное обучение\коррекция ходьбы №5, магнитотерапия на послеоперационную рану №5. На 11-ые сутки после операции пациентка выписана на амбулаторное лечение. На момент выписки показатели шкал были следующими: VAS - 5 баллов, HHS - 44 балла, OHS - 26 баллов. В последующем через 4 месяца после операции пациент получает травму тазобедренного сустава, за медицинской помощью не обращается, отмечает умеренные боли в области левого тазобедренного сустава. Спустя 3,5 месяца после полученной травмы с выраженным болевым синдромам обратилась в поликлинику, поставлен диагноз: Нестабильность бедренного компонента эндопротеза левого тазобедренного сустава. Состояние после тотального эндопротезирования левого тазобедренного сустава с укорачивающей остеотомией от 20.03.2023 г. Несращение в области остеотомии проксимального отдела левого бедра (Рисунок 3).



a *b*

Рисунок 3 - Предоперационная рентгенография тазобедренных суставов: a) прямая проекция, b) боковая проекция

Болевая оценка по VAS 4 балла, функции суставов по HHS 48 баллов, OHS - 21 балл. На рентгенографии тазобедренных суставов в 2-х проекциях положение чаши и головки эндопротеза стабильное, ножка эндопротеза смещена к наружному краю бедренной кости, с R-картиной неконсолидированной подвертельной остеотомии левой бедренной кости, варусном положением фрагментов бедренной кости 13° (угол открыт в медиальную сторону). В плановом порядке проведено оперативное лечение в объеме: Открытый остеосинтез зоны несращения левого бедра блокирующей пластиной и винтами (Рисунок 4).

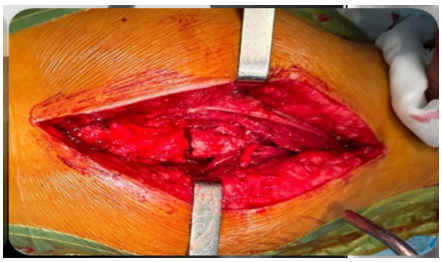


Рисунок 5 - Несращение зоны поперечной подвертельной укорачивающей остеотомии

В раннем послеоперационном периоде пациентка отмечала уменьшеный болевой синдром и хромоту. Ходила при помощи костылей без опорной нагрузки на оперированную конечность. По данным клинических шкал были следующие показатели: VAS - 4 балла, HHS - 60 баллов, OHS - 26 баллов. При контрольной рентгенографии левого тазобедренного сустава отмечается положительная R-динамика: положение

фрагментов бедренной кости и пространственное положение компонентов эндопротеза левого тазобедренного сустава корректное (Рисунок 5).

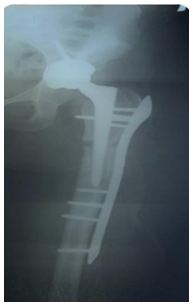
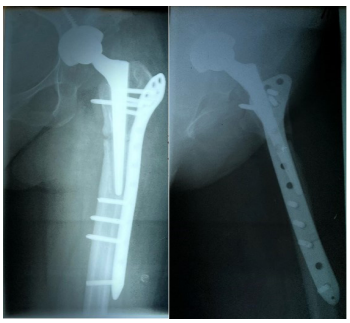


Рисунок 5 - Рентгенография левого тазобедренного сустава в прямой проекции в раннем послеоперационном периоде

Через 2,5 месяцев на амбулаторном осмотре у пациентки была незначительная боль и хромота, по VAS - 2 балла, HHS - 92 балла, OHS - 45 баллов. Проведено реабилитационное лечение и рентгенография левого тазобедренного сустава. На контрольной рентгенограмме в зоне остеотомии отмечается слабая консолидация (Рисунок 6).



a *b*

Рисунок 6 - Рентгенография левого тазобедренного сустава через 2,5 месяцев: a) прямая проекция, b) боковая проекция

Обследование пациента через 12 месяцев показало отсутствие болевого синдрома (VAS 0 баллов), улучшение функции левого тазобедренного сустава (HHS - 99 баллов, OHS - 48 баллов). На обзорной рентгенографии тазобедренного сустава отмечается полная консолидация зоны остеотомии (Рисунок 7).

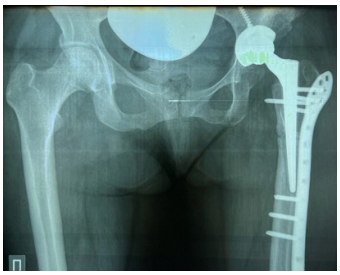


Рисунок 7 - Рентгенография тазобедренных суставов в прямой проекции через 10 месяцов

Обсуждение

ДТС считается одним из тяжелых патологий тазобедренного сустава, что обусловлено анатомическими изменениями и аномалиями недоразвития тазобедренного сустава [8]. ТЭТС данной патологии считается высокотехнологической хирургией, при котором интраоперационное позиционирование компонентов эндопротеза тазобедренного сустава затрудняется с длительной контрактурой мягких тканей и высоким вывихом бедра, а так же гипоплазий вертлужной впадины [3].

ТЭТС в сочетании с ПУО является оптимальным методом для избежание предпрологаемых осложнений, таких как повреждение сосудисто-нервного пучка, некорректное установка компонентов эндопротеза, чрезмерное удлинение нижней конечности [7,9]. Существует разные методы ПУО применяемый у пациентов с ДТС IV типа по Crowe: поперечная, косая, ступенчатая, двойная шевронная. Выбор техники остеотомии зависит от диаметра костномозгового канала и размера бедренной кости, а также от опыта хирурга, выполняющего операцию. Одни авторы предпочитают при таких патологиях применение поперечной остеотомии, а другие - остальных. Однако поперечная ПУО считается самым распространенным и технически простым для выполнения [5], но в литературных источниках частота несращений места остеотомии при поперечной ПУО колеблется 2,8-7,1% [9].

Нет единого мнения о причинах развития несращения, тем не менее большинство авторов

указывают следующее: 1) нарушение кровоснабжении в зоне остеотомии; 2) чрезмерная высокая температура пилы при остеотомиии, вызывающая ожог кости; 3) повреждение эндоста; 4) неполное соответствие проксимального и дистального фрагментов костных поверхностей; 5) ущемление мягких тканей в области остеотомии; 6) преждевременная нагрузка [2].

Стоит отметить, что модель и соответствующий размер ножки эндопротеза тоже имеет немаловажную роль в сращении зоны остеотомии. Мнение авторов о выборе бедренного компонента эндопротеза разноречиво. В настоящее время большинство хирургов выбирают конические бедренные компоненты для прочной фиксации и избежания ротационной подвижности. Zeng W.N. et al. в проведенном исследовании также указывает, что получили хорошие результаты и минимальную степень осложнения при применение модели S-ROM при поперечной ПУО у пациентов с высоким вывихом бедра [12].

