

Fighting Hepatitis B in North Korea: Feasibility of a Bi-modal Prevention Strategy

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In North Korea, the prevalence of hepatitis B is high due to natural factors, gaps in vaccination, and the lack of antiviral treatment. Aid projects are urgently needed, however impeded by North Korea's political and economical situation and isolation. The feasibility of a joint North Korean and German humanitarian hepatitis B prevention program was assessed. Part 1: Hepatitis B vaccination catch-up campaign. Part 2: Implementation of endoscopic ligation of esophageal varices (EVL) by trainings in Germany and North Korea. By vaccinating 7 million children between 2010 and 2012, the hepatitis B vaccination gap was closed. Coverage of 99.23% was reached. A total of 11 hepatitis B-induced liver cirrhosis patients (mean age 41.1 yr) with severe esophageal varices and previous bleedings were successfully treated by EVL without major complications. A clinical standard operating procedure, a feedback system and a follow-up plan were developed. The bi-modal preventive strategy was implemented successfully. Parts of the project can serve as an example for other low-income countries, however its general transferability is limited due to the special circumstances in North Korea.

Keywords: Hepatitis B; Democratic People's Republic of Korea; Mass Vaccination; Esophagoscopy

INTRODUCTION

Hepatitis B is one of the most important public health problems the Democratic People's Republic of Korea (DPRK, North Korea) is currently facing, because of its high prevalence combined with an often deleterious chronic course leading to both physical impairment and sufferings of the patients as well as causing a huge socio-economic burden (1).

Due to its present political and economical situation North Korea faces limitations in obtaining epidemiological data on diseases or health related problems (2). The prevalence of hepatitis B in North Korea can thus only be estimated. Hepatitis B is endemic in the Korean Peninsula (3). The World Health Organization (WHO) calculated a prevalence of 4.5% in 2003. According to verbal statements on unpublished data from a survey among North Korean refugees to South Korea, a prevalence of 9% is more realistic (4). Given the high natural prevalence in the region of up to 20% (5) and the North Korean deficits in vaccination, the true prevalence can be assumed to be even higher.

In North Korea, it can be assumed the transmission of hepatitis B to occur mostly vertical ante- or perinatally and sexually, however, there are no data on the exact transmission rates (6). The younger the patients at the time of infection, the higher is the progression rate from acute to chronic hepatitis B infection, decreasing from 90% for an infection acquired perinatally to

lower than 5% in adults (6,7). The lifetime risk of liver-related death is about 40%-50% for men (8,9) and 15% for women (10). Depending on their clinical situation and the portal venous pressure, between 30% and 85% of cirrhotic patients have esophageal varices (EV) (11,12). About 5%-15% of cirrhotic patients suffer from one bleeding per year with a 6-week mortality of 25% and a risk of re-bleeding of 60% in 1 yr (12).

The management of hepatitis B in North Korea has been very limited (13). There has been neither a comprehensive vaccination until 2004 nor is there any effective treatment for ordinary people available until now. Only since 2004, the national immunization program includes nationwide hepatitis B vaccination of newborn, leaving a gap of 3.8 million unvaccinated children born before 2004.

Despite an extensive state-funded health care structure in North Korea with specialized "Hepatitis Hospitals" in each governmental district, the current treatment of hepatitis B and its complications, e. g. liver cirrhosis, consists of traditional herbal medicine. Antiviral agents such as tenofovir, entecavir, and interferon are known to some doctors, as well as spironolactone, lactulose, and other medications in case of liver decompensation. However, no experience with these treatments and with any interventions such as endoscopy for esophageal varices can be assumed. Beta-blockers are not available for ordinary patients.

Due to the present isolated situation of the country, there is very limited access to current medical information (13). For ordinary doctors, access to the internet is not available, there is no up to date foreign printed literature, and even domestic medical textbooks are only rarely available. The main sources of information are old textbooks and the occasional imported documents. The English language barrier increases the knowledge deficit. Judging from the doctors' behavior in their clinical work, there is low understanding of a scientific approach to medical problems.

While modern treatment and prevention strategies against hepatitis B in North Korea are needed, the implementation of new diagnostic and treatment techniques is extremely difficult. The present study assessed the feasibility of the implementation of a strategy to deal with hepatitis B and some of its associated problems in the special political circumstances in North Korea.

