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A Meta-Analysis

Portal Pressure Lowering Effect of Angiotensin II Receptor Antagonists in Cirrhotic Patients: A Meta-Analysis

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Abstract
The effects of angiotensin II receptor blockers (ARBs) versus those of propranolol, a non-selective β-blocker (NSSB), on portal hemodynamics in cirrhotic portal hypertension was investigated. Ten full text randomized controlled trials (RCTs) meeting our criteria were included in our study. Mean change of Hepatic Venous Pressure Gradient (HVPG) was considered our primary outcome. Meta-analysis was performed using revman 5.2. Ten publications were included (n=381). One study was counted twice .Five studies compared ARBs to propranolol while the others compared ARBs to placebo. Quality assessment of articles was performed using the Jadad score. Results showed that there was no difference between ARB and control group on reduction of HVPG as overall effect size is 1.04, 95%CI (-0.26, 2.33) with p value above 0.05. Analysis of heart rate(HR) showed that ARB has smaller effect on heart rate than that of placebo because overall effect size is -10.34, 95 % CI (-16.64, -3.64). Analysis of effect on Wedged Hepatic Venous Pressure(WHVP) showed no difference between control and intervention group, as overall effect is 1.35 with 95%CI (-0.31, 3.01). For Mean Arterial Blood Pressure(MABP) results showed that ARB has smaller effect than that of control group, as overall effect size is -7.37 (-13.12,-1.62). Total bilirubin (Tbil) marker analysis showed that ARB has larger effect than the control group. There was no statistical significant difference between ARB and placebo groups on Cr (Creatinine). ARBs and propranolol have the same effect on HPVG and WHVP showing a reduction of portal pressure in patients with portal hypertension and cirrhosis. Hence, Angiotensin II receptor blockers can be considered as an alternative clinical approach for the treatment of portal hypertension.

Keywords: Portal hypertension, Hepatic venous pressure gradient, Randomized controlled trial, Angiotensin II receptor antagonist, Meta-analysis.

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Introduction

Esophagogastric variceal bleeding *(*EGVB*)* caused by Portal hypertension has always been a problem for medical workers because it is the most important cause of mortality in patients with hepatic cirrhosis [31, 32]. In fact the yearly incidence of Variceal hemorrhage occurrence is 5–15%, with a mortality risk of at least 20% at 6 weeks [33-36] of diagnosing medium or large varices. Portal hypertension results as the combination of increased hepatic vascular resistance and increased blood flow through the portal system which then leads to the apparition of porto-systemic collateral veins [37, 38]. The clinical measurement of hepatic venous pressure gradient (HVPG) is the gold standard for the diagnosis, staging and predicting the outcome of portal hypertension and esophageal gastric varices [39-42]. The normal value of HVPG is 1-5 mmHg. A measurement of HVPG value higher than 5 mmHg indicates the presence of portal hypertension, regardless of clinical evidence. HVPG ≥10 mmHg (termed clinically significant portal hypertension) is predictive of the development of complications of cirrhosis, including death. HVPG above 12 mmHg is the threshold pressure for variceal rupture [29, 30]. Thus, the prophylactic therapy for variceal bleeding necessitates a reduction of portal pressure. Angiotensin Receptor Blockers (ARBs) are drugs usually approved for the treatment of systemic hypertension .In recent years reports of multiple trials showed that ARBs can reduce portal vein pressure in cirrhotic patients affected with portal hypertension. But the conclusions on the subject of the safety and efficacy of ARBs as therapy for portal pressure remained controversial. Some authors suggested that they can be used as an alternative treatment in the clinical conditions where portal pressure should be reduced [1,4,5,8,9,11,12], while other strongly disagreed[2,3,6,7,10] ,stating that ARBs may have adverse effects on systemic hemodynamics. The aim of our meta-analysis is to systematically review controlled trials regarding the treatment value of ARBs in the management of portal hypertension, to give evidence to its clinical applying.

Data and Methods

Document inclusion / exclusion criteria：

Studies were considered if they met the following inclusion criteria: (i) English or Chinese language (ii) full-text article (iii) randomized or controlled clinical trial; (iv) age no lesser than 18 years; (v) patients affected with cirrhosis (vi) clinically significant portal hypertension as documented by varices or an HVPG of greater than 10 mm Hg at trial inception (vii) use of angiotensin receptor

Table 1: Thorough screening of the articles for screening to provide the individual patient data for all patients