Во многих случаях при имплантации бедренного компонента имеет место ротационная подвижность проксимального либо дистального фрагмента бедра, которое требует дополнительной фиксации. Выбор вида фиксации также зависит от предпочтения хирурга, состояния костной ткани и владения хирургической техникой. Синтез места остеотомии с использованием блокирующей пластины и винтами создает стабильность фрагментов и оказывает благоприятные условия для сращения [14, 15].

Следует отметить, что в нашем исследовании были некоторые ограничения, такие как короткий период наблюдения и один пациент. Мы считаем, что для получения хороших результатов нужно дальнейшее исследование с длительным сроком наблюдения и значительной выборкой пациентов с DDH типа по Crowe.

Выводы

ТЭТС с ПУО бедренной кости может обеспечить хорошую клиническую эффективность и привести к относительно высокой частоте сращения у пациентов с DDH типа IV по Crowe. Однако у некоторых пациентов все еще наблюдается несращение. Необходимо тщательно проанализировать причины несращения и принять активные меры для его предотвращения. Внутренняя фиксация с использованием блокирующей пластины с винтами является эффективным методом лечения в случае возникновения несращения.

Финансирование. Данная работа была профинансирована в рамках программно-целевого финансирования научной и (или) научно-технической программы на 2023-2025 годы BR21881815 «Разработка, изучение безопасности и эффективности использования премиальных инновационных отечественных имплантатов для хирургического лечения пациентов с повреждениями и заболеваниями опорно-двигательного аппарата».

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Конфликт интересов. Авторы заявляют, что у них нет конкурирующих интересов.

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Сан сүйегінің көлденең қысқарту остеотомиясы кезінде жамбастың жалпы артропластикасымен біріктірілген остеотомия аймағының біріктірілмеуі. Клиникалық жағдай

Бекназаров А. [1], Ашимов К. [2], Berk Guclu [3], Октяброва Д. [4], Байдалин Т. [5], Сулейменов Б. [6], Агабеков Е. [7]

[1] Дәрігер травматолог-ортопед, Академик Н.Д. Батпенов атындағы ұлттық травматология және ортопедия ғылыми орталығы, Астана, Қазақстан. E-mail: dr.askar1990@gmail.com

[2] №3 ортопедия бөлімшесінің меңгерушісі, Академик Н.Д. Батпенов атындағы ұлттық травматология және ортопедия ғылыми орталығы, Астана, Қазақстан. E-mail: kairat_ashimov@mail.ru

[3] Ортопедия және травматология кафедрасының меңгерушісі, Уфук университеті, Анкара, Туркия. E-mail: gucluberk@yahoo.com

[4] PhD докторант, Астана медицина университеті; дәрігер травматолог-ортопед, Академик Н.Д. Батпенов атындағы ұлттық травматология және ортопедия ғылыми орталығы, Астана, Қазақстан. E-mail: oktyabrovadana@gmail.com

[5] №7 ортопедия бөлімшесінің меңгерушісі, Академик Н.Д. Батпенов атындағы ұлттық травматология және ортопедия ғылыми орталығы, Астана, Қазақстан. E-mail: t.baidalin@gmail.com

[6] Дәрігер травматолог-ортопед, Академик Н.Д. Батпенов атындағы ұлттық травматология және ортопедия ғылыми орталығы, Астана, Қазақстан. E-mail: bekjan-suleimen@mail.ru

[7] Дәрігер травматолог-ортопед, Академик Н.Д. Батпенов атындағы ұлттық травматология және ортопедия ғылыми орталығы, Астана, Қазақстан. E-mail: yerdaulet.21@mail.ru

Түйіндеме

Жамбас дисплазиясы - бұл дер кезінде диагноз қойылмағанжәне емделмеген жағдайда жамбас буынының қызметінің бұзылуына алып келетін тірек-қимыл аппаратының ауыр патологиясы. Бұл хирургиялық араласуды қажет ететін остеоартритке әкеледі. Ұсынылған есепте көлденең сублаксацияны қысқарту остеотомия аймағының біріктірілмеуі және сол жақ жамбас буынының жамбастың толық ауыстырылуымен біріктірілген клиникалық жағдай сипатталған.

Біздің баяндамамызда/зерттеуімізде қысқа бақылау кезеңі және жалғыз науқастың болуы сияқты кейбір шектеулер болғанын атап өткен жөн. Жақсы нәтижелерге қол жеткізу үшін ұзақ мерзімді бақылаумен және Crowe типті DDH бар науқастардың үлкен үлгісімен қосымша зерттеулер қажет деп есептейміз. Бұл зерттеу және науқасты бақылау жалғасуда.

Түйін сөздер: жамбас дисплазиясы, эндопротездеу, сублаксацияны қысқарту остеотомиясы, біріктірілмеу.

Osteotomy Site Non-union in Transverse Femoral Shortening Osteotomy Combined with THA. A clinical Case Study

Askarjan Beknazarov [1], Kairat Ashimov [2], Berk Guclu [3], Durdana Oktyabrova [4], Timur Baidalin [5], Bekzhan Suleimenov [6], Yerdaulet Agabekov [7]

[1] Traumatologist-orthopedist, National scientific center of traumatology and orthopedics named after academician N.D. Batpenov, Astana, Kazakhstan. E-mail: dr.askar1990@gmail.com

[2] Head of the Department orthopedics No3, National scientific center of traumatology and orthopedics named after academician N.D. Batpenov, Astana, Kazakhstan. E-mail: kairat_ashimov@mail.ru

[3] Head of the Department of orthopedics and traumatology, Ufuk University, Ankara, Turkey. E-mail: gucluberk@yahoo.com

[4] PhD student at the the Astana Medical University, traumatologist-orthopedist, National scientific center of traumatology and orthopedics named after academician N.D. Batpenov, Astana, Kazakhstan. E-mail: oktyabrovadana@gmail.com

[5] Head of the Department orthopedics No7, National scientific center of traumatology and orthopedics named after academition N.D. Batpenov, Astana, Kazakhstan. E-mail: t.baidalin@gmail.com

[6] Traumatologist-orthopedist, National scientific center of traumatology and orthopedics named after academition N.D. Batpenov, Astana, Kazakhstan. E-mail: bekjan-suleimen@mail.ru

[7] Traumatologist-orthopedist, National scientific center of traumatology and orthopedics named after academician N.D. Batpenov, Astana, Kazakhstan. E-mail: yerdaulet.21@mail.ru

Abstract

Hip dysplasia is a severe pathology of the musculoskeletal system which, if not diagnosed and treated in time, leads to impaired function of the hip joint. This leads to osteoarthritis, which requires surgical intervention. This report describes a case of non-union of the transverse subluxation shortening osteotomy zone combined with total hip replacement of the left hip joint.

