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PREVALENCE OF ANEMIA IN PATIENTS WITH HEPATITIS C ON RIBAVIRIN COMBINED THERAPY AT RWANDA MILITARY HOSPITAL.

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ABSTRACT

Viral hepatitis is an infection affecting the liver and causing its inflammation due to viruses mostly hepatitis B and C viruses. Hepatitis C virus infection is a serious global health issue leading to morbidity and mortality worldwide. Anemia can occur because the anti-HCV drug mostly ribavirin which can cause the red blood cells prematuraly die. To assess anemia, hemoglobin levels in blood samples are measured and levels less than 11 g/dl for women and less than 12 g/dl for mens are considered to be anemia but it depends with the guidelines of the hospital. This study entitled: "prevalence of anemia in hepatitis c patients on ribavirin combined therapy at Rwanda Military Hospital" was a retrospective study carried out from November to December 2017. The main objective was to know the prevalence of anemia in HCV patients on combined ribavirin therapy. A total of 256 patients were eligible in the research. Anemia in harvoni and combined ribavirin therapy patients were identified by searching in open clinic system their hemoglobin. The results for patients on harvoni and combined ribavirin therapy were statistically analyzed using SPSS 20. The results have showed that the prevalence of anemia in patients who took ribavirin combined therapywas high and the anemia in patients who took harvoni were lower than that of patients who took combined ribavirin therapy. The statistics showed that anemia prevalence for combined ribavirin therapy was higher than that of Harvoni with 28.1% and 0.74% respectively. Gender were the only significant demographic characteristic for patients on harvoni (Gender, p=0.012). In conclusion harvoni had no anemic effects therefore it represented a significant therapeutic advancement for the treatement of HCV infection than combined ribavirin. Education of the population about HCV infection were urgently recommended in order to prevent HCV infection and increasing the availibility of harvoni treatement by reducing the prices were recommended to the Ministry of health.

KEYWORDS: *Hepatitis C, Ribavirin Therapy, Anemia*

INTRODUCTION

Hepatitis C virus (HCV) is a hepatotropic RNA virus that causes progressive liver damage in humans, which might result in liver cirrhosis and hepatocellular carcinoma s Major risk factors for this blood-borne virus infection are unsafe injection drug use and unsterile medical procedures (Manns *et al., 2017*). HCV infection is a major global health issue. Previous global burden of disease estimates published by the World Health Organization (WHO) include only burden from acute HCV infection. Available estimates indicate that worldwide there were 54,000 deaths and 955,000 disability adjusted life-years associated with acute HCV infection. The major burden from HCV infection comes from sequelae from chronic

infection. Estimates indicate that three to four million persons are newly infected each year, 170 million people are chronically infected and at risk of developing liver disease including cirrhosis and liver cancer, and 350,000 deaths occur each year due to all HCV-related causes (Stanaway *et al.,* 2016). The standard of care (SOC) therapy for patients with chronic hepatitis C virus (HCV) infection has been the use of both peginterferon (PegIFN) and ribavirin (RBV). These drugs was administered for either 48 weeks (HCV genotypes 1, 4, 5, and 6) or for 24 weeks (HCV genotypes 2 and 3), inducing sustained virologic response (SVR) rates of 40%-50% in those with genotype 1 and of 80% or more in those with genotypes 2 and 3 infections (Chung *et al*., 2015).