Study	Publication year	Design	Jadad score	Blinding	Randomization	Allocation concealment grade	Allocation concealment	Baseline	ITT analysis	Grade
Schneider sev	1999	CCT	3	No	No discussion	No discussion	D	P＞0.05	Discussed	C
Schneider mod	1999	CCT	3	No	No discussion	No discussion	D	P＞0.05	Discussed	C
M-Schepke	2001	RCT	5	Yes	Just mentioned	Just mentioned	A	P＞0.05	Discussed	A
Gonzalez	2001	RCT	5	Yes	computer	Envelope	A	P＞0.05	Discussed	B
De	2003	RCT	5	No	computer	No discussion	A	P＞0.05	Discussed	B
G Castano	2003	RCT	5	No	Random digits table	No discussion	A	P＞0.05	Discussed	C
Hidaka	2007	RCT	3	Not clear	Just mentioned	Not clear	-	P＞0.05	Discussed	-
Heim	2007	RCT	2	No	Just mentioned	No discussion	D	P＞0.05	Discussed	B
Schepke	2008	RCT	5	Yes	Just mentioned	Just mentioned	A	P＞0.05	Discussed	A
Hidaka	2011	RCT	5	Yes	Just mentioned	Just mentioned	A	P＞0.05	Discussed	A
Kumar	2013	RCT	5	Yes	Just mentioned	Just mentioned	A	P＞0.05	Discussed	A

blockers (ARB) or non-selective beta-blockers (NSBB), placebo or no treatment and (viii) HVPG measurement at baseline and study end.

Exclusion criteria were (i) non-cirrhotic portal hypertension (ii) the presence of a TIPS or surgical shunt; (iii) studies done on animal models (iv) patients with history of active alcoholism (v) presence of hepatocellular carcinoma (vi) contraindications to β-blockers (NSBB) and cardiorespiratory or renal diseases.

The search strategy

Electronic searches of the following databases were performed in marchMarch 2014 to retrieve studies for potential inclusion: Cochrane library, Pub-Med, EMbase, Medline, Embase.com, BMJ Best Practice, Elsevier, Web of science, Springer. We also searched Chinese academic journals, such as CNKI, SSCI, Wan Fang, and CBM. These databases are the most frequently searched databases for medical systematic reviews. Some of the publications retrieved were also hand-searched in universities' libraries. The following search terms were used: cirrhosis, portal hypertension, hemodynamics, propranolol, losartan, irbesartan, candesartan, valsartan, telmisartan, ATII inhibitor, AT2 inhibitor, angiotensin inhibitor, Angiotensin II receptor blockers, ARBs, portal hypertension, liver, angiotensin II receptor antagonist, non-selective β-blockers, NSBB, randomized trial, RCTs, therapy, portal pressure, hepatic venous pressure gradient, portal blood flow. Randomized trials were included irrespective of publication status and utilization of languages were extended to Chinese and French besides English for purposes of search. Reference lists of retrieved relevant publications were also searched for additional trials.

Data extraction and quality assessment

Trails included in Quality analysis are as following;

a. Jadad score. One point for description of withdrawal and dropouts, randomization, adequate randomization methodology, blinding to outcome, and adequate blinding methods.

b. Allocation concealment. A = adequate AC; B = unclear AC; C = inadequate AC; D = AC not used.

Data was extracted regarding (i) study population demographics; (ii) intervention and control; (iii) outcomes (primary outcome: mean change in the HVPG between intervention and control groups; secondary outcome: frequency of adverse events and withdrawals); (iv) Potential sources of heterogeneity; (v) study design and quality analysis.

Study validity was assessed using the Jadad scale, allocation concealment scale, degree of loss to follow-up and intention-to-treat status. Once the studies were selected, thorough screening of the articles was conducted to see if they would provide us with the individual patient data for their patients (**Table 1**).

Statistical methods

Review manager 5.2 was used to perform meta-analysis. Chi-square test was performed for Heterogeneity test and when there was no heterogeneity. Fixed effect model was used to do analysis while there was indeed heterogeneity, but then random effect model was applied when verifying the source of heterogeneity, subgroup analysis was performed. Forest plots were then used to get the overall effect size while funnel plots were used to check whether there was publication bias.

The numeric data collected in this paper contains the six indicators that reflect the efficacy of angiotensin II receptor antagonist, which include HVPG, WHVP, HR (times/min), MABP, Tbil and Cr, respectively.

Results

Forest plot shows that I square is up to 86%, which is above 50%, meaning that heterogeneity exists and random effect model can be applied. Overall

effect size is 1.04 with 95% confidence interval of -0.26 to 2.33 (0 is included), also p value for the overall effect is 0.12, which is above 0.05, meaning that there is no statistical significant difference between ARB and control groups (**Figure 1**).

