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Cost-Effectiveness Analysis of Chemoprophylaxis of Malaria Treatment

Eun-Jung Kim*

Department of Nursing, Pyeongtaek University, Gyung-gi, Korea

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***Correspondence:**
Dr. Eun-Jung Kim, Associate Professor, Department of Nursing, Pyeongtaek University, Gyung-gi, Korea, Tel: 82-31-659-8301 Fax: 82-2-927-7220,
Email: ejkim7888@gmail.com

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ABSTRACT

Background: This study will analyze the existing studies and provide the basis for immunity and immune duration that can be obtained by prophylactic chemotherapy.

Methods: Based on the data of the patients who take preventive chemotherapy (taking group) and those who do not (non-taking group), cost benefit analysis is conducted considering the direct and indirect benefits obtained by taking malaria treatment.

Results: The results of economic evaluation of preventive use of malaria chemoprophylaxis that higher malaria incidence rates of non-taking groups showed a (+) positive value for the NPV, a CBR of greater than 1 (1.34), so economically viable vaccine with a high benefit per cost.

Conclusion: Chemoprophylaxis could be cost-effective if the incidence of non-taking group in the risk area is maintained above 50%. Therefore, it will be possible to block the incidence of malaria in the future through analysis of the trend of incidence of malaria, and to inform the effect of the chemoprophylaxis method through educational and public relations activities.

Introduction

Malaria is an infectious disease in developing and underdeveloped countries that is a major threat to health. It is known to be transmitted through female mosquitoes to female parasites[1]. In Korea, there is a Vivax malaria virus in the vicinity of the ceasefire line. In this case, the fever that gradually increases with the feeling of boredom lasts for several days in the early days, and chills, fever and fever after repeated fever may accompany headache, nausea, and diarrhea[7]. In the case of vivax malaria, the annual number of patients increased from the first patient in 1993 to more than 4,000 in 2000. It is a mosquito-borne infectious disease originating from North Korea, mainly caused by soldiers working near the armistice. It then declined rapidly to 800 in 2004[3]. However, since 2005, it has increased again, and since 2006, more than 2,000 patients have occurred each year. As of 2015, there are about 600 cases per year[6,7].

At the beginning of the epidemic, it occurred in the center of the soldiers near the armistice. However, the incidence of civilian patients has increased due to preventive chemotherapy in the army. Since 1997, it has started to take prophylactic doses of chloroquine and primaquine. From 2001, the patient was treated with Primaquine for 2 weeks before discharge to prevent spread of infection after discharge. Thus, the incidence rate of civilians and soldiers (including those who are discharged) is 6: 4, which is significantly lower than that of civilians[5].

However, malaria does not have a vaccine. Therefore, the area where malaria mosquitoes appear is designated as a high-risk area and preventive chemotherapy is applied. There are chloroquine and primaquine as therapeutic agents. In the case of chloroquine, a total of 25 mg/kg is orally administered for 3 days. That is, 5 mg/kg is administered after 6 hours, 24 hours and 48 hours after the first 10 mg/kg. In the case of chloroquine, there is an effect of removing the protozoan in the blood. In the case of Primaquine, 15 mg/day for 14 days is given once a day, which prevents the recurrence by eliminating hepatic[5].

In Korea, except for the general public who travel to dangerous areas, soldiers are treated with preventive chemotherapy for malaria in the area where malaria mosquitoes appear. Prophylactic chemotherapy is then performed using chloroquine. Because there is no problem of drug resistance, chloroquine can be used as a therapeutic agent. We also use Primaquine to eradicate the hypnozoite in the liver. The area where the two treatments are used in parallel is malaria, which is changing every year. The soldiers assigned to the troops stationed in the malaria risk area selected by the Korean Centers for Disease Control are taking Primaquine alone. Prophylactic chemotherapy is taken once a year around July to October.

However, the arguments for and against prophylactic treatment of these drugs are also being criticized. Especially in areas with low malaria risk, extensive prophylactic chemotherapy risks not only economical but also medical aspects[14]. Neuropsychiatric side effects have been reported with hemolytic anemia as well as minor side effects such as nausea, general weakness and abdominal pain. Thus, there is a claim that prophylactic chemotherapy should be performed more carefully[14]. On the other hand, some studies report that the prevalence of malaria can be significantly reduced due to the prophylactic chemotherapy administered, and the side effects are very small, making it the most effective way to prevent malaria[13].

