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ORIGINAL ARTICLE

Effect of misoprostol on acute phase of viral hepatitis B in Iran

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ABSTRACT

Background: Most therapeutic interventions in acute phase of viral hepatitis B patients are conservative. Prostaglandins have absorbed many scientists' attention for improving these patients condition, therefore, the present study was designed to evaluate misoprostol (PGE1 Analogue) effect on acute phase of viral hepatitis B.

Materials and methods: A randomized matched controlled clinical trial was performed on two equal groups each included fifteen male acute phase hepatitis B patients who were anti HBC IgM and HBs Ag positive, hepatitis C negative and their total bilirubin level was more than 10 mg/dl. The experimental group received 800µg misoprostole (200µg × 4 times a day) while the control group received placebo for 14 days. Their bilirubin and serum transaminases concentrations as well as PT and PTT were checked before and after the therapy and compared by chi square and t-student tests using SPSS software.

Results: At the end of the treatment phase, serum bilirubin**,** SGPT and PTT were significantly lower in the experimental group. After three weeks follow up, only SGOT was not significantly lower in experimental group. At the end of the 4th and the 5th week after treatment initiation, serum bilirubin**,** SGPT, alkaline phosphatase and PTT were significantly lower in experimental group.

Conclusion: These results confirm that misoprostol improves hepatitis B patients' condition and reduces their serum bilirubin**,** SGPT, alkaline phosphatase and PTT.

Keywords: *Hepatitis B, Misoprostol, Prostaglandin E_1.*
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INTRODUCTION

World Health Organization (WHO) has estimated 250 to 500 millions persons are involved by hepatitis B virus in the world (1). Hepatitis B prevalence in Iran is estimated to be 3% (2). Although most of hepatitis B patients will be cured, this disease is of utmost importance since 1% of the sufferers and 15 to 60% of newborns who are borned from chronic carrier mothers will be carrier and 5-7% of patients will suffer from chronic hepatitis and 1-3% of them will suffer from fatal fulminant hepatitis. Virus carriers are dangerous potentially and threat public health (3).

Most therapeutic interventions in acute phase of viral hepatitis B patients are conservative and we can not decrease chronic carriage chance. Disease nature and patient immune system response are the main prognostic factors (3). Recently, new interventions have been achieved to increase cure rate of acute phase hepatitis B patients and to decrease chronic carriage chance. Prostaglandins, especially prostaglandin E_1, prescription is a choice (4). Several investigators have studied misoprostol

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effects as a PGE_1 analogue on acute phase of viral hepatitis B patients.

Ping Lim et al. study showed that misoprostol improves hepatic perfusion by decreasing venous and sinusoids casts with ischemia reperfusion injury and increasing anastomosis formation in terminal portal vein areas (5). Flisiak et al. clinical trial confirmed beneficial effect of misoprostol treatment on decreasing liver size and lowering serum alkaline phosphatase in hepatitis B patients and reducing their admission periods (4). Another study by Yasuhiko et al. reported beneficial effects of misoprostol in cirrhotic patients by decreasing serum transaminases and increasing serum IL6 and nitrate with no significant side effect (6).

Since prostaglandins have absorbed many investigators' attention as a choice to improve hepatitis B patients' condition, the present study was designed to evaluate the beneficial effects of misoprostol among Iranian patients during acute phase of viral hepatitis B.

PATIENTS and METHODS

Thirty patients with acute phase hepatitis B were included in a randomized matched controlled clinical trial. All the patients were anti HBc-IgM and HBs-Ag positive. Their total bilirubin was 10mg/dl or more and hepatitis C was ruled out. To avoid the risk of misoprostol use in pregnancy, only male patients were accepted for the study.

Subjects who have fulfilled the abovementioned criteria (inclusion criteria) were assigned randomly into two equal groups, each consisted of 15 patients. Groups were matched according to the age, serum bilirubin, transaminases concentration, PT and PTT.

Having completed the initial laboratory examinations including serum bilirubin, SGOT, SGPT, alkaline phosphatase, PT, and PTT; the experimental group received 800µg misoprostol (200µg × 4 times a day) while the controls received placebo tablet for 14 days.