MATERIALS AND METHODS

Caritas Germany, the Ministry of Public Health of North Korea (MoPH), and the Medical Mission Institute Wuerzburg, Germany (MMI) developed a joint strategy to deal with hepatitis B and its associated problems. A bi-modal approach was chosen focusing on the primary prevention of hepatitis B by vaccination and the secondary prevention of esophageal variceal bleedings as a life-threatening complication. The humanitarian aid project was funded with donations from Germany and Republic of Korea (South Korea).

The Hepatitis Prevention Hospital (HPH) in Pyongyang was selected as the project's central health care facility. As a national hepatitis B reference center, the hospital is not only responsible for preventive measures but also for the care of severe cases of hepatitis B-induced liver cirrhosis referred from other hospitals.

Nationwide hepatitis B vaccination campaign

A hepatitis B vaccination catch-up campaign was initiated by Caritas Germany and the MoPH in 2010 according to WHO recommendations (14). The program started in February 2010 with a first phase covering Pyongyang area. The campaign was subsequently extended to all North Korean provinces until February 2012. The target group included children in the age of 6 to 16 yr. Each child received three shots in time intervals of 0, 1, and 6 months.

Vaccine (1 mL of purified HBsAg 20 mcg, EUVAX B[®], LG Life Science, Korea) and syringes were supplied from South Korea and shipped through China to North Korean district and provincial stores. From here, the vaccination teams - at least two including a household doctor and a primary health facility worker - picked up the vaccine in iced boxes to maintain the cooling chain. Before that, vaccination teams were instructed by local

health officials.

The children were vaccinated in their primary and secondary school classes. Parents and children were informed about the campaign beforehand and responded generally positively. During the campaign, no cases of relevant negative side effects were reported. In total, 15 monitoring trips were made by a humanitarian aid specialist from Caritas Germany during the campaign.

Implementing and training of endoscopic variceal ligation

This part of the aid program consisted of two steps. In step one, two senior physicians from the HPH received endoscopy training in the MMI in Germany. The objective was to familiarize the North Korean doctors with endoscopic technique and indication, but also to get in contact with western science-based medicine. Endoscopic equipment, consisting of two video gastroscopes (Pentax EG 2930 K), a video processor (Pentax EPK 700/EPK) and a re-usable endoscopic ligation device (Euroligator[®], Mandel und Rupp, Germany), were shipped to North Korea and installed in the HPH in Pyongyang. This is the first video endoscopy unit in North Korea.

The second step was a one-week training of doctors and nurses in gastroscopy and endoscopic intervention by an experienced German endoscopist in the HPH in Pyongyang. After presentations and discussions about hepatitis B, the general management of liver cirrhosis, esophageal varices (EV) and the gastroscopy techniques, a clinical standard operating procedure (SOP) on performing gastroscopies and EV ligation technique was established. The guidance derived step-by-step from the initial lectures, the group debates and the experiences during the procedures and was set up as much as possible according to international guidelines (12) and current medical evidence as well as to personal experience, and it took into account the local possibilities, e. g. traditional herbal medicine (15). A hand-over-hand training method was used according to the development of the performance in gastroscopy of the North Korean physicians.

Patient's safety was a major concern, since only elective interventions were performed. Therefore, thorough local anesthesia with topical lidocaine using a specially developed spraying tube and close patient contact was preferred over sedation. In the rare cases sedation was necessary, it was done with midazolam in low and slowly increasing doses limited to a maximal amount under close oxymetric and clinical monitoring. First response to adverse reaction was explained and practiced.

Patients were carefully selected for the procedures under strict weighing of the presumed benefits and possible disadvantages of the treatment. Since patients with previous EV bleedings have the highest mortality from any re-bleeding, these patients were preferred (16). Informed consent according to local standards was obtained in each patient.

A database of the patients with all details of the interventions

Table 1. Vaccination coverage in North Korea's regions during the campaign rounds 2010-2012

Province	No. children	1st round	%	2nd round	%	3rd round	%
Pyongyang	499,240	498,432	99.84	498,036	99.76	497,735	99.70
South Pyongan	503,105	500,786	99.54	499,963	99.38	499,591	99.30
North Pyongan	441,193	439,637	99.65	439,213	99.55	438,644	99.42
Nampo City	137,103	136,666	99.68	136,542	99.59	136,467	99.54
South Hwanghae	401,347	400,402	99.76	399,966	99.66	399,362	99.51
North Hwanghae	349,207	348,453	99.78	347,755	99.58	347,435	99.49
Kangwon	227,194	226,311	99.61	225,980	99.47	225,709	99.35
South Hamkyong	472,390	470,976	99.70	469,318	99.35	467,742	99.02
North Hamkyong	352,672	351,978	99.80	351,375	99.63	349,791	99.18
Rason City	29,621	29,586	99.88	29,528	99.69	29,509	99.62
Jakang	212,579	211,036	99.27	209,724	98.66	207,655	97.68
Ryangang	126,326	125,298	99.19	124,444	98.51	123,521	97.78
Total	3,751,977	3,739,561	99.67	3,731,844	99.46	3,723,161	99.23

was prepared and daily updated. A follow-up schedule was set up to maintain the care for the patients.