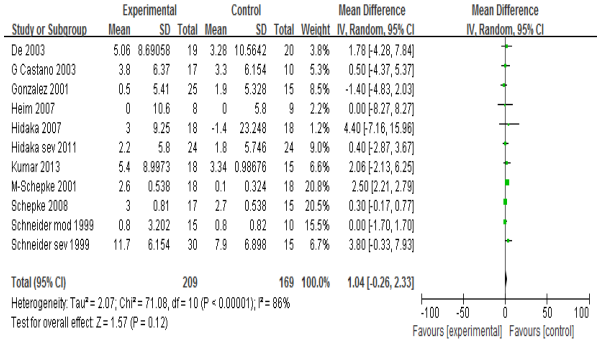

Figure 1: Forest plot for effects of Angiotensin II receptor Antagonists on HVPG

Given that heterogeneity of HPVG is too large, subgroup analysis is performed. Subgroup analysis shows that I square for placebo is 52%, which did not reduce after splitting researches by type of control, meaning that type of control is not the origin of heterogeneity (**Figure 2, 3**).

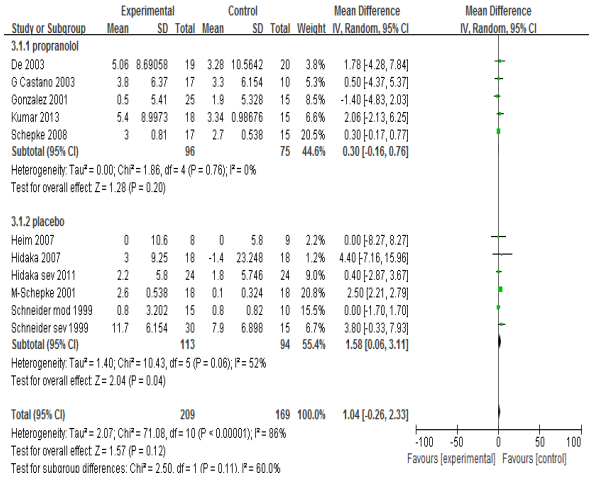

Figure 2: Subgroup Analysis by Type of Control on HPVG

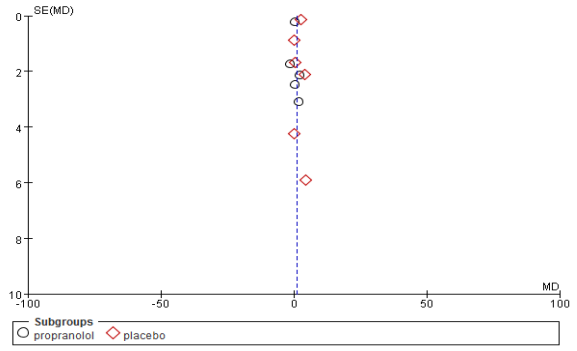

Figure 3: Funnel Plot of HPVG

Heterogeneity test shows that I square is 0% with p value of 0.8, meaning that there is no heterogeneity. Overall effect size is 1.35(-0.31,3.01) with p value of test of overall effect over 0.05, that is to say ,no statistically significant difference exists between ARB and placebo groups (**Figure 4, 5**).

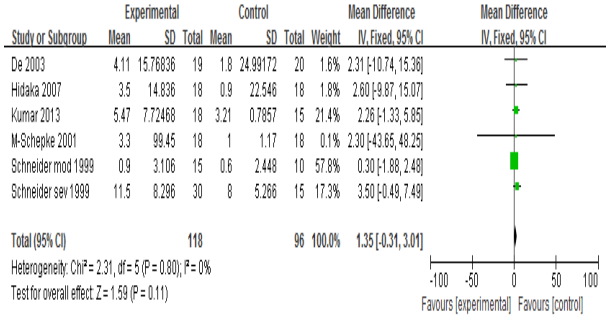

Figure 4: forest plot for Effects of Angiotensin II receptor Antagonists on WHVP

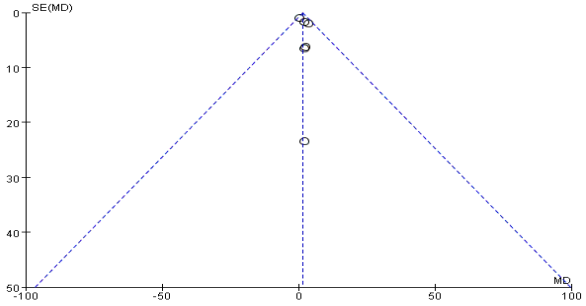

Figure 5: Funnel Plot of WHVP

Heterogeneity test shows that I square is 0% with p value of 0.91. Since there is no heterogeneity, fixed effect model is applied. Overall effect size is -10.34, with 95% confidence interval of -16.64 to -3.64 (0 is not included). That is to say, ARB has smaller effect on heart rate than that of placebo (**Figure 6, 7**).