However, a large number of patients remained viraemic and chronically infected. In addition, many patients suffered from severe side effects while receiving this combination therapy. These are the reasons they found medications with higher SVRs, better tolerability and shorter treatment regimens than the previous treatment (Naggie *et al*., 2015). Recently the new oral direct-acting antiviral (DAA) treatments have transformed the treatment of HCV, with cure rates higher than 90%, using short duration oral regimens and providing pan-genotypic efficacy. The extraordinary clinical efficacy of DAA and recent substantial price reductions have provided now being advanced as a public health intervention to control the HCV infection at global level (Lanini *et al*., 2016). The decrease in Hemoglobin can define anemia. Hemoglobin is a substance that helps red blood cells carries more than 98% of the oxygen to the rest of body's cells. Without enough oxygen, your cells can't work as well. This causes to feel tired, weak, or unable to think clearly. The World Health Organization defines anemia as a decrease in haemoglobin level up to 2g/dL. Anemia occurs in up to 36% of patients receiving Pegylated-interferon and Ribavirin combination therapy. They've been proven in study done by (Rafique *et al*., 2017) that anemia was the major side effect 0f ribavirin comination therapy and the dosage reduction in Ribavirin was the first step in managing symptomatic drug induced anemia. In the study done about the newest combination therapy most used: Harvoni (sofosbuvir+ledipasvir) the most common adverse events reported by patients were fatigue, headache, nausea, and insomnia (Gritsenko *et al*., 2015). Hepatitis C Virus (HCV) infection is a major global health challenge; it is estimated that more than 80 million people are chronically infected worldwide, with 3–4 million new infections and 350 000 deaths occurring each year because of HCV-related complications. Egypt is the country with the highest HCV prevalence in the world (Kandeel *et al*., 2017). Before 2013 the standard of care therapy combined and was associated with a range of treatment-limiting adverse effects. RBV-induced anemia is a frequent adverse event leading to drug discontinuation in 36% of cases in real-life studies (Loustaud-Ratti *et al*., 2016). By now the newest combinations therapy of DAA (sofosbuvir/ledipasvir (Harvoni), sofosbuvir/daclatasvir, sofosbuvir/velpatasvir and a combination of ambitasvir, paritaprevir and dasabuvir) has shown extraordinary efficacy and safety for clinical therapy (Lanini et al) but there is not enough study about the impact of the newest combination therapy. In Rwanda, HCV seroprevalence has been estimated between 3.1–4.1% via antenatal care, blood donor and HIV screening programs (Gupta *et al*., 2017). Interferon combined with ribavirin was the HCV treatment used in Rwanda before being replaced by DAAs. In the study conducted at Kanombe reported that, 3.2% of patients screened for Hepatitis C before 2015 had anemia (Umumararungu *et al*., 2017) and Other study done in Kigali, Rwanda on hepatitis c treatment outcomes using interferon and ribavirin-based therapy has shown adverse events occurred in 69 patients who were on 24 weeks of treatment, the major laboratory abnormalities were hematology: anemia (30% 21/69) (Riedel *et al*., 2016). Also in Rwanda, There is paucity information about the anemia as side effect of HARVONI and yet not study has been done to compare the anemic side effect of the Ribavirin combination and the new introduced therapy such as Harvoni. This has to be investigated.

MATERIALS AND METHODS

Research Design

This study was a retrospective study that was carried out between October and December 2017. It included patients of all ages and gender infected of HCV. We used hematological information of patients who have been treated by combined ribavirin therapy and those who have been treated with harvoni.

Target Population

This study included infected hepatitis C patients and treated with combined Ribavirin therapy since 2014 until 2015 and the treated with harvoni since April until June 2016 in all ages and gender who attended Rwanda Military Hospital.

Sample size

The population size was unknown; the sample size was determined by the number of eligible patients who attended and have received treatment from the Hospital and have asked for a full blood count test. 256 patients have been identified in the research.

Ethical Consideration

As this study was a retrospective, there was no patients' consent form to sign, instead, after the project proposal defence, ethical clearance letter was taken from INES-Ruhengeri, and submitted at RMH where RMH Ethics Committee reviewed the research and allowed the researchers to access patients' files.

Sampling Techniques

Hematological information about patients infected with hepatitis C and treated by ribavirin combined therapy and also those treated by harvoni was eligible for the research.

Data Collection

Data were collected using observational method. The data for prevalence of anemia in hepatitis C patients were collected from the results of the blood samples tested in haematology section. Observational methods were used to collect data on socio-demographic characteristics of the infected patients.

Data Analysis

After data collection, the SPSS version 20.0 program was used for data analysis. To compare variables and association between anaemia and HCV seropositivity and demographic characteristics were assessed using chi-square test. Frequency and percentages were used to calculate the prevalence. The p-value, $P< 0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS

Demographic Characteristics of the Population

In this study the socio-demographic characteristics of the population were established to characterize the population. Table 1 summarizes the socio-demographics characteristics of the population.

Table: 1 Socio-Demographic Characteristics of Study Population

Socio Demographic Characteristics					
		Harvoni		Ribavirin	
Variable		Frequency	Percentage	Frequency	percentage
sex					
	female	75	55.6	51	42.1
	male	60	44.4	70	57.9
age	young	5	3.7	16	13.2
	adult	46	34.1	56	46.3
	old	84	62.2	49	40.5

As shown in table 1, among 256 HCV patients, 135 were on Harvoni with 75 females (55.6%) and 60 males (44.4%), 121 were on Ribavirin with 51 females (42.1%) and 70 males (57.9%). Age groups were arranged in young [1-35], adult [36-50] and old ≥51 years. The patients according to age group on Harvoni were: 5 young (3.7%), 46 adults (34.1%), 84 old (62.2%), those one on Ribavirin were: 16 young (13.2%), 56 adults (46.3%), 49 old patients (40.5%).

