

EFFECT OF RENAL HEMODIALYSIS IN END STAGE RENAL DISEASES ON THE LEVEL OF HEPATITIS SURFACE ANTIBODIES AFTER VACCINATION

By

Hala I. Mohamed, Ahmed Hassan* and Shreif Swar**

Departments of Laboratory, Nephrology*, and Urology**,
National Institute of Urology and Nephrology, Cairo, Egypt

ABSTRACT

Background: The prevalence of viral hepatitis is higher in end stage renal diseases(ESRD) patients with dialysis than in general population, because of the opportunity for exposure during dialysis to blood products, and shared hemodialysis equipments. The impaired efficacy of HBV vaccine has been attributed to numerous factors such as immune compromised state because of uraemia, age. Immunization is the most effective way to prevent transmission of HBV.

Objective: To evaluate the effect of chronic renal hemodialysis on the level of hepatitis B surface antibodies after vaccination and to compare between immunogenic seroconversion response to HBV vaccine in hemodialysed patients and healthy individuals.

Patients and Methods: One hundred eighty cases were included in the study (60 controls and 120 hemodialysed patients) at national institute of urology and nephrology (NIUN). The patients were subdivided into 2 subgroups: 1) Sixty hemodialysed diseased patients due to immunological disease. 2) Sixty hemodialysed diseased patients due to other causes of renal diseases including diabetes mellitus (D.M.) and hypertension (HT). All subjects received 3 doses of HBV vaccine starting from 11/2013 till 5/2014 (0,1, 6 months). Patients have double the dose (2 ml) of the controls. After one year of complete vaccination, all subjects were investigated for Hepatitis B surface antibodies titer (HBs Abs titer) in their sera.

RESULTS: There was a statistically significant difference between patient and control groups as regards urea, creatinine, uric acid, sodium, and potassium. No statistically difference between male and female patients as regards HBs Ab titer, and statistically significant difference of HBs Ab seroconversion when comparing between patients and controls. There was a statistically significant difference between subgroup 1 and subgroup 2. No significant correlation between age, adequacy of dialysis, and HBsAb titer in groups of patients.

Conclusion: The study reported a high response rate to hepatitis-B vaccination among hemodialysed patients. Gender and efficiency of dialysis have no association with response to HBV vaccine. Young age was associated with good response to hepatitis B vaccine, while diabetes mellitus has a poor response to hepatitis B vaccine.

Key Words: ESRD, HBs Ab, immunological causes, diabetes mellitus, hypertension.

INTRODUCTION

Viral hepatitis infection is a serious global health problem. The prevalence of

viral hepatitis is higher in dialysed patients than in general population because of the opportunity for exposure during dialysis. Viral infection leads to

serious liver diseases including acute and chronic hepatitis, cirrhosis and primary hepatocellular carcinoma. Liver disease is a significant cause of morbidity and mortality in patients on maintenance dialysis. Hemodialysed (HD) patients are at increased risk of acquiring HBV because of increased exposure to blood products, shared hemodialysis equipments, frequent breaking of skin and immune deficiency state (**Duranti and Duranti, 2011**).

Immunization is the most effective way to prevent transmission of HBV. However, it is well established that patients with ESRD including dialysed patients, have an impaired immune response to HB vaccine (**Vandepapeliere et al., 2008**). So, they have lower seroconversion rates compared to subjects with intact renal function. Moreover, after the completion of vaccination schedule, anti-hepatitis B titer of responder in dialysed patients have low titer that decline logarithmically with time (**Ralli Chiara et al., 2016**). The impaired efficacy of HBV vaccine has been attributed to numerous factors such as immune compromised state because of uraemia, age, gender and nutritional status.

Hepatitis B vaccination of hemodialysed patients is performed all over the world. There are also recommendations from world health organizations to vaccinate patients with chronic kidney disease (CKD) prior dialysis, but the implementation of hepatitis B vaccination program is less common and not well

organized (**Alicja and Grzegorzewska, 2012**). Numerous inherited and/or acquired factors are implicated in diminished immunization following hepatitis B vaccination.