All patients were examined for possible side effects of misoprostol and general conditions daily. In case of earlier discharge during the first 14 days of therapy, his therapeutic protocol was continued till the day 14^{th} under precise supervision. Weekly till the 6^{th} week, we performed liver function tests including serum bilirubin, SGOT, SGPT, alkaline phosphatase and PT, PTT in both experimental and control groups.

All data were analyzed using SPSS (version 11) software. Chi square, Fisher's exact test and student's t-test were used, when appropriate.

The study protocol was approved by the ethical committee of Shaheed Beheshti University of Medical Sciences while patients were requested to fill an informed consent.

RESULTS

All patients were anorexic and icteric. Six patients, in each group, had fever. There were no significant differences in nausea and vomiting at the beginning of trial. Biochemical indices of liver injury, measured before and after the therapeutic protocol once a week, are shown in table 1 and figure 1. These indices failed to show significant differences between groups. Following this 14-day therapy, bilirubin, SGPT, and PTT decreased in both groups, but they were significantly lower in the experimental group.

One week after the treatment cessation, all indices were lower in experimental group except SGOT. These results repeated one and two weeks later as well. One patient of control group died because of disease severity one week after the treatment. Another patient left the hospital on his desire and, unfortunately, died two days later. Moreover, one patient from the experimental group was excluded because of severe nausea and vomiting, but a new patient was substituted. Fisher's exact test revealed no significant differences in mortality rate between two groups.

Table1. *Mean values of biochemical indices of liver injury in consecutive weekly evaluation after treatment beginning in misoprostol (experimental) and control groups*

	Group	Bilirubin (mg/dl)	SGOT (U/l)	SGPT (U/l)	ALP (U/l)	PT (second)	PTT (second)
Before treatment	E	20.7 ± 9.5	1193 ± 882	1356 ± 913	523 ±137	16.5 ± 5.8	50.7 ± 14.4
	C	16.7 ± 4.1	1156 ± 906	1289 ±1106	584 ± 240	15.9 ± 6.1	47.2 ± 8.3
One week after treatment initiation	E	18.1 ± 9	9617 ± 795	969 ± 824	439 ± 115	14.7 ± 2.5	47.8 ± 14.1
	C	19.2 ± 6	1068 ± 876	1220 ± 941	515 ± 114	16.6 ± 7.1	51.4 ± 8.6
Two weeks after treatment initiation	E	12.6 ± 8.3	668 ± 654	599 ± 541	405 ± 112	13.8 ± 2.1	41.8 ± 9.2
	C	18.6 ± 2.1	871 ± 604	1064 ± 611	457 ± 119	14.8 ± 2.2	53 ± 5
One week after treatment cessation	E	7.1 ± 6.5	416 ± 572	391 ± 479	334 ± 60	13 ± 1.6	38 ± 7.4
	C	17.4 ± 4	701 ± 550	867 ± 563	401 ± 80	14.8 ± 2.2	49.2 ± 7
Two weeks after treatment cessation	E	3.9 ± 3.6	278 ± 422	239 ± 357	305 ± 68	12.7 ± 1.1	35.1 ±6.8
	C	13.5 ± 4.7	554 ± 521	634 ± 525	367 ± 70	14.1 ± 2.8	46.7 ± 9.6
Three weeks after treatment cessation	E	2.4 ± 2.2	128 ± 168	121 ± 170	307 ± 73	12.5 ± 1	34.3 ± 4.3
	C	9.5 ± 4.9	393 ± 410	461 ± 427	322 ± 59	13.5 ± 2.4	42.7 ± 8