Therefore, this study will analyze the existing studies and provide the basis for immunity and immune duration that can be obtained by prophylactic chemotherapy. Based on the data of the patients who take preventive chemotherapy (taking group) and those who do not (non-taking group), cost benefit analysis is conducted considering the direct and indirect benefits obtained by taking malaria treatment. In spite of various opinions, prophylactic chemotherapy has been carried out, and there has been no objective and systematic evaluation. Therefore, there is a need for systematic judgment and policy establishment based on accurate evidence. This study aims to provide a basis for quantitative indicators to evaluate the economic performance of prophylactic chemotherapy.

Methods

To evaluate the efficacy and effectiveness of prophylactic chemotherapy, related studies were collected through literature searches. Then, a single effect was derived by meta - analysis using the study results. To search the literature, the research period was defined as 2000.1.1 ~ 2015.12.31, and the related research was collected. At this time, we set the criteria for the evaluation of theses. If there is an existing domestic study, the study was adopted. The results were selected only for the study in which the odds ratio or the relative risk value was expressed.

The results of this study are as follows. According to Yeom *et al*. (2005), the incidence of malaria was compared using the difference in the prophylactic chemotherapy periods of Paju and Cheolwon areas, where malaria occurs frequently[15]. As a result, the efficacy of malaria prevention using primaquine was 80-100%. In addition,[4] reported randomized, open-label placebo-controlled trials of non-immune populations in Papua New Guinea. In an analysis of the efficacy of the Primaquine vaccine in a dose of 30 mg every day for 20 weeks in 97 people, it was found to be 92% effective in preventing the vivax malaria[4].

On the other hand, the data sources used to obtain information on the subjects affected by malaria are as follows. In order to identify the incidence in the army, the DMSIS, a hospital information management system, was used to analyze the incidence of malaria in the army and to identify the current incidence in 2012[2-3, 15]. The characteristics of DMSIS include information on the date of onset, average length of stay, hospitalization and outpatient treatment status, and personal information of soldiers. In addition, indirect estimation was made through the purchase amount of the therapeutic agent to identify the target of preventive use of the therapeutic agent. Of course, it is necessary to identify and correct excess and insufficient quantities along with the quantity of treatment purchased in that year, but this study will use this annual purchase cost because it focuses more on purchasing amount only.

For the analysis of non - taking group, we crossed out by sex, age, and region through annual statistical report on health insurance. The incidence rate of malaria in civilians living in Gangwon (Cheolwon), Gyeonggi (Yeoncheon, Paju) and Incheon (Ganghwa and Ongjin). However, since the variance is large by year, the maximum rate of occurrence (65.28, 2010) and the minimum value (23.32, 2012) for the period 2008-2012 were used for the benefit calculation (Table 1).

Each item was selected for cost benefit analysis. In the case of the cost, the measurement was made including the treatment cost and the fee. In the case of preventive use of the therapeutic agent, it is not inoculated, so no consideration is given to the personnel expenses of medical

Table 1: Incidence per 100,000 people among non-taking group in risk area (excluded the case of abroad infection and active soldier)

	2008	2009	2010	2011	2012
Gangwon (Cheolwon)	50.4	65	58	28.9	6.2
Gyeonggi (Yeoncheon)	57.1	44.1	64.1	35.5	8.9
Gyeonggi (Paju)	27.3	24.6	28.9	14.7	10.3
Incheon (Ganghwa)	106.1	68.4	126.7	65.7	80.7
Incheon (Ongjin).	46.6	39.3	48.7	10.5	10.5
Average	**57.5**	**48.28**	**65.28**	**31.06**	**23.32**

Source: Korean Center for Disease Control, 2013, Malaria Management Guidelines.

staff including nurses. In addition, management fee of vaccine was not considered because it is not necessary to manage vaccine through cold chain[12].