It should be noted that our report/study had some limitations, such as a short follow-up period and one patient. We believe that further research with a long follow-up period and a larger sample of patients with Crowe type DDH is needed to obtain good results. This study and patient follow-up are ongoing.

Key words: Hip dysplasia, endoprosthesis, subluxation shortening osteotomy, nonunions.

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Original article

Optimization of Positive end-expiratory Pressure in Reverse Trendelenburg Position During Laparoscopic Surgery in Adult Patients

Gulfairus Yessenbayeva [1], Sanzhar Shalekenov [2], Dmitriy Klyuyev [3], Vilen Molotov-Luchanskiy [4], Irina Mukatova [5], Dinara Zharlyganova [6], Altynai Kassenova [7], Andrey Yaroshetskiy [8]

[1] Chief specialist of the science department, National Research Oncology Center, Astana, Kazakhstan. E-mail: yessenbayeva.gulfairus@gmail.com
[2] Chairman of the Board, National Research Oncology Center, Astana, Kazakhstan. E-mail: s.shalekenov@gmail.com
[3] Director of the Institute of Life Sciences, Karaganda Medical University, Karaganda, Kazakhstan. E-mail: klyuev@qmu.kz
[4] Professor of internal medicine Department, Karaganda Medical University, Karaganda, Kazakhstan. E-mail: Molotov-luchanskiy@qmu.kz
[5] Professor of Pulmonology Department, Astana Medical University, Astana, Kazakhstan. E-mail: kozlovapulm@gmail.com
[6] Head of Department of Science, National Research Oncology Center, Astana, Kazakhstan. E-mail: dinarazh@mail.ru
[7] Anesthesiologist of Department of Anesthesiology and Reanimation, Multidisciplinary Hospital №1, Karaganda, Kazakhstan. E-mail: Zhamaukan@mail.ru
[8] Professor of Pulmonology Department, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia. E-mail: dr.intensivist@gmail.com

Abstract

The optimal level of PEEP during laparoscopic surgery without lung injury remains unclear and controversial. We hypothesized that personalized adjustment of positive end-expiratory pressure (PEEP) by best compliance could improve perioperative gas exchange and respiratory biomechanics in adult patients undergoing laparoscopic surgery in the reverse Trendelenburg (RT) position.

Objective: The primary objective of the study was to determine the difference in oxygenation between the groups. Secondary objectives were differences in intraoperative dynamics of compliance and driving pressure.

Methods. A randomized trial was conducted with patients undergoing laparoscopic cholecystectomy, divided into two groups. In the PEEP titration group (iPEEP), PEEP was adjusted according to best compliance. PEEP titration was performed in 1 cmH2O increments. In control group (PEEP5) we set PEEP of 5 cmH2O.

Results. Sixty patients were included in the study. PEEP during pneumoperitoneum (PNP) did not differ between the two groups at 5 minutes and 1 hour after PNP (t2, 5.3±4.58 vs 5.0±0.0 cmH2O, t3 5.93±5.09 vs 5.0±0.0 cmH2O, respectively, both P>0.05) and corresponded with esophageal pressure monitoring. Oxygen saturation (SpO2) levels were comparable throughout surgery. Higher driving pressure (DP) was observed in the iPEEPgroup at 5 minutes post-PNP, but DP values remained within protective limits. Compliance decreased in both groups 5 minutes post-PNP but was lower in the iPEEPgroup. These differences in DP and compliance disappeared one hour after PNP and by the end of surgery. The P/F ratio was significantly higher in the iPEEPgroup compared to the PEEP5 group 1 hour and 24 hours post-surgery (p<0.05), although the iPEEPgroup had higher preoperative P/F values.

Conclusions. During laparoscopic cholecystectomy in RT position PEEP 5 is sufficient, but some patients need personalized adjustment. Intraoperative titrated PEEP improved perioperative oxygenation and did not affect on respiratory mechanics.

Keywords: PEEP, compliance, oxygenation, laparoscopy, lung protective ventilation.

Corresponding author: Yessenbayeva Gulfairus, *Chief specialist of the science department, National Research Oncology Center, Astana, Kazakhstan*.
Postal code: Z05K4F4
Address: Kazakhstan, Astana, Kerei-Zhanibek khandar str.,3
Phone: +7 778 843 45 63
E-mail: yessenbayeva.gulfairus@gmail.com

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Introduction

Annually, approximately 230 million patients worldwide require surgery with general anesthesia and mechanical ventilation (MV) [1]. Laparoscopic procedures are increasingly becoming the primary method of surgical intervention each year. This technique involves making a minimal surgical incision to allow camera access, insufflating the abdomen with carbon dioxide (CO2), and placing additional ports under direct visual control through the camera to facilitate the insertion of laparoscopic instruments [2].

Pneumoperitoneum (PNP) and the patient position required for laparoscopic surgery lead to pathophysiological changes that complicate anesthesia [3]. PNP is characterized by increased intra-abdominal pressure (IAP) and cranial displacement of the diaphragm, which can lead to intraoperative atelectasis and decreased end-expiratory lung volume (EELV) [4,5]. Moreover, PNP can reduce respiratory system compliance by 30-50% in healthy patients [6,7]. During elective abdominal surgeries under general anesthesia, atelectasis forms in almost 90% of patients [8] and may become a focus of postoperative pneumonia. One method of preventing the effects of PNP on lung tissue is the use of positive end-expiratory pressure (PEEP) [9]. PEEP is recognized as a component of lung protective ventilation (LPV) along with a low tidal volume (TV) of 6-8 ml/kg [10,11]. On the other hand, excessive PEEP can lead to lung overdistension, causing volutrauma [12] and hemodynamic instability. It is crucial to use appropriate PEEP levels to minimize atelectasis, improve respiratory mechanics, and maintain oxygenation.

