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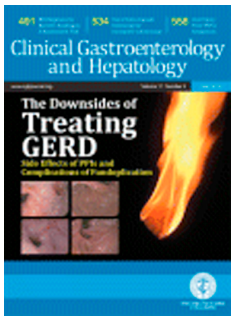

Efficacy of High-dose, Rapid, Hepatitis A and B Vaccination Schedules in Patients With Cirrhosis

A.J. Wigg, R. Wundke, R. McCormick, K.R. Muller, J. Ramachandran, S. Narayana, R.J. Woodman

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TITLE PAGE

Title:

Efficacy of High-dose, Rapid, Hepatitis A and B Vaccination Schedules in Patients With Cirrhosis

Short Title: High dose, rapid hepatitis vaccination in cirrhosis

Authors:

AJ Wigg[1], R Wundke[1], R McCormick[1], KR Muller[1], J Ramachandran[1], S Narayana[1] and RJ Woodman[2].

[1]Hepatology and Liver Transplant Medicine Unit, Flinders Medical Centre, Adelaide.
[2]Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide.

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Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus.

Correspondence:

Associate Professor Alan J Wigg

Hepatology and Liver Transplantation Medicine Unit, Flinders Medical Centre, Bedford Park, Adelaide, South Australia, 5042, Australia.

Email: alan.wigg@sa.gov.au

Phone: + 61 8 8204 5511

Fax: + 61 8 8204 4964

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Author contributions:

AJ Wigg; study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis.

R Wundke; study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript.

R McCormick; acquisition of data.

KR Muller: critical revision of the manuscript for important intellectual content.

J Ramachandran; critical revision of the manuscript for important intellectual content.

S Narayana; critical revision of the manuscript for important intellectual content.

RJ Woodman; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis.

Introduction:

Patients with cirrhosis have increased morbidity from hepatitis A (HAV) and B (HBV) infections, and vaccination against these infections is an important standard of care (1) (2). However, vaccination in patients with cirrhosis is hindered by immune dysfunction and there is limited high quality literature available. The aim of this work was therefore to compare immune responses of standard dose (SD) with high dose, accelerated (HDA) vaccination in cirrhotic patients.

Patients and Methods:

A single centre, prospective, non-randomized controlled trial, comparing SD versus HDA HAV and HBV regimens in consecutive patients with cirrhosis.

The SD HAV schedule was intramuscular Twinrix® 720 µg at 0, 1 and 6 months. For 23% of patients the SD HAV schedule was intramuscular Havrix® 1440 µg at 0 and 6 months. For patients failing to seroconvert, a single 1440 µg Havrix® booster was given. The HDA HAV schedule was Havrix® 1440 µg at 0, 1 and 2 months, with a single 720 µg booster for patients failing to seroconvert.

The SD HBV schedule was intramuscular Twinrix® or Engerix®-B 20 µg at 0, 1 and 6 months with a 40 µg booster of Engerix®-B if non-immune. The HDA HBV schedule was Twinrix® or Engerix®-B 40 µg at 0, 1 and 2 months, with the schedule repeated as a booster if non-immune. The combined vaccine Twinrix® was used for initial vaccination in 48% of patients.

The HDA regimens were designed following review of literature and to provide approximately double the SD in one third of the time. The SD (HAV and HBV) cohort study occurred during the time period of 2009-2011. The HDA cohort study occurred during a separate time period during 2012-2014.

For multivariate models those variables significant at $p<0.20$ were considered for inclusion in the model.

Results:

In the HAV arm, 73 and 35 patients received SD and HDA schedules, respectively. In the HBV vaccination arm, 97 and 51 patients received the SD and HDA regimens, respectively. Groups were well matched for important clinical characteristics. The percentage of patients with decompensated (Childs-Pugh B/C) disease in the HAV and HBV study arms was 38% and 43%, respectively. 18 patients did not adhere to boosting protocols and were excluded from relevant per protocol analyses.

In the HAV arm, initial response rates were 79.5% (58/73) in the SD arm and 94.3% (33/35) in the HDA arm ($p=0.065$). Boosting regimens were successful in 66.7% (8/12) in the SD arm and 100% (1/1) in the HDA arm. Per protocol immune response rates for the SD HAV vaccination arm was 94.3% (66/70) and 100% (34/34) in the HDA arm ($p=0.16$).

In the HBV arm, the initial response rates were 51.5% (50/97) in the SD arm and 45.1% (23/51) in the HDA arm ($p=0.49$). Boosting regimens were successful in 28.6% (12/42) in the

SD group and 52.6% (10/19) in the HDA arm (p=0.07). Per protocol immune response rates was 67.4% (62/92) in the SD arm and 78.6% (33/42) in the HDA arm (p=0.19).

Only one factor across both HAV and HBV studies, low albumin in the HBV SD arm, was significantly associated with immune non-response on multivariate analysis (Tables 1A and 1B).

There were no vaccination-related serious adverse events seen in any patients.