The impaired response to hepatitis B vaccine in dialysed patients has been also attributed to male gender (**Yassin and Gupta, 2013**). Also, age plays an important role as seroconversion rate to anti-HBs positivity after vaccination was 84% in HD patients below 40 years and only 33% in those ≥ 60 years (**Surquin et al., 2010**). Moreover, Poor nutritional status, mainly low serum albumin concentration (**Brown et al., 2011**), serological positivity for hepatitis C virus (HCV) or human immunodeficiency virus (HIV) (**AlGhamdi et al., 2013**), diabetes mellitus (**AlAvian and Tobatabaei, 2010**), and vitamin D deficiency were associated with a poor antibody formation upon hepatitis B vaccination (**Zitt et al., 2012**).

The present work aimed to compare between immunogenic seroconversion response to HBV vaccine in hemodialysed patients and healthy individuals.

SUBJECTS AND METHODS

One hundred and eighty subjects at the NIUN were included in the study starting from 11/2013 till 5/2014. They were divided into 2 groups:

- 1) Sixty apparently healthy individuals were included as the control group consisting of 26 males & 34 females (age of 47.8 ± 9.7 , ranging from 24 to 57 years old).

II) One hundred and twenty ESRD patients were included as the patients group consisted of 63 males and 57 females (age of 48.8 ± 14.3 , range from 20 to 55 years old). They were subdivided into 2 equal subgroups according to the underlying cause of dialysis:

- 1) Hemodialysed diseased patients due to immunological diseases.
- 2) Hemodialysed diseased patients due to other causes of renal diseases including D.M. and HT.

All individuals were subjected to:

Full history taking especially for patients including the underlying diseases, date of starting dialysis, history of vaccination, and infection with HBV.

Routine kidney function tests (creatinine, uric acid, urea, Na, K.) were measured using fully automated analyzer (DIMENSION, RXL MAX, USA).

Measurement of HBs Ab titer after complete vaccination by one year using Vidasapparatus (Biomérieux, France) that measures HBsAb by enzyme linked fluorescent assay (ELFA). Subjects with anti-HBs Ab more than 12 mIU/m L (according to kits) and those having previous history or suffering from HBV were excluded from the study before vaccination. The results were automatically calculated using calibration curves stored by the instrument (4-parameter

logistics model), and were expressed in mIU/ml. The measuring range was 3-500 m IU/ml.

Vaccination program: All subjects received 3 doses of HBV vaccine starting from 11/2013 till 5/2014 (0,1,6 months). Patients have double the dose (2 ml) of the controls. After one year of complete vaccination, all subjects were investigated for HBs Abs titer in their sera.

5) According to the kit manufacturer interpretation of results, the seroconversion level of anti-HBs Ab were negative titer < 8 , equivocal $8 \leq$ titer < 12 , and positive titer ≥ 12 (**Huzly et al., 2008**).

Statistical analysis: Data were analyzed using statistical program for social science (SPSS) version 20. Quantitative data were expressed as means \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage. We used the following tests: t-test Mann Whitney U, Kruskal Wallis, Chi-square (X^2), Pearson's correlation coefficient (r). Probability was considered significant when (p-value < 0.05).

RESULTS

There was no significant difference between patient and control groups as regards age and sex, while a statistically highly significant difference was obvious as regards kidney function tests (Cr, BUN, U.A, Na, K)(Table1).

Table (1): Demographic characteristics and laboratory data of groups.

Parameters \ Groups	Control	Patients	P- value
Age	48.8 ± 14.3	47.7 ± 9.7	>0.05
Sex: Male	63 (52.5%)	26(43.3%)	>0.05
Female	57(47.5%)	34(56.7%)	
Creatinine	10.0 ± 2.9	0.9 ± 0.3	<0.001
BUN	53.5 ± 16.2	17.4 ± 14.3	<0.001
Uric acid	7.7 ± 2.9	5.2 ± 1.9	<0.001
Na	132.5 ± 5.5	137.2 ± 4.6	<0.001
K	4.8 ± 0.9	4.3 ± 0.5	<0.001

There was no statistically significant difference between males and females as regards HBs Ab titer (Table 2).