A recent systematic review and meta-analysis of intensive care unit (ICU) patients without acute respiratory distress syndrome (ARDS) found no reduction in in-hospital mortality or duration of ventilation in patients with higher PEEP. However, hypoxemia and ARDS occurred less frequently with higher PEEP (assessed by arterial partial pressure of oxygen (PaO2) or the PaO2/FiO2 ratio) [13]. In a large observational study of general surgery patients without obesity, a PEEP of 5 cmH2O was identified as a protective factor associated with fewer postoperative pulmonary complications (PPC) [14]. Additionally, zero PEEP was associated with worse outcomes, including increased hypoxemia, ventilator-associated pneumonia, and in-hospital mortality [15]. One systematic review and network meta-analysis suggested that individually tailored PEEP combined with a recruitment maneuver (RM) may be the optimal ventilation strategy in combination with low VT in abdominal surgery, but it involved mixed groups of patients undergoing laparoscopic and open surgery [16]. A recent systematic review and meta-analysis found that high and individualized PEEP during laparoscopic surgery in non-obese patients can improve oxygenation and respiratory mechanics without causing clinically significant effects on hemodynamics. While a moderate PEEP may be insufficient to improve airway compliance and oxygenation, low PEEP may result in decreased airway compliance and impaired oxygenation [17]. In obese patients, higher PEEP may be used, as some studies indicate worsening respiratory mechanics in this group [18,19]. Although low VT is recognized as a protective component during surgery, randomized controlled trials (RCTs) comparing PEEP levels during laparoscopic surgery have been small and have shown conflicting results regarding the effects of PEEP on oxygenation, respiratory mechanics, and hemodynamic stability [20–25]. Thus, the optimal level of PEEP during laparoscopic surgery without lung injury remains unclear and controversial.

Due to the ambiguity of available data, many authors are actively developing the idea of personalized intraoperative PEEP titration [26–28], and further studies are needed to determine an effective and safe intraoperative PEEP level during laparoscopic surgery.

Materials and methods

Subjects. We conducted a prospective, blinded, randomized controlled trial (RCT) at Professor Makazhanov H.J. Multidisciplinary Hospital from April 2021 to June 2022 in Kazakhstan. The study protocol was approved by Local Bioethics Committee of Karaganda Medical University (assigned number 66, protocol №18, dated 12.04.2021). Written informed consent was obtained from all patients before inclusion in the study. This manuscript adheres to the CONSORT guidelines.

Sixty consenting patients with ASA physical status I-II (see Figure 1 for CONSORT study profile) were included in the study. All patients underwent laparoscopic cholecystectomy between April 2021 and June 2022. Exclusion criteria were age < 18 and > 65 years, BMI > 30 kg/m2, pregnancy, ASA III-IV patients, life-threatening cardiac rhythm disturbances and/or systolic blood pressure < 80 mm Hg despite norepinephrine at a dose > 2 μg/kg/min, primary lung diseases (e.g., interstitial lung disease, interstitial lung disease, pulmonary emphysema) or tumor metastases to the lungs, chronic decompensated disease with extrapulmonary organ dysfunction (tumor progression, cirrhosis, congestive heart failure), Glasgow Coma Scale score < 14 points, upper airway obstruction. Patients were withdrawn from the study and replaced in case of protocol violation and when conversion to open laparotomy cholecystectomy occurred.

Baseline electrocardiogram (ECG), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), hemoglobin oxygen saturation (SpO2), and end-tidal carbon dioxide (ETCO2) were recorded in the operating room using a multi-frame monitor. Baseline arterial blood gases (ABG) were measured. After induction of anesthesia with standard doses of fentanyl, propofol, and rocuronium, general anesthesia was maintained in TIVA mode by continuous infusion of propofol and fentanyl. Intravenous crystalloids and norepinephrine were administered as needed at the discretion of the attending anesthesiologist. After induction and intubation, an arterial catheter was placed in the radial artery for repeated arterial blood gas sampling.

Mechanical ventilation was performed in volume control mode with inspiratory square flow. Tidal volume was 6 mL/kg ideal body weight, FIO2 was set to maintain SpO2 > 92%, and respiratory rate was adjusted to achieve and maintain end-expiratory carbon dioxide concentration at 30-45 mm Hg. The inspiratory time was 33% of the total respiratory cycle time, and the inspiratory pause was equal to 20% of the inspiratory time. Initially, PEEP was not added. According to the anesthesia maintenance plan, propofol was administered intravenously at a rate of 2-10 mg/kg/h, fentanyl 0.05-0.15 mg/kg/min, and emergency rocuronium.

Study protocol. All patients were randomized into one of two groups (main or control) using a computerized randomization sequence (www.sealedenvelope.com); assignment was communicated to the attending physician before the patient entered the operating room. The main group were patients with calculous cholecystitis who underwent ventilation with PEEP adjustment titrated by best static compliance; the control group were patients with calculous cholecystitis who underwent standard ventilation with PEEP of 5 cm H2O throughout surgery.

In the PEEP titration group (iPEEP), PEEP was adjusted according to best compliance. PEEP titration was performed in 1 cm H2O increments. In the control group (PEEP5), a PEEP of 5 cm H2O was set. Esophageal pressure monitoring was used in both groups. Group allocation was concealed in a sealed envelope before induction of anesthesia.

In both groups, FiO2 was chosen by the anesthesia staff to maintain an SpO2 > 92% and a plateau respiratory system pressure (P plat) < 30 cm H2O according to our institutional protocol. When SpO2 decreased to 92%, FIO2 was increased first, followed by PEEP, after excluding common possible causes such as endotracheal tube misplacement or airway secretions. If SpO2 persistently remained below 92%, a recruitment maneuver was performed with continuous hemodynamic monitoring. In the iPEEP group, PEEP was adjusted to achieve the best static compliance.

Tidal volume was based on ideal body weight (6 ml/kg), the inspiratory/expiratory ratio was set to 1:2, and the breathing frequency was adjusted to maintain an end-tidal carbon dioxide value <55 mm Hg in both groups. Furthermore, recruitment maneuvers could be performed based on clinical judgment if SpO2 was <92%. During recovery from anesthesia, patients were transferred to the postanesthesia care unit while spontaneously breathing room air or, when required, oxygen via a Venturi face mask.

Study steps were defined as follows: baseline, before starting surgery (t0); after intubation in the absence of external PEEP (t1); randomization and 5 minutes after PEEP application (t2); after 5 minutes of pneumoperitoneum application (t3); after 5 minutes the reverse Trendelenburg and changing position (t4); and 24 hours after surgery (t24).

Measurements. Demographic characteristics such as sex, age, ASA physical status, body mass index, and ideal body weight were recorded for each subject. Arterial pH, the ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FIO2), and arterial carbon dioxide partial pressure were assessed at randomization, as well as at one hour and 24 hours after the end of surgery. Hemodynamic status was continuously monitored throughout the study, with mean arterial blood pressure and heart rate recorded from t1 to t4. At each step from t1 to t4, occlusion maneuvers at both end-expiration and end-inspiration were performed to measure static pressures in the airways (Pplat) and in the chest. These values were used to compute static compliance. Volumetric capnography was also recorded, and the driving pressure of the respiratory system was calculated.