Discussion:

Results from this study suggest a potential benefit from an initial HDA HAV regimen in all cirrhotic patients. Benefits of this approach include: a clinically significant 15% improved immune response, rapid immune response, and minimal increased cost.

Results do not support the routine use of the initial HDA HBV vaccination regimen in cirrhotic patients, but do suggest a potential benefit from HDA boosting of initial non-responders. The HDA boosting regimen was associated with a clinically significant 23% improved response rate.

Neither HAV nor HBV immune non-response were associated with MELD or Child-Pugh score or older age, as suggested by some authors (3-5) (6, 7). The association of low albumin (a possible surrogate for advanced liver disease) with non-response to SD HBV vaccine, suggests that HDA boosting regime may have greatest utility in these patients.

The non-randomized study design and lack of statistical power are weaknesses of our study, which limited our ability to draw firm conclusions. Post-hoc power analysis suggested that 76 patients (HAV) and 120 patients (HBV) per group were required for the trends seen in initial HDA HAV and secondary HDA HBV immune responses to achieve statistical significance. Nevertheless, it should be noted that there are no randomized studies in this field and our study is one of the largest vaccination studies in cirrhotic patients to date. A further strength was the selection of a cirrhotic population with a range of disease severity and aetiology, enabling improved external generalizability of findings to cirrhotic patients seen typically in hepatology services.

In conclusion, we believe the study findings provide the rationale for future randomized, adequately powered studies investigating benefits of an initial HAV HDA regimen and a secondary HBV HDA boosting regimen in cirrhotic patients.

Keywords: immune response, seroconversion, vaccination, cirrhosis, hepatitis A and B

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Table 1A. Univariate and multivariate logistic regression for Hepatitis A vaccination response using per protocol analysis

	Univariate (n=108)		Multivariate[1] (n=108)	
	Odds ratio (95 CI)	**p-value**	**Odds ratio (95 CI)**	**p-value**
Age	0.96 (0.86, 1.06)	0.407	0.95 (0.84, 1.06)	0. 329
Gender (M vs F)	1.76 (0.18, 17.56)	0.629	2.37 (0. 18, 131.8)	0.848
Child score	1.18 (0.63, 2.22)	0.608		
Smoker	1.70 (0.16, 17.65)	0.657		
Drinker	1.16 (0.12, 11.61)	0.901		
High vs Low dose	2.65 (0.32, ∞)	0.400	3.10 (0.37, ∞)	0.326
Total dose (µg)	0.999 (0.998, 1.000)	0.344		
Albumin	1.04 (0.89, 1.22)	0.600		
INR	1.81 (0.03, 96.9)	0.769		
Bilirubin	1.00 (0.96, 1.05)	0.771		
Creatinine	0.999 (0.976, 1.023)	0.968		
Meld score	1.057 (0.81, 1.38)	0.685		
Combined vaccine	0.35 (0.03, 3.45)	0.366		
Etiology				
HCV	1.00	-		
ETOH	2.61 (0.15, 44.01)	0.505		
HCV and ETOH	0.83 (0.05, 14.48)	0.900		
NASH	0.72 (0.04, 12.64)	0.824		

[1]Included high versus low dose and age and gender.

Table 1B. Univariate and multivariate logistic regression for hepatitis B vaccination response using per protocol analysis

	Univariate (n=134)		Multivariate[1] (n=134)	
	β (95 CI)	**p-value**	**β (95 CI)**	**p-value**
Age	0.959 (0.926, 0.994)	0.021	0.96 (0.93, 1.00)	0.053
Gender (M vs F)	0.57 (0.25, 1.30)	0.178	0.55 (0.23, 1.33)	0.184
Child score	0.95 (0.79, 1.16)	0.63		
Smoker	1.53 (0.52, 4.44)	0.44		
Drinker	1.32 (0.61, 2,88)	0.48		
High vs Low dose (@albumin=34.5)	1.77 (0.75, 4.18)	0.189	1.98 (0.77, 5.13)	0.157
Total dose (µg)	0.991 (0.985, 0.997)	0.005		
Albumin				
Low dose arm	1.12 (1.03, 1.21)	0.008	1.12 (1.03, 1.21)	0.008
High dose arm	0.92 (0.82. 1.04)	0.185	0.94 (0.82, 1.07)	0.323
INR	1.53 (0.39, 6.04)	0.55		
Bilirubin	1.00 (0.99, 1.01)	0.82		
Creatinine	0.992 (0.978, 1.007)	0.311		
Meld score	1.03 (0.94, 1.12)	0.50		
Renal disease	0.817 (0.072, 9.282)	0.871		
Etiology				
HCV	1.00	-		
ETOH	1.13 (0.32, 3.97)	0.856		
HCV and ETOH	1.00 (0.19, 5.15)	1.000		
NASH	0.72 (0.15, 3.54)	0.686		
Other	0.70 (0.13, 3.79)	0.679		

[1]Included high versus low dose, albumin and age and gender and an interaction term for albumin X dose.