Original Article

Lifetime Cost Effectiveness of Phenylketonuria Screening National Program in Iran

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Abstract

Background: Phenylketonuria (PKU) is an autosomal recessive disorder that screening and timely control of this disorder can prevent the adverse effects. Regarding the high prevalence of PKU in Iran, the PKU screening program was started in Iran in 2006. This study was conducted to determine the cost-effectiveness of PKU screening in Iran.

Methods: An economic evaluation was performed among screened and treated individuals compared to no screening in 2013. The study population included 1356132 newborns that screened for PKU diagnosis. Lifetime costs, quality-adjusted life year (QALY) gains and incremental cost-effectiveness ratio (ICER) were calculated from the perspective of government. A discount rate of 3% was considered for both QALYs and costs. A one-way sensitivity analysis was used for assessing the robustness of the results.

Results: The discounted lifetime cost of intervention and non-intervention were $59528953.8 and $85295501.6 respectively. Therefore, the total estimated cost saving was $25766547.84. PKU screening produces an ICER of $1844420 per QALY gained.

Conclusion: Screening and early treatment for PKU is highly cost-effective. Therefore, the screening can improve quality of life of the patients and increase financial saving in health system.

Keywords: Cost effectiveness; Economic evaluation; Phenylketonuria; Newborn screening

Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder caused by a deficiency of phenylalanine hydroxylase enzyme (1). PKU is the most common hereditary metabolic disorder in the world (2). Patients with PKU show high levels of phenylalanine in the blood serum and thus suffer from nervous disorders. Phenylalanine at high levels is toxic for brain; therefore, patients who do not get treatment show different grade of mental retardation, seizure, or behavioral disorders. In order to prevent such injuries, patients should be identified earlier and their Phe-limited diet during their lifetime are followed (3).

Newborn Screening (NBS) is a major achievement of public health for the identification of congenital disorders (4). In the 1960s, PKU was the first disorder that detected through NBS (5). Early diagnosis and initiation of control for PKU will prevent mental disabilities successfully. Control of PKU contains a phenylalanine (phe)-restricted diet. The strongest factor in achieving an effective outcome is maintaining a low level of

blood phe, which is achieved with an exact adherence to the diet (6). Before the NBS program, PKU was diagnosed after parents had noticed a delay in their child developmental skills, which at that time often had an irreversible brain damage (5).

Regarding the high prevalence of PKU in Iran (7-9), the PKU screening program was started in Iran in 2006 and blood samples were taken from all newborns on the third to fifth day of birth. Individuals with Phe 4 mg/dL or higher were referred for confirmation of diagnosis by (High-performance liquid chromatography) HPLC test. Then, those who have a phe level equal to or higher than 4 mg/dL are monitored regularly. If the level of phe is equal or more than to 7 mg/dL, the diet begins phe-restricted diet (10). In addition to the necessity of identifying and prevention this disorder, especially in the first years of life, the limitation of fund the resources in the health sector has made health policymakers and planners pay more attention to costs. Recently, due to increase in health care costs due to the development of health services and control as well as numerous problems, countries face health financing and health managers need to use resources more efficiently (11). Therefore, screening programs should be systematically evaluated. The results of this assessment can change the service delivery process and affect the management of public health care (12).

Cost-effectiveness method facilitate decision-making process and enables policy makers to make the best alternative (13). Despite the nature of the cost effectiveness of newborn screening, several countries do not provide these services or provide services to a portion of their population. Moreover, considering generalizability of results, the results of economic evaluation in one study cannot be generalized for various reasons such as demography factors, epidemiology of disorder, health infrastructure, clinical practice and health care costs. In addition, PKU diagnosis and management methods vary between countries (14,15). Although, a study was conducted in an Iranian province before the implementation of the national phenylketonuria screening program in Shi-

raz city (11), but the current study is the first study was conducted after the national implementation of the PKU screening program at the national level with a lifetime horizon in Iran. The aim of this study was to determine the cost effectiveness of PKU screening national program in Iran.