Table (2): Comparison between males and females patients according to Hbs Abs titer.

Hbs Ab titer \ Gender	Means ± SD	Median	P-value
Males	227.3 ± 22.6	100(488)	0.577
Females	251.7 ± 2.5	123(491)	

There was a statistically significant difference of HBS Abs seroconversion comparing between patient and control groups (Table 3).

Table (3): Comparison between patient and control groups according to HBs Ab titer.

Groups \ Seroconversion titer	Control	Patients	Chi- square test p-value
Negative [<8]	23 (91.2%)	4 (6.7%)	p<0.01
Equivocal [≥8- <12]	7 (5.8%)	0 (0%)	
Positive [≥12]	90 (75%)	56 (93.3%)	
Total	120(100%)	60 (100%)	

There was a statistically significant difference between subgroup 1, and subgroup 2 (Table 4).

Table (4): Comparison between patient subgroups regarding seroconversion of HBs Ab titer.

Subgroups	subgroup(1)	subgroup (2)	Chi- Square test P- value
HBs Ab titre			
Negative [<8]	6 (10%)	17 (28.3%)	<0.05
Equivocal [$\geq 8- <12$]	2 (3.3%)	5 (8.3%)	
Positive [≥ 12]	52 (86.7 %)	38 (63.3%)	
Total	60 (100%)	60 (100%)	

There was no significant correlation between age, adequacy of dialysis and HBs Ab titer (Table 5).

Table (5): Correlation between HbsAbtiter, age and adequacy of dialysis.

HBsAb titer	r	P-Value
Patients		
Age (years)	0.071	0.439
Adequacy of dialysis	0.072	0.434

DISCUSSION

Hemodialysis patients are at high risk of contracting HB infection as well as other types of blood-borne infections due to the fact that they are exposed to blood and blood products more frequently than the general population (**Duranti and Duranti, 2011**). Therefore, vaccinating hemodialysed patients against HBV have become the standard of care. However, it is well known that patients on hemodialysis are immune compromised, and this state is mainly due to over-production

of interleukin 6 and tumor necrosis factor (TNF) alpha and relatively low production of interleukin 10 (**Sharif et al., 2015**). This immune suppression status is responsible for a poor response of hemodialysed patients to HB vaccine as opposed to the general population. The efficacy of the vaccine is investigated by measuring titer of HBs Ab in the serum with minimum titer of 10 mIU/mL considered to be a response (**Al Saran et al., 2014**). The seroconversion rate in hemodialysed patients ranges from 50% to 80%, as compared to the general population where

the seroconversion rate is over 95% (Keyvani et al., 2014). In consistent with the previous studies, our study showed that the response rate to the vaccine was 75% in ESRD patients on hemodialysis as compared to normal individuals 93.3%. Hepatitis B vaccine in HD patients would be useful to define factors that may affect vaccine response in HD patients. Unresponsiveness to HBV vaccine is multifactorial, and linked to the presence of several interacting factors. Various findings have shown that response rates are greatest among HD patients younger than 40 years. Younger people on hemodialysis are more likely to be responders to the vaccine and maintain that type of immune response with the highest ratio being for the age group 18 - 55 years old (El-Charabaty et al., 2015). This was in association with our data, as the age of our patients ranged from 20-58 years old.

On contrast to our study, Al Saran et al. (2014) showed that the urea reduction ratio and other factors indicating the efficacy of hemodialysis particularly kt/V has been associated with a good response to the vaccine. However, Chang and Liaw (2014) showed weaker response to HBV vaccine associated with inadequate HD. Our study revealed that gender did not affect the response to hepatitis B vaccine. This result was in agreement with that reported by Pin et al. (2009).