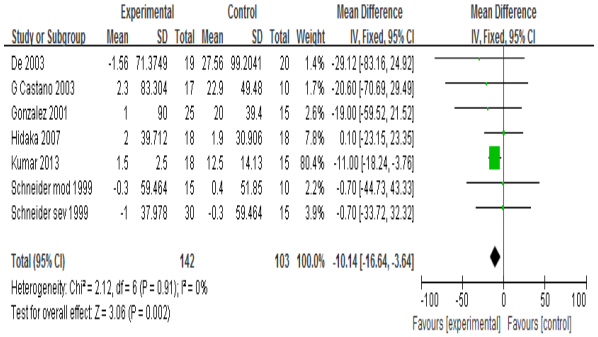

Figure 6: Forest plot of heart rate for effects of Angiotensin II receptor Antagonists on Hr

Heterogeneity test shows that I square is 23%, which is lower than 50% with p value above 0.05, so there is no heterogeneity and fixed effect model is applied. Overall effect size is -7.37 and 95% confidence interval is -13.12 to -1.62 (0 is not included), meaning that ARB has smaller effect on MABP than that of control group (**Figure 8**).

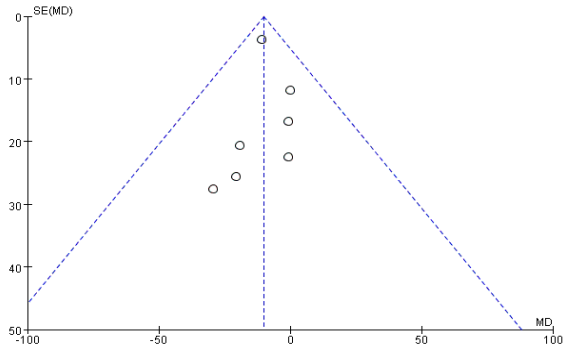

Figure 7: Funnel plot of heart rate

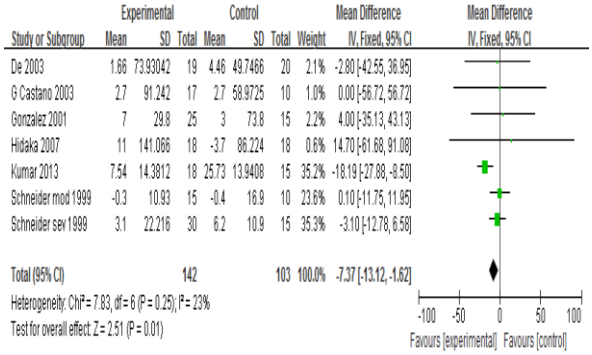

Figure 8: forest plot for Effects of Angiotensin II receptor Antagonists on MABP

Funnel plot shows that researches are not quite symmetrically distributed, indicating publication bias and egger test is needed, which cannot be done with revman. It should be cautious to make conclusion (**Figure 9**).

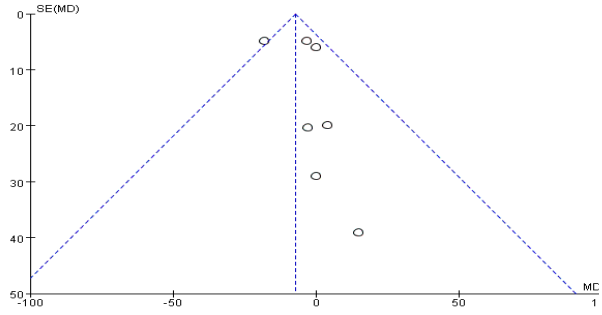

Figure 9: Funnel plot of MABP

Effects of Angiotensin II receptor Antagonists on Tbil

Heterogeneity test shows that I square is 46% with p value of 0.14, which is above 0.05, meaning that there is no heterogeneity and fixed effect model is applied. Overall effect size is 0.06 and 95% confidence interval is 0.02 to 0.1 with p value of test of overall effect below 0.004, meaning that there is statistically significant difference between the two groups and ARB has larger effect on Tbil than that of placebo (**Figure 10**).

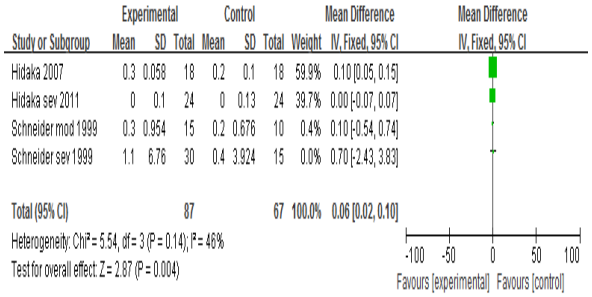

Figure 10: forest plot for effects of Angiotensin II receptor Antagonists on Tbil

Funnel plot shows that researches are symmetrically distributed, meaning that there is no publication bias and study conclusion is reliable (**Figure 11**).