Prevalence of Anemia

Among 135 patients who took Harvoni only one patient had anemia and the total prevalence was 0.74%. The prevalence of anemia for Harvoni was high compared to the prevalence of anemia by Alqahtani *et al.* (2015) which was 0.092%. However, among 121 patients who took Ribavirin 34 patients had anemia and the total prevalence was: 28.1%. The prevalence of anemia for ribavirin combined therapy was low compared to the prevalence of anemia for ribavirin combined therapy by Riedel (2016) which was 30% (Alqahtani *at al.,* 2015; Riedel, 2016).

Prevalence of Anemia Across Gender

Among 75 females who were on Harvoni, only one (0.96%) had anemia and in 60 males, none had anemia, and among 51 females who were on Ribavirin, 15 (12.4%) had anemia and in 70 males, 19 (15.7%) had anemia. By considering that the normal range for women was between 11 and 17 and for men it was between 12 and 18. The figure 2 summarizes the prevalence of anemia across gender.

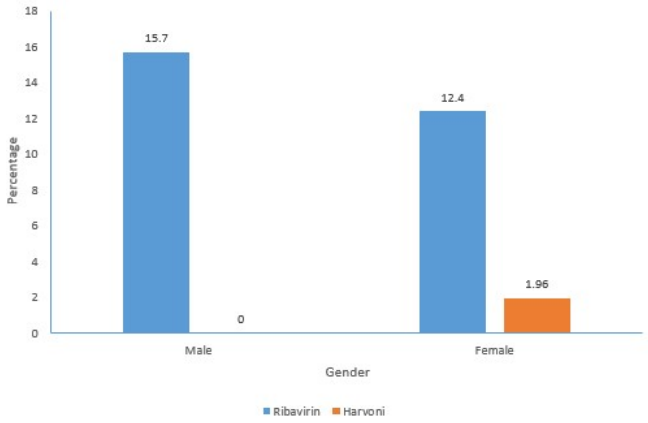

Figure 1: Prevalence of Anemia across Gender.

These findings are not in accordance with other results Alqahtani *et al*. (2015) were there was no anemia in females and males who took harvoni which explain that in this study the prevalence of anemia across gender for harvoni was high. However, according to the study by Loustaud-Ratti the prevalence of anemia was 30% so that the prevalence of anemia across gender for ribavirin in this study was low (Alqahtani *et al.,* 2015; Loustaud-Ratti *et al.,* 2016).

Prevalence of Anemia across Age

By referring to the figure 3, among patients who were on harvoni: 5 young, no anemia had been identified, among 46 adults, no anemia had been identified, among 84 old, 1 (1.19%) had anemia this doesn't correlate with other findings <1% of older patients had anemia Alqahtani. (2015) but in this study the prevalence of anemia across age for patients on harvoni is high. Among patients who were on Ribavirin: 16 patients young, 3(18.75%) had anemia, among 56 adults patients, 14(25%) had anemia, and among 49 old patients, 17(34.69%) had anemia which is in contrast study done by (Riedel *et al.,* 2016) 14.4% was old patients 15.6% was adults and no young had anemia (Riedel *et al.,* 2016).