The diagnosis of diabetes mellitus in patients on hemodialysis was an independent risk factor of being non-responder to the vaccine in our study. This can explain the statistically significant difference of HBs Abs titer as compared between immunological causes

of ESRD patients and other causes of ESRD patients as most of them were diabetics. This result is in agreement with that reported by Tseng et al. (2008) who stated no any significant differences of antibody production against hepatitis B surface antigen between diabetic and non-diabetics or male and female subjects.

CONCLUSIONS

Factors associated with serum antibody level against hepatitis B surface antigen were different in our HD patients, and various factors might be responsible for antibody production and more multicenter investigations need to define these related factors. There was a high response rate to hepatitis-B vaccination among hemodialysed patients. Gender and efficiency of dialysis have no association with response to HBV vaccine. Young age was associated with good response to hepatitis B vaccine, while diabetes mellitus has a poor response to hepatitis B vaccine.

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تأثير غسيل الكلى فى المرحلة الأخيرة من أمراض الكلى على مستوى الأجسام المضادة بعد التطعيم بمصل الإلتهاب الكبدى بى

هالة إبراهيم محمد ، احمد حسن *، شريف صوار *

المعامل الرئيسية وأمراض الكلى* والمسالك البولية **
المعهد القومى للكلى والمسالك البولية- جمهورية مصر العربية

خلفية البحث: يعتبر ارتفاع معدل إنتشار الإلتهاب الكبدى بى بين مرضى الغسيل الدموي من أهم المشاكل الصحية التى تواجه العالم. ولذلك فإن التطعيم من أفضل وأهم الوسائل التى تحد أو تمنع إنتشار هذا المرض. وتعود أسباب فشل الإستجابة للتطعيم بين هؤلاء المرضى إلى عدم قدرة الجهاز المناعى على التفاعل ضد الفيروس نتيجة للتأثير السلبى لإرتفاع نسبة البولينا فى الدم .

الهدف من البحث: المقارنة بين مستوى الأجسام المضادة لفيروس بى و مدى الإستجابة للتطعيم بين مرضى الغسيل الكلى الدموى والأصحاء.

خطة البحث: تمت متابعة ١٢٠ يجرى لهم مريض غسيل كلوى فى المعهد القومى للكلى والمسالك البولية، وتم قياس الأجسام المناعية ضد فيروس بى قبل التطعيم للتأكد من عدم الإصابة السابقة بالمرض أو التطعيم. وقد تم تطعيم المرضى والأصحاء (١٨٠ حالة) بثلاث جرعات من المصل على مدى ستة شهور، مع ملاحظة أن جرعة المريض (٢ملى) ضعف جرعة الأصحاء (١ملى). وتم إعادة قياس الأجسام المناعية ضد فيروس بى بعد عام من إنتهاء التطعيم.

النتائج: وجدت دلالة إحصائية عالية فى مقاييس البولينا والكرياتينين وحامض البوليك ونسبة الصوديوم والبوتاسيوم فى الدم عند مقارنة مجموعة المرضى بالمجموعة الضابطة. ولم توجد علاقة واضحة عند مقارنة نسبة الأجسام المضادة بالنسبة للجنس فى مجموعة المرضى. وكانت هناك دلالة إحصائية عند مقارنة نسبة التحول المصلى بين مجموعة المرضى ومجموعة الأصحاء. وكما وجدت دلالة إحصائية عند مقارنة نسبة التحول المصلى بين مجموعة المرضى نوى الأسباب المناعية، ومجموعة المرضى لأسباب أخرى مثل مرض السكر وإرتفاع ضغط الدم. ولم توجد علاقة واضحة عند مقارنة كفاءة الغسيل والسن ونسبة الأجسام المضادة فى الدم فى مجموعة المرضى .

الاستنتاج: إكتسب مرضى الفشل الكلى مناعة ضد فيروس ببو لم يكن للجنس وكفاءة الغسيل علاقة بمدى الإستجابة للتطعيم، وكلما قل سن المريض كلما زادت الإستجابة للتطعيم؛ وكانت الإستجابة ضعيفة لدى مرضى السكر.