Statistics. The statistical analysis was carried out using the Statistical Package for the Social Sciences program, version 26 (SPSS Inc., Chicago, Illinois, USA). Intergroup comparisons for variables with a normal distribution were conducted through Student's t-test, while variables lacking normal distribution were assessed using the Mann–Whitney U test. The χ^2 test was employed for intergroup comparisons of categorical data, and paired samples t-test was used for intragroup comparisons. Results are presented as mean (M) ± SD when quantitative data were normally distributed. In non-normal distribution, quantitative data were described based on the median (Me) and upper and lower quartiles (Q25, Q75). A significance level of $P < 0.05$ was considered statistically significant.

Sample size calculations were performed using the PASS 15.0 program. The sample size determination was based on observations obtained in a study conducted by Sen and Erdogan Doventas (29). In this study, the group with PEEP 10 demonstrated a mean PaO2 of 176.1 (37.9) mmHg after 30 minutes of pneumoperitoneum, while the group with PEEP 5 had a mean PaO2 of 135.2 (36.9) mmHg. To detect a similar difference in PaO2 at 80% power and α 0.05 error, the sample size was 14 persons per group. Considering possible dropout from the study, total 60 adults were included.

Results

From April 2021 to April 2022, 82 patients were eligible for inclusion in the study, but 22 were not included. Of these, 10 did not meet the inclusion criteria, one refused to participate, and one was excluded for other reasons, resulting in 60 patients being included in the study. No patients dropped out or had incomplete follow-up (Figure 1).

The baseline characteristics of the study groups are summarized in Table 1. Both groups were well-matched in terms of gender, age, body mass index (BMI), weight, height, and smoking status. The iPEEP group consisted of 6 males and 24 females, while the PEEP5 group had 8 males and 22 females, with no significant difference in gender distribution (p=0.54).

Table 1 - Basic characteristics of the study group

Characteristics	IPEEP	PEEP5	p
Sex (M/F)	6/24	8/22	0.54
Age, years	42.46/12.29	47.37/ 14.02	0.14
BMI, kg/m²	25.91/ 3.05	25.26/ 3.58	0.49
Weight, kg	71.70/ 11.91	67.53/ 11.39	0.29
Height, sm	166.03/ 8.48	163.33/ 6.90	0.41
Smoker, yes/no	5/25	6/24	0.74

Data presented as mean ± SD. BMI - body mass index. A value of P < 0.05 was considered statistically significant. F - female, M – male

The mean age was 42.46 ± 12.29 years in the iPEEP group and 47.37 ± 14.02 years in the PEEP5 group, without a statistically significant difference (p = 0.14). Similarly, there were no significant differences in BMI (25.91 ± 3.05 kg/m^2 vs. 25.26 ± 3.585 kg/m^2, p = 0.49), weight (71.70 ± 11.91 kg vs. 67.53 ± 11.39 kg, p = 0.29), and height (166.03 ±

8.48 cm vs. 163.33 ± 6.90 cm, p = 0.41) between the groups. Smoking status was also comparable, with 5 smokers in the iPEEP group and 6 in the PEEP5 group (p = 0.74). These findings confirm that the study groups were comparable, allowing for a fair assessment of the effects of different mechanical ventilation strategies.

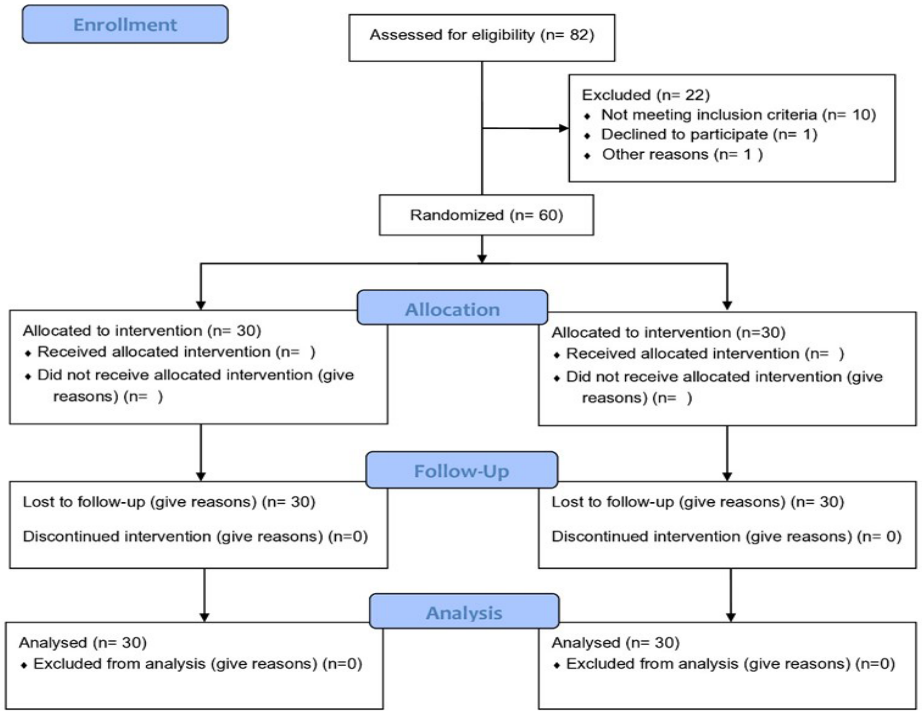

Figure 1 - CONSORT Flow Diagram

In terms of oxygenation parameters, SpO2 levels were similar between the groups throughout the study. The P/F ratio, a key indicator of oxygenation, was consistently higher in the iPEEP group at all time points (Figure 2). At t0, the median P/F ratio was 452.85 (Q25-Q75: 406.19-547.61) in the iPEEP group, compared to 391.19 (Q25-Q75: 367.14-470.95) in the PEEP5 group (p = 0.028). This trend persisted at t1, with medians of 438.57 (Q25-Q75: 393.33-614.28) vs. 402.85 (Q25-Q75: 353.09-455.83) (p = 0.020), and at t24, with medians of 480.95 (Q25-Q75: 385.23-619.04) vs. 378.80 (Q25-Q75: 333.80-463.09) (p = 0.010). Similarly, the partial pressure of arterial oxygen (PaO2) was significantly higher in the iPEEP group one hour and 24 hours after surgery, indicating improved oxygenation under the iPEEP strategy.