RESULTS

Nationwide hepatitis B vaccination campaign

Eventually, 3.7 million unvaccinated children were vaccinated during the catch-up campaign, leading to a coverage of 99.23% according to the MoPH (2012) (Table 1). It can be assumed that the huge gap of unvaccinated children left before the initiation of the national vaccination plan in 2004 is now closed.

Implementing and training of endoscopic variceal ligation

During the week of the endoscopy training, a total of 30 gastroscopies were performed in 25 patients (23 men, 2 women) with liver cirrhosis due to hepatitis B. These diagnoses had previously been established by clinical and sonographic signs, and positive HBsAg and anti-HBc markers. Most of the patients had a history of recent gastrointestinal bleeding (60%). There were no patients suffering from alcoholism. Their mean age was 41.1 with range from 33 to 55 yr. The patients' clinical condition was generally good; all were able to walk and had no clinical signs of cirrhotic decompensation. Any scoring, such as CHILD or MELD, was not possible due to lack of laboratory tests in North Korea.

The grading of the EV was done in 2 grades according to international recommendations (small, < 5 mm diameter, veins minimally elevated, completely collapsing when insufflating air; large ≤ 5 isn't it ≥ 5 mm, largely occluding the esophageal lumen, curvy) (12,15). It was also noted if red wale marks and red cherry spots were present. Eventually, 11 EV ligations were successfully carried out (Table 2).

There were no major safety problems or adverse events during the endoscopies or in the days after, apart from mild chest pain in 3 patients after the ligation procedure. The combination of presentations, group discussions and the practical training with explanations and hand-over-hand training was highly ef-

Table 2. Distribution of varices and their features, and ligation treatment

Clinical features	Esophageal varices			Total n (%)
	Small	Large	No varices	
Grade, n (%)	5 (20)	12 (48)	8 (32)	25 (100)
Features				
Red spots, n (%)	1 (4)	5 (20)	0 (0)	6 (24)
Red wale marks, n (%)	0 (0)	3 (12)	0 (0)	3 (12)
Previous bleeding, n (%)	4 (16)	10 (40)	1 (4)	15 (60)
EVL treatment, n (%)	1 (4)	10 (40)	0 (0)	11 (44)

fective, as measured by the course of the week. The whole team increased its self-confidence and speed, and diagnoses and treatment decisions were made more and more independently.

DISCUSSION

Developing a strategy against hepatitis B in North Korea is an extraordinarily challenging task because of the special political situation (13). The usual, mainly financial, technical, and logistic shortcomings of a low-income country had to be taken into account. The substantial lack of knowledge, experience, and materials in preventing and treating hepatitis B due to the isolation of the country created special problems. The almost ubiquitous political impacts that any foreign aid in North Korea imposes had to be considered specifically (17). This is why further measurements, e.g. any antiviral treatment of hepatitis B patients or beta-blocker therapy of patients with EV, were not considered to be realistic in the current North Korean context. Scrutiny of the literature revealed that there are no similar studies of our study could be compared with.

Humanitarian aid in health care focuses on cost-effective and large-scale improvements of widespread diseases. Prevention programs such as vaccinations thus have a high priority. Vaccination against hepatitis B has been a well-accepted method of primary prevention for decades. South Korea implemented full vaccination coverage about 25 yr ago (3). Its efficacy and cost-effectiveness in low-income-countries was proven by a vast

amount of research studies (18). The implementation of our vaccination campaign was rather a logistic problem, taking into special account the recurrent political tensions in the region. Two international political crises - the Cheonan warship sinking in March 2010 and the Yeonpyeong Island shelling in November 2010 - interrupted the vaccination program twice for several months each.