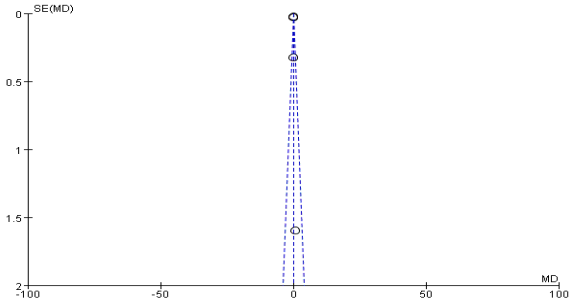

Figure 11: funnel plot if Tbil

Heterogeneity test shows that I square is up to 100%, which is too large and meta-analysis is not recommended. Even if meta-analysis is applied, random effect model is performed as shown in figure 11 and overall effect size is -0.04 with p value of test of overall effect size above 0.05, meaning that there is no statistically significant difference between ARB and placebo group on Cr (**Figure 12**).

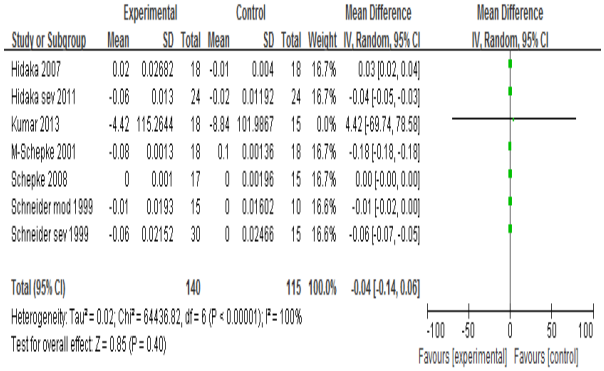

Figure 12: Forest plot for Effects of Angiotensin II receptor Antagonists on Cr

The above given heterogeneity is too large, sensitivity analysis should be applied but can not be done with revman. Subgroup analysis shows that I square of subgroup of placebo is 100%, which is still higher than 50%, meaning that type of control is not the origin of heterogeneity (**Figure 13, 14**).

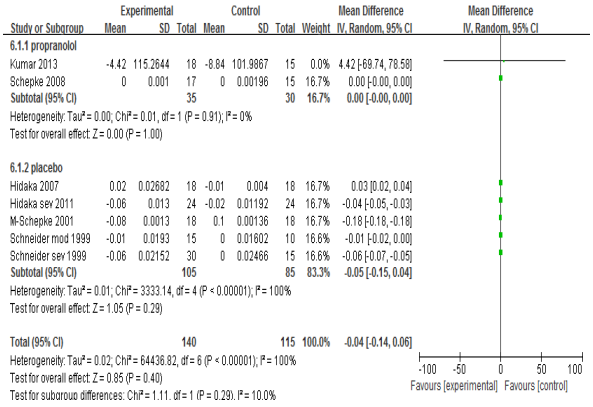

Figure 13: Subgroup analysis of Cr

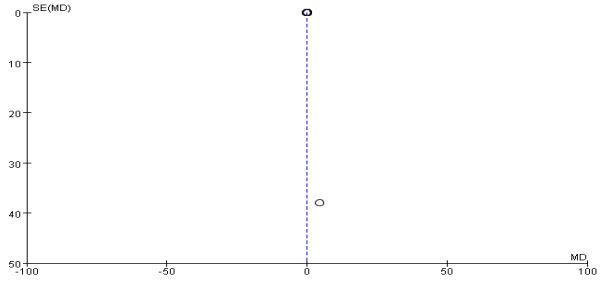

Figure 14: Funnel plot of Cr

About Subgroup analysis of WHVP, In each subgroup, p value of overall effect size is above 0.05, meaning that there is no difference between propranolol and ARB; there is neither difference between placebo and ARB.ARB can significantly reduce WHVP.

Subgroup analysis of Heart rate showed that In each subgroup, p value of overall effect size is under 0.05, meaning that there is difference between ARB and propranolol or ARB and placebo, and ARB has an effect on heart ratecompared to propranolol ARB can reduce the heart rate.

Subgroup analysis of HVPG There is no difference between ARB and propranolol hemodynamic response, while ARB has bigger effect than placebo ($p<0.05$).

Subgroup analysis of MABP ARB has smaller effect than propranolol and ARB has smaller effect than placebo.which is in contradiction with study by Schepke et al which suggested that some patients developed hypotension causing them to discontinue therapy during trial.

Subgroup analysis of Tbil ARB has bigger effect on Tbil than control group; meaning that ARB could induce renal dysfunction like suggested in the study by Schepke et al.

Subgroups analysis of Cr there is no difference between ARB and propranolol or ARB and placebo as p value are above 0.05.