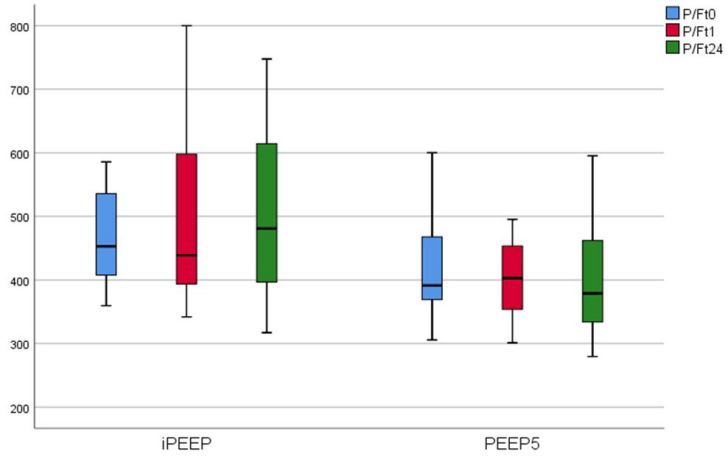

Figure 2 - Oxygenation parameters

P/F - the ratio of partial pressure of oxygen in arterial blood (PaO2) to the fraction of inspiratory oxygen concentration (FiO2) is an indicator of pulmonary shunt fraction.
t0 - before starting surgery;
t1 - 1 hours after surgery;
t24 - 24 hours after surgery

Conversely, the partial pressure of arterial carbon dioxide (PaCO2) did not differ significantly between the groups at any time point. At t0, the median PaCO2 was 33.30 (Q25-Q75: 32.20-35.60) in the iPEEP group, compared to

35.95 (Q25-Q75: 32.97-38.95) in the PEEP5 group (p = 0.067). Similar non-significant differences were observed at t1 and t24 (p = 0.164 and p = 0.554, respectively).

When examining driving pressure (DP) and static compliance (Cstat), the iPEEP group showed significantly higher DP at early time points (Figure 3 and 4, respectively). At DP1, the median DP in the iPEEP group was 12.00 (Q25-Q75: 11.000-14.250), compared to 10.00 (Q25-Q75: 9.075-12.000) in the PEEP5 group (p = 0.042). At DP2, the difference was even more pronounced, with medians of 11.00 (Q25-Q75: 10.000-12.000) vs. 9.5 (Q25-Q75: 8.00-11.00) (p = 0.008). However, no significant differences in DP were observed at later time points (DP3 and DP4), and static compliance (Cstat) did not differ significantly between the groups at any time point.

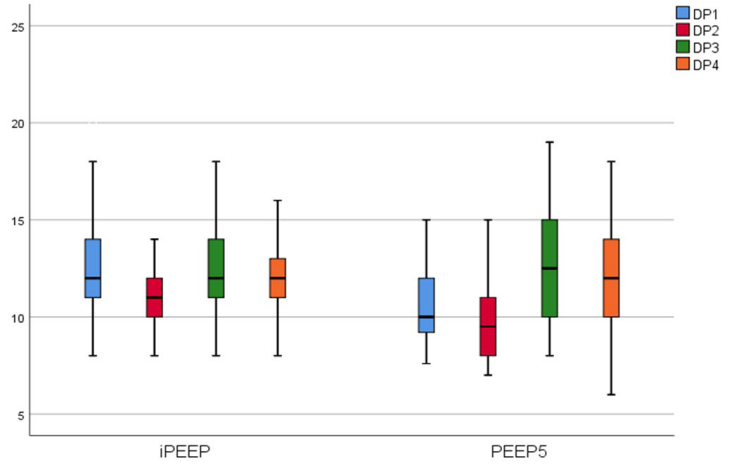

Figure 3 - DP parameters.
DP – driving pressure.
1 - after intubation in the absence of external PEEP (t1);
2 - randomization and 5 minutes after PEEP application (t2);
3 - after 5 minutes of pneumoperitoneum application (t3);
4 - after 5 minutes the reverse Trendelenburg and changing position (t4)

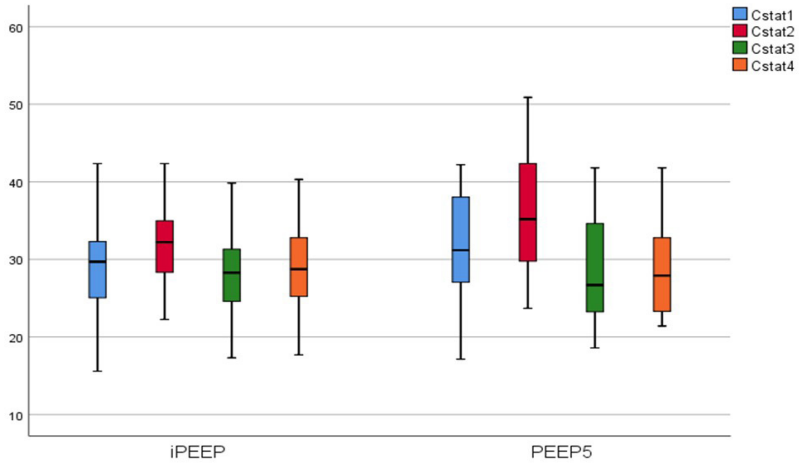

Figure 4 - Cstat parameters.
Cstat – static compliance.
1 - after intubation in the absence of external PEEP (t1);
2 - randomization and 5 minutes after PEEP application (t2);
3 - after 5 minutes of pneumoperitoneum application (t3);
4 - after 5 minutes the reverse Trendelenburg and changing position (t4)

Finally, gas exchanges parameters during ventilation, including VCO2 (volumetric capnography), PetCO2 (partial pressure of end-tidal carbon dioxide), and EELV (end expiratory lung volume), did not show statistically significant differences between the iPEEP and PEEP5 groups (table 2). For example, VCO2 and PetCO2 medians were comparable between the groups at all time points, with p-values exceeding 0.64 and 0.08, respectively. Similarly, EELV measurements showed no significant differences, with p-values greater than 0.09 at all measured intervals.

In conclusion, the iPEEP strategy resulted in significantly better oxygenation (higher P/F ratio and PaO2) compared to the PEEP5 strategy, without significantly affecting carbon dioxide elimination, driving pressure at later time points, static compliance, or overall ventilation parameters. These findings suggest that iPEEP may offer advantages in maintaining superior oxygenation during mechanical ventilation without compromising other aspects of respiratory mechanics.