According to official North Korean sources from the MoPH (2012), there is now a hepatitis B vaccination coverage of 99.23 % in the country. Due to the hierarchic structure of North Korea's health care system and the thorough vaccination observed in personal random visits in the countryside by Caritas Germany experts, this high figure is likely to be correct. It can be assumed that after the vaccination campaign and given the current continuation of the vaccinations, the prevalence of hepatitis B must be dropping in the long term, as long as there is a sufficient supply of vaccines. Verbal feedback from primary care centers where patients with hepatitis symptoms usually present first confirms this impression. However, as the transmission of hepatitis B in North Korea is mostly perinatal, an effect of the vaccination catch-up campaign can be expected in several years. Most likely, the effect observed is to be attributed to the regular national vaccinations started in 2004. To gather reliable data, further prevalence studies are needed, however it is difficult to obtain due to the political situation in North Korea.

Modern technical assistance in health care in low-income countries is usually only reasonable under special circumstances due to its costs and complexity. If a 'high-tech' method is implemented, it should be easy to perform and fast to learn, without side effects and with a good risk-benefit-ratio for the patients. The functioning and maintenance of the equipment should be assured.

With its high prevalence of remarkably young hepatitis B patients with advanced cirrhosis and its life-threatening esophageal bleeding complications, the situation in North Korea is most likely globally unique. This justifies a limited and well-planned approach in technical aid using gastroscopic treatment with a good clinical success of a low number needed to treat (19,20). After considerable high initial costs for the endoscopy equipment, the maintenance costs are low, consisting mainly of rubber rings for the ligations. The side effects of esophageal varices ligation are low, mainly occasional post-interventional dysphagia and chest pain; and rarely bleedings from post-ligation ulcers in no more than 5% of the patients (21).

Because the endoscopy training was short, special safety precautions were taken. Adequate indications and a good technical performance were assured by the SOP guidance, which was implemented during the training. In addition to that, a sustained effect of the short training was ensured by feedback from the German endoscopist via a self-designed video capture software added to the endoscopy video processor to save procedure im-

ages and films. Sending the updated patient database to Germany to discuss cases also helped to maintain the training achievements.

Both parts of the project had a visible impact on the North Korean health care workers and patients involved. During the endoscopy training, the frequent visits from doctors from Pyongyang medical university and other hospitals underlined the great interest in the technique, most likely a rare possibility for North Korea doctors to get in closer contact with practical 'modern medicine.' The whole endoscopy team, especially the physicians performing the gastroscopies, was highly motivated and eager to increase its knowledge and skills.

There are several conditions that explain the success of this bi-modal aid program. There is the exceptional situation of a non-existence of neither comprehensive hepatitis B vaccination nor effective treatment. The hierarchically structured health care system in the totalitarian North Korean state, as problematic it may otherwise be, was now helpful to implement the complex nationwide vaccination campaign (22). The high affinity of North Korean health care workers to technology resulted in good gastroscopy training results in only one week and assures the maintenance of the technical equipment.

At the same time, these special circumstances limit the transferability of our strategy to other low-income countries. Hepatitis B vaccinations are clearly advisable (18), however the high vaccination rate in a broad program with millions of children is unlikely to be achieved because of organizational deficits. Also, technical problems with the gastroscopes might be more difficult to solve in low-income countries with a cultural behavior of distance to medical technology. However, the training method itself with its clinical guidance and safety measures can be regarded as a model for similar projects in other countries.

Further steps planned are a continuation of the EV ligations using the supervision and feedback mentioned above focusing especially on safety measurements. Referrals of patients from smaller hospitals in North Korea to the HPH are preferred and encouraged over the expansion of the endoscopy program to other hospitals. The treatment of gastric varices by injection of cyanoacrylate seems currently not feasible, given the low prevalence of gastric varices and a low risk of life-threatening bleedings, the difficulties to obtain the expensive glue and its problematic handling with a risk of damages of the endoscopes.

The hepatitis B project has no political objective and is a purely medical humanitarian aid program. However, the unavoidable positive personal contact of North Koreans with the world outside their country might be a tiny step to open North Korea's devastating isolation. Eventually, in a long-term perspective this could be helpful to improve the living conditions for the general North Korean population.

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DISCLOSURE

The authors have no conflicts of potential interest to disclose.

AUTHOR CONTRIBUTION

Conception and coordination of the study: all authors. Data collection: Unnewehr M. Data review: all authors. Manuscript preparation: Unnewehr M. Critical review of the manuscript: Stich A. Manuscript approval: all authors. Agreement of accountability: all authors

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