E: Experimental group, C: Control group

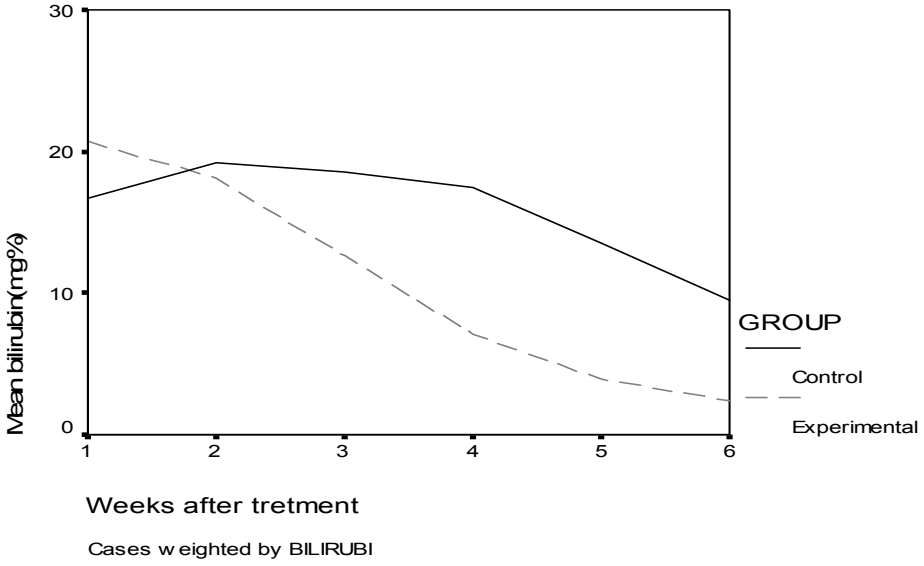

Figure 1. *Serum concentration of bilirubin in misoprostol (experimental) and control groups*

DISCUSSION

As Ping Lim et al. study showed, liver casts from rats subjected to 90-min ischemia and 24-h reperfusion with placebo treatment resulted in gross disruption of normal architecture, characterized by clusters of closed sinusoids, cavities, varicosities, and narrow sinusoids whereas in rats with misoprostol treatment, hepatic microvascular was generally intact with mild focal unfilled areas. The majority of the sinusoids were of normal size and no clusters of blind ending sinusoids were detected. They concluded that the primary site of ischemia-reperfusion injury to the liver is at the level of the sinusoids (5).

Yasushiko et al. conducted a prospective, randomized trial in cirrhotic patients undergoing subsegmentomy, under ischemia induced only by Pringle's maneuver for evaluating the effects of prostaglandine E_1 analogue (misoprostol) on liver ischemia by measuring the plasma levels of aminotransferases (ALT and AST), cytokines (IL-6, IL-1beta and tumor necrosis factor (TNF)-alpha) and nitrate/nitrite. Their study demonstrated that aminotransferases, IL-6, and nitrates plasma levels were significantly lower in the prostaglandine E_1 group. They concluded PGE_1 exerts a protective effect against hepatic ischemia/reperfusion injury, and that IL-6 appears to play an important role in this effect (6).

According to Flisiac et al study in Poland, the beneficial effect of misoprostol treatment confirmed in patients with viral hepatitis B and this was mentioned that a possible mechanism of this action seems to be its effect on serum concentration of beta2-microglobulin, related to transportation of the viral antigens on the hepatocyte surface and decreasing hepatic inflammation by lowering plasma level of beta2-microglobulin as an acute phase protein (7, 8).

In the present study, misoprostol resulted in significant decrease of biochemical indices of hepatocellular injury. Previously, Filisiak et al. have reported that the use of misoprostol for 28 days could decrease serum bilirubin and transaminases after two to five weeks (4).

In another trial, Filisiak et al reported that a 14-day course of misoprostol 200 μg orally four times daily may decrease bilirubin, transamunases, PT and alkaline phosphatase (9).

These results confirm beneficial effects of misoprostol treatment in patients with liver injury, and reveal that shortening the course of treatment to 14 days may be possible.

Our study entails some limitations. Due to ethical concerns, liver biopsy was impossible before and after the treatment phase.

Further studies are strongly recommended to evaluate misoprostol effect on histological findings of liver, clearance of serum and tissue HBs-Ag and HBV-DNA, and the prognosis and mortality rate of hepatitis B patients.

In summary, misoprostol is recommended in non-pregnant acute viral hepatitis B patients who have serum bilirubin level of >10mg/dl.

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