Table 1 - Gas exchanges parameters during ventilation

	IPEEP	PEEP5	p
N	30	30	
VCO2_1	95.50 (82.50-114.00)	96.00 (78.00-109.50)	0.90
VCO2_2	93.00 (78.00-103.50)	99.00 (76.50-108.00)	0.69
VCO2_3	96.00 (82.50-102.50)	93.00 (78.00-126.00)	0.64
VCO2_4	102.00 (84.00-109.50)	99.00 (90.00-120.00)	0.91
PetCO2_1	28.82 (25.919-31.507)	32.18 (27.757-35.771)	0.49
PetCO2_2	37.00 (32.75-38.25)	36.00 (34.00-40.25)	0.08
PetCO2_3	36.00 (33.75-38.00)	36.00 (34.00-39.00)	0.73
PetCO2_4	38.00 (35.75-41.25)	40.00 (37.00-43.00)	0.08
EELV_1	-	-	
EELV_2	167.71 (81.78-250.35)	210.94 (162.94-265.13)	0.09
EELV_3	169.56 (57.70-289.84)	147.77 (117.04-205.09)	0.83
EELV_4	146.40 (45.85-296.83)	152.28 (122.06-192.73	0.50

Data presented as median and 25th, 75th percentiles. A value of P < 0.05 was considered statistically significant.
VCO2 – volumetric capnometry, PetCO2- - arterial partial pressure of carbon dioxide.
1 - after intubation in the absence of external PEEP (t1);
2 - randomization and 5 minutes after PEEP application (t2);
3 - after 5 minutes of pneumoperitoneum application (t3);
4 - after 5 minutes the reverse Trendelenburg and changing position (t4).

Discussion

Our study demonstrated that the PEEP titration strategy resulted in significantly better oxygenation compared to the fixed PEEP of 5 cm H_2O. This was evident from the consistently higher P/F ratios and PaO_2 levels in the iPEEP group at all measured time points, indicating that the iPEEP strategy is more effective in maintaining oxygenation during mechanical ventilation.

These findings align with previous research, which also highlighted the potential benefits of individualized PEEP settings. For instance, the study by Meininger et al. [30[found that higher PEEP levels during robot-assisted laparoscopic surgery improved oxygenation, particularly during prolonged procedures. Although the beneficial effects of PEEP on oxygenation were more pronounced with longer pneumoperitoneum durations, our study indicates that even in shorter surgeries, a tailored PEEP approach can yield significant oxygenation benefits.

Interestingly, despite the improvement in oxygenation, there was no significant difference in $PaCO_2$ levels between the two groups in our study. This suggests that while PEEP titration can enhance oxygenation, it does not adversely affect carbon dioxide elimination, maintaining respiratory function stability. However, in a previous study, during pneumoperitoneum, PaCO2 was found to be significantly increased from baseline in both groups (31). This could be a consequence of intra-abdominal carbon dioxide insufflation combined with Trendelenburg position. However, it did not cause significant disturbances in acid-base status.

In terms of respiratory mechanics, our findings revealed that driving pressure (DP) was significantly higher in the iPEEP group at early time points, but this difference diminished over time. This aligns with the hypothesis that PEEP titration may initially increase DP as lung recruitment improves, but as the lungs adapt, DP stabilizes without significantly affecting static compliance (Cstat). This result is in line with other research suggesting that individualized PEEP settings can optimize lung mechanics without increasing the risk of ventilator-induced lung injury [32,33].

Moreover, ventilation and respiratory volume parameters such as VCO_2, $PetCO_2$, and EELV did not show statistically significant differences between the groups, indicating that the PEEP titration strategy did not compromise other aspects of respiratory mechanics. This further supports the safety and efficacy of the iPEEP strategy in clinical practice.

Conclusion

In the context of laparoscopic cholecystectomy performed in the reverse Trendelenburg (RT) position, a fixed PEEP of 5 cmH_2O generally suffices. However, some patients may benefit from personalized PEEP adjustments. Our study demonstrated that titrating PEEP based on individualized measurements significantly enhances perioperative oxygenation without adversely affecting respiratory mechanics. Thus, PEEP titration is a feasible and potentially superior alternative to fixed PEEP settings. Future research should investigate the long-term effects of this strategy, especially in broader patient populations and various surgical settings.

Competing interests. No

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Author contributions. Y.A.I. - study design, data collection, analysis and interpretation, script writing and revision; Y.G.A. - study design, data collection, analysis, script writing, and revision; M.I.Y. - study design, data interpretation, manuscript revision; K.D.A. - data analysis and interpretation; K.A.K. - data analysis and interpretation; M.V.B. - data collection; Z.D.S. - data collection; S.I.K. - data collection. All authors revised the drafted manuscript, and all read and approved its final version.

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Ересек науқастарда лапароскопиялық хирургия кезінде кері Тренделенбург жағдайында оң экспираторлық қысымды оңтайландыру

Есенбаева Г.А. [1], Шалекенов С.Б. [2], Клюев Д.А. [3], Молотов-Лучанский В.Б. [4], Мукатова И.Ю. [5], Жарлыганова Д.С.[6], Касенова А. К. [7], Ярошецкий А.И. [8]

[1] Ғылым бөлімінің бас маманы, Ұлттық ғылыми онкология орталығы, Астана, Қазақстан. E-mail: yessenbayeva.gulfairus@gmail.com

[2] Басқарма төрағасы, Ұлттық ғылыми онкология орталығы, Астана, Қазақстан. E-mail: s.shalekenov@gmail.com

[3] Өмір туралы ғылымдар институтының директоры, Қарағанды медицина университеті, Қарағанды, Қазақстан. E-mail: klyuev@qmu.kz

[4] Ішкі аурулар кафедрасының профессоры, Қарағанды медицина университет, Қарағанды, Қазақстан. E-mail: Molotov-luchanskiy@qmu.kz

[5] Пульмонология кафедрасының профессоры, Астана медицина университеті, Астана, Қазақстан. E-mail: kozlovapulm@gmail.com

[6] Ғылым бөлімінің бастығы, Ұлттық ғылыми онкология орталығы, Астана, Қазақстан. E-mail: dinarazh@mail.ru

[7] Анестезиология және реанимация бөлімшесінің анестезиологы, №1 Көпсалалы аурухана, Қарағанды, Қазақстан. E-mail: Zhamaukan@mail.ru

[8] Пульмонология кафедрасының профессоры, И. М. Сеченов атындағы Бірінші Мәскеу мемлекеттік медицина университеті (Сеченов университеті), Мәскеу, Ресей. E-mail: dr.intensivist@gmail.com

Түйіндеме

Өкпеге зақым келтірмейтін лапароскопиялық операциялар кезінде дем шығарудың соңында оң қысымның (ДСШҚ) оңтайлы деңгейі әлі де белгісіз және даулы болып қалып отыр. Біз оңтайлы комплаенс арқылы ДСШҚ жеке түзету ересек пациенттерде лапароскопиялық хирургия кезінде, кері Тренделенбург (КТ) позициясында, периоперациялық газ алмасуды және тыныс алу биомеханикасын жақсарта алады деп болжадық.