Methods

This study is an economic evaluation of PKU screening among screened and controlled individuals compared to no-screening in 2013. The study population included 1356132 newborns that have been screened for PKU. Based on national public health surveillance system, 322 were confirmed with PKU.

A retrospective cost analysis was performed from the health provider and patient perspectives. These costs included the capital and current costs. The cost of conducting PKU screening program included the capital costs (laboratory equipment and transportation) and current costs (staff wage, medical consumables, diagnosis of non-classic cases and education costs). These costs calculated based on cost price of services. When a place is used to do multiple programs and the amount used by a particular program from that place is very low, cost of the construction and its current costs can be ignored (16). Therefore, cost of construction and its current costs (water, electricity, gas and telephone) were not considered.

The cost of timely control of PKU included Therapeutic team at the selected hospitals, powdered milk, the paraclinical services, and medication costs. These costs calculated based on cost price of services and approved tariff of the Ministry of Health.

Costs of caring for the unscreened patients included physician visit, powdered milk, paraclinical services, medication, rehabilitation, hospitalization, patient maintenance, care, and exceptional education costs. These costs calculated based on approved tariff, patient's medical records and specialist's opinion. No inflation rate was used

because cost values were extracted from the real price list of the public sector. At cost data collection time in 2013, the market exchange rate on average was 29100 Iran Rials (IRR) to 1 US dollar (USD).

To measure the effectiveness, nutritionists who worked as unit responsible of nutrition in 33 PKU selected hospitals participated in the study. Since the screening target group are newborns and cannot answer the questions, healthcare professionals were asked to accurate estimation of the outcomes, because their better understanding of the disorder. Considering the role of the nutritionists includes diet planning throughout the lives of patients, this group, with the opinion of the scientific and executive experts, is the best people who can comment on the quality of life in PKU patients. OF 33 responsible, 31 of them agreed to complete the questionare (a response rate of 94%). The U.S. Panel on Cost-Effectiveness in Health has suggested QALY (Quality Adjusted Life Years) as the most proper effectiveness tool for health economic analysis (17). Therefore, QALY was computed as the measure of effectiveness. The time tradeoff method (TTO) was utilized to measure QALY by questionnaire. The questionnaire consists of two parts: the first part is related to the person with PKU and the second part is related to the screened and treated person. The questionnaire contains descriptions of the disorder, the status of the affected people, the treatment method and the subjects that the respondents should be aware of it. Using this technique, in each part, respondents were asked whether they choose to live with PKU for 10 years, or preferred to give up some life years to live without PKU for shorter period than 10 years (11). The effectiveness of each status was obtained from the following equation:

Effectiveness in a specific health status = Length of living in perfect health / amounts of time spent in that health state.

The time horizon of study was the lifetime. The future costs and QALYs were discounted with a 3% discount rate. Incremental Cost Effectiveness Ratio (ICER) was calculated by dividing the difference in intervention (screening and timely treatment) and nonintervention costs (caring for the unscreened patients) by the difference in QALYs estimated for the patients in two states of intervention and non-intervention. A one-way sensitivity analysis was performed to detect key parameters that have an effect on the ICER. Moreover, it was determined the high and low acceptable values for gained QALYs, 95% confidence interval was added to and was subtracted from the mean. The results of other studies were used to estimate other parameters. For analysis, Excel-office 2010 was used.

Results

The cost per screened case, the annual cost of conducting PKU screening and lifetime cost of timely treatment were $9.13, $12383011.9 and $109556477.5 respectively. Therefore, total lifetime costs of intervention was obtained $121939489.4. The lifetime cost of non-intervention was computed to be $205911818. The discounted lifetime cost of intervention and non-intervention were $59528953.8 and $85295501.6 respectively. The total estimated cost saving was $25766547.84.

The mean QALY score of the patients screened and treated was commuted as 0.735, while the mean QALY score of the unscreened patients was 0.296. ICER of PKU screening was $1844420 per QALY gained (Table 1). The ICER indicate that PKU screening is the dominant and cost-effective intervention. Key parameters affecting the ICER of included the percentage of seizure in patients, life expectancy, gained QALYs and discount rate. One-way sensitivity analysis showed that discount rate had the most impact on results and percentage of seizure in patients had the lowest impact. The screening in the worst scenario can save $1135090.2 per PKU patient and in the best scenario the saving can be $4301630.1 per PKU patient. Therefore, the results are valid (Table 2).