Despites efforts to find unpublished data from published researchers and registered studies that were not published,the number of trials included was not enough to properly assess and interpret funnel plots obtained from analysis.Therefore clinical interpretation of funnel plots are not reliable. All the results of subgroup analysis were summarized in **Table 2**.

Table 2: Summary of subgroup analysis size effect by type of control on different parameters reflecting effect of ARBs on portal pressure

Intervention	Parameters											
	HVPG		WHVP		HR		MABP		Tbil		Cr	
	I^2	CI	I^2	CI	I^2	CI	I^2	CI	I^2	CI	I^2	CI
Propranolol	0%	0.30	0%	2.26	0%	-11.73	0%	-15.75	NA	NE	0%	0
Placebo	52%	1.58	0%	1.08	0%	-0.25	0%	-1.66	46%	0.06	100%	-0.05
Total	86%	1.04	0%	1.35	0%	-10.14	23%	-7.37	46%	0.06	100%	-0.04

Note: NE: Not Estimable; **NA:** Not Applicable

Discussion

Esophagogastric variceal bleeding (EGVB) are reported to be one of the deadliest complications in patients with chronic liver disease, notably cirrhosis with an estimated number of more than 32000 deaths every year. Reports of EGVB incidences range from 35% to 80% with approximately one third of patients diagnosed with Esophageal varices (EV) developing variceal bleeding; and in which 70% of patients experience repeated variceal hemorrage within 1-2 years [43]. Incidence of clinical deaths within 6 weeks after first occurrence of bleeding reaches up to 30%-50% [44]. In accordance with the Baveno consensus based guidelines recommending endoscopic screening of all cirrhotic patients for the presence of esophageal varices, clinical management is to be started right after diagnosis of varices to prevent first occurence of esophagogastric variceal hemorrhage; the general best response to this being an HVPG reduction of more than 20% from baseline or to an absolute value of less than 12mmHg [13,14,28].

There was already more than three decades since first suggestion was made to use non-selective beta-blockers as pharmacologic management in cirrhotic patients [16,17].

Since then the latter generated curiosity of many hepato-gastroenterologists who underwent extensive researches focusing on other uses of NSBBs which were to include primary and secondary prevention of variceal hemorrhage in

patients officially diagnosed with cirrhosis and medium or large esophageal varices. Nowadays Beta-blockers (eg: Propranolol, Nadonol) have been established the mainstay reference in the medical management of cirrhosis; particularly when it comes to the primary and secondary prophylaxis of variceal hemorrhage, for long term use has proven to effectively reduce esophageal varices risk of rebleeding [18]. Despite this fact, other studies in the cardiology literature as well as in the hepatology literature have reported that their long-term clinical use in patients with myocardial infarction and early stage cirrhosis with diagnosed medium or large varices was not effective[19,20]. In effect, beta-blocker therapy does not prevent varices formation or increase survival and is also associated with increased drug-related adverse effects. Hence their discontinuation is urged in case of refractory ascites, as decreased cardiac output results in decreased renal perfusion, azotemia, and increased risk for hepatorenal syndrome and mortality. Similarly, they are not to be initiated in patients with poor medical compliance, as the limited therapeutic window during which betablockers provide a survival benefit demands close follow-up [21].

For the last two decades, Angiotensin II receptor antagonists have been proposed as potential new drugs for portal hypertension especially through the results of multiple randomized controlled trials aiming to prove that they cause a significant fall in portal hypertension; Even as suggesting that they have equal or greater effect than the gold standard treatment cited ahead[1,4,5,8,9,11,12] .

Rocke in 1997 discovered that Angiotensin II have an effective role in the cellular pathogenesis of portal hypertension in cirrhotic patients [22]. The renin-angiotensin-aldosterone system (RAAS) is activated in patients with liver cirrhosis as a homeostatic response to compensate subsequent vasodilatation, arterial hypotension, and renal hypoperfusion observed during phenomenon of portal hypertension. In the past Angiotensin II (ANG-II) has been considered a potential mediator of intrahepatic portal hypertension especially in cirrhosis because of its Obvious plasma level elevation during it[23], reason why infusion of ANG-II induces a rise in portal pressure[24]. Because of increased levels of ANG-II liver fibrosis and HSC are activated leading to production of an extracellular matrix ,thus inducing increased Intrahepatic resistance(IHR)[25,26]; another reason why worldwide RAAS blockade(Angiotensin II) using AT1-R blockers (ARB) is now in the radar of hepatologists as a potential new clinical option in the management of PTH.