In the case of benefit, the level of improvement of health condition according to chemoprophylaxis and the improvement level of productivity loss due to decrease of deaths were considered. The effect of immune accumulation of Malaria therapeutic agents is not considered. In order to estimate the benefit of the disease reduction due to the preventive use of the therapeutic agent, the incidence of the civilians in the area adjacent to the troop where the malaria treatment was taken prophylactically was investigated. However, there is a limit to obtain the incidence rate at the small administrative level of municipalities, so the incidence of malaria in civilians living in Cheolwon, Gyeonggi, Yongcheon, Paju, and Ongjin. However, since the fluctuation of the annual incidence rate is large, the maximum value (65.28, 2010) and the minimum value (23.32, 2012) of 2008-2012 are applied.

The number of deaths to malaria was investigated in the epidemic monitoring annual report to take into account the benefits resulting from the reduction of deaths due to preventive use. There were two deaths in 2011, 0 in 2012, three in 2013 and five in 2014.

However, the cause of death was caused by malaria imported from overseas, not from the vivax malaria that occurs in Korea. Therefore, it is assumed that there are no deaths from infected malaria in[5, 10].

Results

The incidence rate of non -taking group was 23.32 ~ 65.28 per 100,000 population. This was calculated through the existing literature for the evaluation of the efficacy of prophylactic dosing. In addition, the number of deaths among infected persons was not applied.

In 2012, 112,355 people will be required to use the chemoprophylaxis, and 26.2 to 73.3 cases have not been treated. Among these, the number of patients who can prevent the onset through the chemoprophylaxis use of the therapeutic agent was assumed to be 23.5 to 65.75. And the cost of the patient was calculated as a benefit. In order to calculate the per capita hospitalization cost, we used the 2012 Annual Health Insurance Statistical Yearbook. The cost of medical care is the sum of the deductible (insurer's contribution) and the patient'. The average hospitalized cost for the last 5 years was calculated. In addition, the non-paying self-pay rate was applied by using the result of the survey on actual condition of the patient's medical expenses for 2009 ~ 2013 (based on the admission fee). The total cost of medical treatment was calculated by summing up the cost of medical treatment and the amount of non-paying patients. As a result, the cost-benefit results as shown in [Table 2] were derived.

Discussion

The results of economic evaluation of preventive use of malaria chemoprophylaxis are as follows. Higher malaria incidence rates of non-taking groups showed a (+) positive value for the NPV, a CBR of greater than 1 (1.34), so economically viable vaccine with a high benefit per cost. However, if the incidence is low, NPV is negative and CBR is less than 1 (0.47), which is not economically feasible. Of course, we do not consider economical due to the CBR to be more than 1.0. According to the criteria of the public investment analysis proposed by the US government's Office of Management and Budget (OMB), it is recognized that the minimum cost benefit ratio is 1.26 or more considering the excess burden due to tax distortion[11]. However, in other studies, the 1.0 standard is applied, so we will judge it based on the equity level.

In the case of cost-effectiveness analysis, it is necessary to evaluate it somewhat conservatively and conclude that the preventive use of malaria treatment is not cost effective. However, CBR = 1 (NPV = 0) was calculated at the 50% incidence rate in the uncomplicated group, so it is important to investigate the annual incidence of malaria patients.

On the other hand, there are various opinions on the preventive use of malaria chemoprophylaxis. Primaquine has been increasingly prescribed for the

Table 2: The cost-benefit of the malaria chemoprophylaxis

				Parameter
Cost	**Therapeutic agent cost**[1)]	**Chloroquine** (1pck, 30tbl)	**A**	5,240
		Primaquine(1pck, 100tbl)	**B**	2,600
	Therapeutic agent quantity[1)]	**Chloroquine** (1pck, 30tbl)	**C**	10000
		Primaquine(1pck, 100tbl)	**D**	10000
	Total cost(won)		**E(=A×C+B×D)**	78,400,000
Benefit due to decreasing incidence	**Soldiers in risk area troops(person)**[1)]		**F**	112,355
	Incidence rate of non-taking group(1 million)		**G**	23.32~65.28
	The effect of chemoprophylaxis(%)		**H**	89.7
	Inpatient cost per one person(won)		**I(=M/J)**	1,498,794
	Patients(no.)[9]		J	127
	Cost(won)[9]		K	141,047,000
	Uncovered rate(%)[8]		L	25.9
	Total medical cost(won)		M(=K/(1-L/100))	190,346,829
	Total benefit due to decreasing diseases(won)		**O (=F×G/100000 ×H/100×I)**	min:36,723,798 Max: 102,801,439
NPV(won)				min: -41,676,202 Max: 24,401,439
CBR				min: 0.47 Max: 1.34