Зерттеудің негізгі мақсаты - топтар арасындағы оттегімен қанығу айырмашылығын анықтау. Екіншілік мақсаттар - комплаенс пен қозғаушы қысымының операциялық динамикасындағы айырмашылықтарда анықтау.

Әдістері. Лапароскопиялық холецистэктомиядан өткен пациенттер арасында рандомизацияланған сынақ өткізілді, олар екі топқа бөлінді. ДСШҚ реттеу тобында (iPEEP) ДСШҚ оңтайлы сәйкестікке сәйкес реттелді. ДСШҚ реттеу 1 смН2О қадамымен жүргізілді. Бақылау тобында ДСШҚ 5 смН2О (PEEP5) деңгейінде орнатылды.

Нәтижес. Зерттеуге 60 пациент қатысты. Пневмоперитонеум (ПНП) кезінде ДСШҚ 5 минуттан және ПНП-ден 1 сағат өткен соң екі топта да айырмашылық болмады (t2, 5,3±4,58 қарсы 5,0±0,0 см Н2О, t3 5,93±5,09 қарсы 5,0±0,0 см Н2О, тиісінше, екеуі де P>0,05) және өңеш қысымын бақылауға сәйкес келді. Операция барысында оттегімен қанығу деңгейі (SpO2) ұқсас болды. ПНП-ден кейін 5 минут өткен соң iPEEP тобында қозғаушы қысым (ҚҚ) жоғары болды, бірақ ҚҚ мәндері қорғаныс шектерінде қалды. Сәйкестік екі топта да ПНП-ден кейін 5 минуттан соң төмендеді, бірақ iPEEP тобында төмен болды. Бұл ҚҚ және сәйкестік айырмашылықтары ПНП-ден 1 сағат өткен соң және операция соңына дейін жоғалып кетті. P/F арақатынасы iPEEP тобында PEEP5 тобымен салыстырғанда операциядан кейін 1 сағат және 24 сағаттан кейін едәуір жоғары болды (p<0,05), бірақ iPEEP тобында операция алдындағы P/F мәндері жоғары болды.

Қорытынды. Лапароскопиялық холецистэктомия кезінде КТ позициясында ПДКВ 5 жеткілікті, бірақ кейбір пациенттерге жеке түзету қажет. Ішкі операциялық реттелген ДСШҚ периоперациялық оттегімен қанығуды жақсартты және тыныс алу механикасына әсер етпеді.

Түйін сөздер: дем шығарудың соңында оң қысым, комплаенс, оттегімен қанығу, лапароскопия, өкпені қорғайтын желдету.

Оптимизация положительного давления в конце выдоха в обратном положении Тренделенбурга во время лапароскопической операции у взрослых пациентов

Есенбаева Г.А. [1], Шалекенов С.Б. [2], Клюев Д.А. [3], Молотов-Лучанский В.Б. [4], Мукатова И.Ю. [5], Жарлыганова Д.С.[6], Касенова А. К. [7], Ярошецкий А.И. [8]

[1] Главный специалист отдела науки, Национальный научный онкологический центр, Астана, Казахстан. E-mail: yessenbayeva.gulfairus@gmail.com

[2] Председатель правления, Национальный научный онкологический центр, Астана, Казахстан. E-mail: s.shalekenov@gmail.com

[3] Директор Института наук о жизни, Медицинский университет Караганды, Караганда, Казахстан. E-mail: klyuev@qmu.kz

[4] Профессор кафедры внутренних болезней, Медицинский университет Караганды, Караганда, Казахстан. E-mail: Molotov-luchanskiy@qmu.kz

[5] Профессор кафедры пульмонологии, Медицинский университет Астаны, Астана, Казахстан. E-mail: kozlovapulm@gmail.com

[6] Начальник отдела науки, Национальный научный онкологический центр, Астана, Казахстан. E-mail: dinarazh@mail.ru

[7] Анестезиолог отделения анестезиологии и реанимации, Многопрофильная больница №1, Караганда, Казахстан. E-mail: Zhamaukan@mail.ru

[8] Профессор кафедры пульмонологии, Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский университет), Москва, Россия. E-mail: dr.intensivist@gmail.com

Резюме

Оптимальный уровень ПДКВ (положительного давления в конце выдоха) во время лапароскопических операций без повреждения легких остается неясным и вызывает споры. Мы предположили, что индивидуальная настройка ПДКВ на основе наилучшей податливости (compliance) может улучшить периоперационный газообмен и биомеханику дыхания у взрослых пациентов, перенесших лапароскопическую операцию в положении обратного Тренделенбурга (ОТ).

Цель исследования: Основной целью исследования было определить разницу в оксигенации между группами. Второстепенные цели включали различия в интраоперационной динамике податливости и давления вождения (ДВ).

Методы. Проведено рандомизированное исследование среди пациентов, перенесших лапароскопическую холецистэктомию, разделенных на две группы. В группе титрации ПДКВ (iPEEP) ПДКВ настраивалось в соответствии с наилучшей податливостью. Титрация ПДКВ проводилась с шагом 1 см H2O. В контрольной группе ПДКВ было установлено на уровне 5 см H2O.

Результаты. В исследование было включено 60 пациентов. ПДКВ во время пневмоперитонеума (ПНП) не различалось между двумя группами через 5 минут и 1 час после ПНП (t2, 5,3±4,58 против 5,0±0,0 см H2O, t3 5,93±5,09 против 5,0±0,0 см H2O, соответственно, оба P>0,05) и соответствовало данным мониторинга давления в пищеводе. Уровни сатурации кислорода (SpO2) были сопоставимы на протяжении всей операции. В группе iPEEP наблюдалось более высокое давление на вдохе через 5 минут после ПНП, но значения ДВ оставались в пределах защитных границ. Податливость снизилась в обеих группах через 5 минут после ПНП, но была ниже в группе iPEEP. Эти различия в ДВ и податливости исчезли через час после ПНП и к концу операции. Соотношение P/F было значительно выше в группе iPEEP по сравнению с группой PEEP5 через 1 час и 24 часа после операции (p<0,05), хотя в группе iPEEP были выше предоперационные значения P/F.

Выводы. Во время лапароскопической холецистэктомии в положении ОТ ПДКВ 5 см H2O является достаточным, но некоторым пациентам требуется индивидуальная настройка. Интраоперационное титрование ПДКВ улучшило периоперационную оксигенацию и не повлияло на механику дыхания.

Ключевые слова: ПДКВ, податливость, оксигенация, лапароскопия, протективная вентиляция легких.

МАЗМҰНЫ

СОДЕРЖАНИЕ

CONTENT