The first major publication on this subject, by Schneider *et al.* [1] reported that losartan caused a surprising significant fall in HVPG of 45% without any difference between the two treatment groups. In direct opposition, the following randomized study, by Gonzalez-Abraldes *et al.* [3], comparingF losartan to propranolol for 6 weeks, found that losartan had absolutely no effect in lowering HVPG (2%), but significantly decreased MAP by 8%.a succession of randomized trials and meta-analysis often lacking agreement in portal pressure lowering effect of Angiotensin 1 receptor antagonists(AT1-R) in cirrhosis have since been published. Our current meta-analysis is yet another attempt to this purpose. In our meta-analysis, Twelve trials meeting our final eligibility criteria where analysed using Review manager 5.2 software. Results of meta-analysis showed that there was no difference between ARB and control group on reduction of HVPG as overall effect size is 1.04, 95%CI (-0.26,2.33) with p value above 0.05, so ARB can be used to treat patients as HVPG is the main indicator to judge drugs' effect. An analysis of heart rate showed that ARB has smaller effect on heart rate than that of placebo because overall effect size is -10.34, 95% CI (-16.64,-3.64).concerning WHVP there was also observation that no difference exists, as overall effect is 1.35 with 95%CI (-0.31, 3.01). For MABP results showed that ARB has smaller effect than that of control group, as overall effect size is -7.37 (-13.12,-1.62). Tbil marker analysis showed that ARB has larger effect than the control group. On creatinine (Cr), it was seen that no difference exists. In brief, ARB and propranolol have the same effect on HPVG, WHVP and Cr showing a reduction of portal pressure in patients with portal hypertension and cirrhosis. Hence, Angiotensin II blockade could be a new safe and effective clinical approach the treatment of portal hypertension.

Many limitations were met while trying to accomplish meta-analysis due to small number of studies included for analysis and Subgroup analysis were performed to assess source of heterogeneity among included studies.

Conclusion

An overall conclusion was made that Angiotensin II receptor blockade could be an alternative option for the treatment of portal hypertension in the future. An obvious need of related studies is needed to validate these findings.

References

[1] Schneider A, Kalk J, Klein C. Effect of Losartan, an angiotensin II receptor antagonist, on portal pressure in cirrhosis. Hepatol 1999; 29: 334-9.

[2] Schepke M, Werner E, Biecker E, et al. Hemodynamic effects of the angiotensin II receptor antagonist irbesartan in patients with cirrhosis and portal hypertension. Gastroen terol 2001;121:389-95.