Source: 1) The amount of military supply of prevention medicine (2012)
2) National Health Insurance Corporation, 2012 Health Insurance Statistical Yearbook.
3) National Health Insurance Corporation, 2009~2013 Survey of medical expenses

prophylactic treatment of malaria. It is recommended that primaquine 30 mg be given 1-2 days before the expected exposure risk and 7 days after the end of the exposure risk[1]. Primaquine often has side effects such as nausea, weakness in the whole body, and abdominal pain when taken on an empty stomach. Other serious side effects may lead to hemolytic anemia or methemoglobinemia and hypersensitivity reactions in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD)[13]. However, there has been little report of drug-induced liver damage or hepatic failure resulting from the use of recommended standard doses or higher doses of primaquine[13]. It is known that the risk of neuropsychiatric side effects is more than 60 times higher for therapeutic medication than that for taking chemoprophylaxis medication, and studies have been continuously conducted to prove the safety of the medication for prophylactic treatment[14].

However, by 1996, the majority of the patients were in the military, but the number of civilian patients has increased since then. Since 1998, more than half of civilians have been involved, and the proportion of civilians is increasing year by year[5, 15]. The dangerous area that spread widely along east and west along the demilitarized zone has recently been concentrated in some areas such as Northwestern Gyeonggi and Ganghwa-gun. Therefore, the patient surveillance system and education promotion business in non-hazardous areas should be supplemented. In the case of the dangerous area, it is easy to construct the local monitoring system by establishing the early diagnosis system and educating and publicizing the medical institutions. On the other hand, in non-hazardous areas, it is difficult to establish an active patient surveillance system for hundreds of patients every year in over 200 public health centers. Therefore, the scope of the use of chemoprophylaxis for civilians and related education, and surveillance activities will be extended to manage the malaria environment in the future (e.g., North Korea's economic difficulties and global warming).

However, this study adopted the efficacy and efficacy of vaccine through literature search and made various assumptions to apply it to this study. This suggests that there is a possibility of excessive and underestimation. In addition, there is a possibility of overestimation of productivity loss because it does not reflect the yearly change rate of occupational military ratio. When calculating the benefit, we included the loss of productivity, multiplying by the worker's military rate of '0.22', leaving some as a soldier, and some assumed to be part of a community. Actually, the percentage remaining after military service should be used, but the ratio of occupation soldiers among the whole soldiers was used because of difficulties in obtaining data.

In addition, costs may be underestimated because the cost of treating side effects due to prophylactic use of the treatment has not been reflected. According to the report on the vaccination of the KCDC, the adverse side effects caused by the prophylactic uses are only two to

three per 100,000 people. According to data reported in the US Vaccine Adverse Event Reporting System (VAERS), 85% of all adverse drug reactions detected after prophylactic uses are minor symptoms and common febrile responses[14]. Nonetheless, there may be a fatal and serious allergic reaction in the form of anaphylaxis due to the chemoprophylaxis of the drug, which may have left a permanent effect or may have resulted in death.

In addition, the incidence of non-taking group should be estimated through the incidence rate at the unit of the town where the troop contained in the malaria risk area (primaquine + chloroquine mixed dose) belongs. However, the incidence rate was estimated to be very small as the incidence rate in large units was used. This may lead to the possibility of underestimating benefits without measuring accurate preventive effects

Nevertheless, this study provides cost-effectiveness analysis results of chemoprophylaxis. And that chemoprophylaxis could be cost-effective if the incidence of non-taking group in the risk area is maintained above 50%. Therefore, it will be possible to block the incidence of malaria in the future through analysis of the trend of incidence of malaria, and to inform the effect of the chemoprophylaxis method through educational and public relations activities. Also, it can be used as an important basis for policy making.

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