Table 1: Results of base case analysis

Strategy	Discounted costs (USD)	Discounted effect (QALYs)	Incremental cost	Incremental effectiveness	C/E	ICER	Dominance
PKU screening and timely treatment	59528953.8	22.16	-	13.97	2686324.6	-1844420	Dominated
No screening	85295501.6	8.19	25766547.84	-	10414591.1	-	-

QALY: quality adjusted life year, C: cost, E: effectiveness, ICER: incremental cost effectiveness ratio.

Table 2: Key parameters affecting the ICER of PKU screening

Parameter	Parameter estimation				ICER estimation		
	Base case	Low	High	References	Base case	Low	High
Seizure (%)	34	25	50	(18-19)	-1844420	-1854668.2	-1838271.1
QALY of the screened cases	0735	0.639	0.831	Calculated	-1844420	-1894599.1	-1791832.2
QALY score of the unscreened cases	0.296	0.179	0.431	Calculated	-1844420	-2528611.1	-1498926.5
Life expectancy of the screened cases	55	30	60	(20-22)	-1844420	-3427210.5	-1262131.9
Life expectancy of the unscreened cases	70	70	77.2	(20-22)	-1844420	-1844420	-1756265.3
Discount rate: Costs (%)	0.03	0.01	0.05	(22-25)	-1844420	-2741122.5	-1135090.2
Discount rate: QALYs (%)	0.03	0.01	0.05	Calculated	-1844420	-4301630.1	-1834386

Discussion

This study was conducted to evaluate whether the PKU Screening could be a cost effectiveness intervention. Costs of caring for the unscreened patients was much more than cost of intervention. Carroll's et al study in USA in 2006 revealed the cost of each PKU screening test was $ 3.43 and the treatment cost of the disease was $ 1042110. Thus, the results indicated the PKU screening is useful to patients and, in many cases, save money for society (26). In Shiraz, cost of each PKU screening test and treatment cost of PKU were $2. 28 and $9223 respectively (10). These studies confirmed the lower cost of intervention and high cost for no screening. These studies were in line with current study, which

found conducting PKU screening is highly cost saving.

The results of this study showed the mean QALY score among screened individuals was almost 2.5 times more than the unscreened patients were. The mean QALY score in patients with phenylketonuria and screened children was 0.29 and 0.73 respectively (11). Early treated PKU patients can have a normal quality of life (27). Moreover, more than half of adult patients believed that their quality of life was improved after diet (28).

Based on the results of the study, conducting PKU screening is highly cost effective. In Libya, the PKU screening would earn $US1.9 for every $US1 invested and intervention is cost effective compared with no screening (29). In Australia, the Neonatal screening for PKU was a cost sav-

ing intervention so that PKU screening provides net benefits to individuals and their families (30). The PKU screening saves $3386 per patient found and the indicated cost-effectiveness of intervention (11). In England, PKU screening saves 143000 pounds for per detected case and they showed cost effectiveness of intervention (31). Although mentioned studies claim PKU screening can be cost effective, but there are differences in cost and effectiveness values between mentioned studies. These differences could be due to differences in the costing perspective, the medical services tariffs, and time horizon in different studies.

There are some limitations in this study. Because of the use of the government perspective, indirect and intangible costs are not considered. Food for PKU patients and transportation costs did not calculate, because data were available and estimating these costs was complicated. Several assumptions have made that can affect the results of the study. Screened individuals will adhere to dietary restrictions throughout their lives. The results of the study were only for the screened individual, while the family, and especially the parents, also benefited from the positive effects of screening.

Conclusion

PKU screening has high cost saving, effectiveness and cost effectiveness in Iran like many other countries. Therefore, due to the high prevalence of the disease, the quantitative and qualitative development of screening centers in the regional and national dimension for timely diagnosis and treatment of patients, continuous follow up and treatment is essential.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interest.

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