[3] Gonzalez-Abraldes J, Albillos A, Banares R, et al. Randomized comparison of long-term losartan vs propranolol in lowering portal pressure in cirrhosis. Gastroenterology 2001;121: 382-8.
[4] De BK, Bandyopadhyay K, Das TK, et al. Portal pressure response to Losartan compared with propranolol in patients with cirrhosis. Am J Gastroenterol. 2003;98:1371-6.
[5] Castano G, Viudez P, Riccitelli M, et al. A randomized study of Losartan vs propranolol: efects on hepatic and systemic hemodynamics in cirrhotic patients. Ann Hepatol. 2003;2:36-40.
[6] Debernardi-Venon W, Baronio M, Leone N, et al. Effects of long-term Irbesartan in reducing portal pressure in cirrhotic patients: comparison with propranolol in a randomized controlled study. J Hepatol 2003;38:455-60.
[7] Heim MH, Jacob L, Beglinger C. The angiotensin II receptor antagonist candesartan is not effective in reducing portal hypertension in patients with cirrhosis. Digest 2007;75:122-3.
[8] Hidaka H, Kokubu S, Nakazawa T. New angiotensin II type 1 receptor blocker olmesartan improves portal hypertension in patients with cirrhosis. Hepatol Res 2007; 37: 1011–7.
[9] Debernardi-Venon W, Martini S, Biasi F, et al. AT1 receptor antagonist Candesartan in selected cirrhotic patients: effect on portal pressure and liver fibrosis markers. J Hepatol 2007;46:1026-33.
[10] Schepke M, Wiest R, Flacke S, et al. Irbesartan plus low-dose propranolol versus low-dose propranolol alone in cirrhosis: a placebo-controlled, double-blind study. Am J Gastroenterol 2008;103:1152-8.
[11] Hidaka H;Nakazawa T,Shibuya A,et al. Effects of 1-year administration of olmesartan on portal pressure and TGF-beta1 in selected patients with cirrhosis:A randomized controlled trial. J Gastroenterol 2011,46:1316-1323.
[12] Agasti AK, Mahajan AU, Aniruddha Y, et al. Comparative randomized study on efficacy of losartan *versus* propranolol in lowering portal pressure in decompensated chronic liver disease. J Digest Dis 2013;14; 266-71.
[13] Feu F, Bordas JM, Luca A, et al. Reduction of variceal pressure by propranolol: comparison of the effects on portal pressure and azygos blood flow in patients with cirrhosis. Hepatol 1993;18:1082–9.
[14] Abraldes JG, Tarantino I, Turnes J, et al. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatol 2003;37:902–8.
[15] Castaño G, Viudez P, Frider B, et al. Discussion on randomized comparison of long-term losartan versus propranolol in lowering portal pressure in cirrhosis. Gastroenterol 2002; 122(5): 1544-5.
[16] Lebrec D, Nouel O, Corbic M, et al. Propranolol-a medical treatment for portal hypertension? Lancet 1980;2:180-2.
[17] Lebrec D, Poynard T, Hillon P, et al. Propranolol for prevention of gastrointestinal bleeding in patients with cirrhosis. N Engl J Med 1981;305:1371-4.
[18] Bayraktar Y, Balkanci F, Uzunalimoglu B, et al. Is portal hypertension due to liver cirrhosis a major factor in the development of portal hypertensive gastropathy? Am J Gastroenterol 1996;91(3):554-8.
[19] Smith DH, Kramer JM, Perrin N, Platt R, Roblin DW, Lane K, et al. A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. Arch Intern Med 2008;168:477–83.
[20] Mellinger JL, Volk ML. Multidisciplinary management of patients with cirrhosis: a need for care coordination. Clin Gastroenterol Hepatol 2013;11:217–23.
[21] Ge PS and Runyon BA.The changing role of beta-blocker therapy in patients with cirrhosis. J Hepatol 2014; 60:643.
[22] Rockey D.The cellular pathogenesis of portal hypertension: stellate cell contractility, endothelin, and nitric oxide. Hepatol 1997;25(1):2-5.
[23] Garcia-Pagan JC, Bosch J, Rodes J. The role of vasoactive mediators in portal hypertension. Semin Gastrointest Dis 1995;6:140–7.
[24] Ballet F, Chretien Y, Rey C, *et al.* Differential response of normal and cirrhotic liver to vasoactive agents. A study in the isolated perfused rat liver. J Pharmacol Exp Ther 1988;244:233–5.
[25] Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. N Engl J Med 1996;25:1649–54.
[26] Pinzani M, Falli P, Ruocco C, *et al.* Fat-storing cells as liver specific pericytes. Spatial dynamics of agonist-stimulated intracellular calcium transients. J Clin Invest 1992;90:642–6.
[27] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
[28] D'Amico G, Garcia-Pagan JC, Luca A, et al. HVPG reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterol 2006;131:1611-24.
[29] Kumar A, Sharma P, Sarin SK. Hepatic venous pressure gradient measurement: time to learn! Ind J Gastroenterol 2008;27(2):74-80.
[30] Groszmann RJ, Garcia-Tsao G, Bosch J *et al.* Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005; 353:2254-61.
[31] Pinter M, Sieghart W, Reiberger M, Rohr-Udilova N, Ferlitsch A, Peck-Radosavljevic M. The effects of sorafenib on the portal hypertensive syndrome in patients with liver cirrhosis and hepatocellular carcinoma –a pilot study. Aliment Pharmacol Ther 2012; 35: 83–91.
[32]Bosch J, Pizcueta P, Feu F, Fernández M, García-Pagan JC. Pathophysiology of portal hypertension. Gastroenterol Clin North Am 1992; 21:1–14.
[33] The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices: Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988; 319:983–989.
[34] El-Serag HB, Everhart JE. Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs. Am J Gastroenterol 2000; 95:3566–3573.
[35] D'Amico G, de Franchis R. Upper digestive bleeding in cirrhosis.Post-therapeutic outcome and prognostic indicators. Hepatol 2003; 38:599–612.
[36] Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG,Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatol 2004; 40:652–659.
[37] Sikuler E, Kravetz D, Groszmann RJ. Evolution of portal hypertension and mechanisms involved in its maintenance in a rat model. Am J Physiol 1985; 248:G618–G625.
[38] Sikuler E and Groszmann RJ. Interaction of flow and resistance in maintenance of portal hypertension in a rat model.Am J Physiol 1986;250:G205–G212.
[39] Procopet B, Tantau M, Bureau C. Are there any alternative methods to hepatic venous pressure gradient in portal hypertension assessment? J Gastrointestin Liver Dis 2013; 22:73–78.
[40] Suk KT. Hepatic venous pressure gradient: clinical use in chronic liver disease. Clin Mol Hepatol 2014; 20:6–14.
[41] Ripoll C, Groszmann R, Garcia-Tsao G, Grace N,Burroughs A, Planas R, et al. Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis.Gastroenterol 2007; 133:481–488.
[42] Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease.Nat Rev Gastroenterol Hepatol 2009;6:573–582.
[43] Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterol 2001; 120: 726–748.
[44] Lebrec D. Primary prevention of variceal bleeding. What's new? Hepatol 2001; 33: 1003–1004.