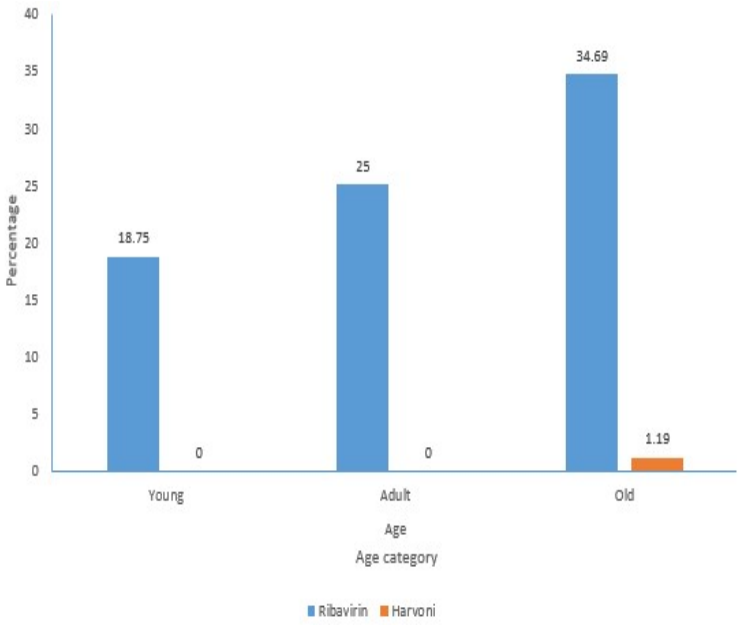

Figure: 2 Prevalence of Anemia across Age

Comparison Between Harvoni and Combined Ribavirin Therapy Induced Anemia

Prevalence of anemia among patients treated with Harvoni: 0.74% is low compared to the prevalence of anemia among patients treated with Ribavirin combined therapy: 28.1%. The prevalence of anemia by Weigand *et al.,* 2017 and Foster *et al.,* (2016) was (20%) ribavirin combined therapy and (0%) for harvoni respectively showed that the prevalence of anemia for ribavirin combined therapy was higher than that of Harvoni. However, there is- no study about comparison between harvoni and combined ribavirin therapy induced anemia (Foster *et al.,* 2016; Weigand *et al.,* 2017).

DEMOGRAPHIC CHARACTERISTICS OF PATIENT WITH ANEMIA

Demographic Characteristics of Patient with Harvoni Induced Anemia

In this study, Chi-square test revealed that only gender were significant demographic characteristic for anemia for patients who took Harvoni (Gender , p = 0.012), age were not significant (Age, p= 0.866) as demonstrated in table 2.

Table: 1 Conditions Associated with Harvoni Intak

N=135

Variable		Anemia	Normal	High	p-value
Gender					
	Male	0	59	1	0.012*
	Female	1	62	12	
Age					
	Young	0	4	1	0.866
	Adult	0	42	4	
	Old	1	75	8	
* P≤ 0.05 is Significant at 95% confidence level					

According to Harvoni Initial U.S. Approval (2014) there was no association between gender characteristic and Harvoni induced anemia which is in contradiction with our findings, also in this article there have not identified differences between harvoni induced anemia and age characteristic (Harvoni, 2014).

Demographic Characteristics of Patient with Combined Ribavirin Therapy Induced Anemia

For patients who were on combined Ribavirin therapy, Chi-square test revealed that gender were not a significant demographic characteristic for anemia (Gender , p = 0.469), age were also not a significant demographic characteristic (Age, p= 0.248) in this study as shown in table 3.

Table: 2 Conditions Associated with Ribavirin Combined Therapy Intake

n=121

Variable		Anemia	Normal	High	P value
Gender					
	Male	19	49	2	0.469
	Female	15	36	0	
Age					
	Young	3	13	0	0.248
	Adult	14	42	0	
	Old	17	30	2	
P>0.05 is not significant at 95% confidence level					

These findings correlate to other results in the reports on ribavirin induced anemia where by Gender was not a

significant characteristic for combined Ribavirin therapy induced anemia Sievert *et al*. (2011) (p=0.673). These findings are not the same with those of combined Ribavirin therapy induced anemia by Oze *et al.* (2006) where age was a significant demographic characteristic for 60 years old or more with combined Ribavirin therapy induced anemia (p<0.001) (Oze *et al.,* 2006; Sievert *et al.,* 2011).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This research on comparison of anemic side effects of Harvoni and combined Ribavirin therapy has been carried out on HCV infected patients who received treatments at Rwanda Military Hospital. Among the infected patients at RMH, the prevalence of anemia on patients who took Harvoni was lower than that of combined Ribavirin therapy. This study has shown that Harvoni have no anemic side effects than combined-ribavirin therapy. Therefore ledipasvir-sofosbuvir combination therapy (harvoni) represents a significant therapeutic advancement for the treatment of patients with HCV infection than combined ribavirin therapy.

Recommendations

Mass education of the population and sensitization campaigns about the means of transmission of HCV infection is recommended to the government. The prevention of infection should be the primary goal of treatment for HCV, to prevent complications, and to prevent the spread of this disease to other individuals. The Ministry of Health must contribute to this significant therapeutic advancement through increasing accessibility and availability of Harvoni treatment (shorter duration treatment) by reducing the prices and eliminating ribavirin from HCV therapy.

- Data availability
- The data used to support the findings of this study are available from the corresponding author upon request.
- Conflict of interest
- The authors declare that they have no conflicts of interest.
- Acknowledgement
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