Controversies in Hepatology

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Primary prevention of variceal haemorrhage: A pharmacological approach

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Gastro-intestinal bleeding from oesophago-gastric varices or portal hypertensive gastropathy due to cirrhosis is a life-threatening complication. During the last decades, mortality rates of variceal bleeding in patients with cirrhosis have been falling, but portal hypertensive bleeding continues to be amongst the leading causes of death [1].

For primary prophylaxis of variceal bleeding, non-selective beta blockade (NSBB) and endoscopic band ligation (EBL) are both used as they are effective therapies [2,3]. Which therapy should be the one of first choice can be considered a controversy. However there are several issues that go beyond the initial assessment of differences in survival, for which there are none or first bleeding, and for which EBL has a statistical advantage over NSBB.

The safety of the endoscopic procedure is the first consideration. EBL can cause fatal iatrogenic bleeding [4,5], also reported in the largest trial with the longest follow-up [6].The increased expense and need for specialized staff of EBL compared to NSBB is the second consideration. As mortality is not different between therapies, the cost-effectiveness could be mainly related to the cost of the extra variceal bleeding episodes in the NSBB treated patients versus the equipment and staff costs for EBL. This has been evaluated prospectively in trials comprising patients on liver transplant waiting lists with mixed results, as a US trial found a NSBB strategy more expensive [7] and a European trial found the EBL to cost more [8]. Fatal iatrogenic bleeding was not "costed" and it is unclear how it could be evaluated in such an analysis. The third consideration is that EBL cannot prevent bleeding from portal hypertensive gastropathy, which is the case for NSBB [9]. The fourth consideration is that EBL has only been evaluated in patients with medium/large varices. Patients with small varices and severe liver disease are candidates for primary prophylaxis [3]. In a single trial based on patients with contraindications to NSBB, some of whom also had small varices, fatal iatrogenic bleeding occurred with EBL and the trial was stopped prematurely [5]. Conversely NSBB are effective in patients with small varices [10] and are effective independent of cause and severity of cirrhosis, the presence of ascites and variceal size [11]. Despite this long-standing evidence, the common perception amongst endoscopists is that NSBB are less effective in patients with decompensated cirrhosis. Another common misconception is an increased risk of hepatic encephalopathy with administration of beta-blockers. This has not been documented in placebo-controlled trials and is not a contraindication to receiving beta-blockers.

A further consideration is that preventative therapy, particularly in asymptomatic patients, should be easy to administer, have few and no serious adverse effects, and be effective. NSBB on paper fulfils these criteria better than EBL, but unfortunately these aspects have not been evaluated in randomised comparative studies. Although a survey on patient preferences in the prophylactic setting has been published favouring EBL, the potential iatrogenic bleeding with EBL was not part of the questionnaire [12].

There are 16 randomised trials in patients with medium to high risk varices comparing EBL to propranolol [6–8,13–25]. In the meta-analysis of the 16 studies, EBL significantly reduced the risk of first variceal bleeding compared to propranolol (relative risk difference 9.2%, 95% CI 5.2%-13.1%, and POR 0.5, 95% CI 0.37–0.68). However, mortality in the same meta-analysis was not statistically different (POR 0.94, 95% CI 0.70–1.28). Recently, nadolol and isosorbide mononitrate combined were found to have similar efficacy as EBL [26]. A summary of the meta-analytical data is set out in Table 1 and Fig. 1A and B. The number of patients needing treatment with EBL to save one episode of bleeding is 11 (95% CI 7–21 by random effects model). It requires an average of three endoscopic sessions to eradicate varices, so this means, on average 33 endoscopic procedures discounting follow-up endoscopies after eradication. Conversely NSBB remains cheap, as haemodynamic monitoring is not required in this setting [27].

The important conclusion, when considering the merits of NSBB or EBL for primary prophylaxis against variceal bleeding, is that mortality is no different. Survival following variceal bleeding, including that of more severely ill patients is improving [28]. As several of the randomised trials were undertaken before the universal use of antibiotics, which improve survival in acute variceal bleeding [3,29], it is likely that mortality from bleeding is already better and will further improve. Moreover, data is emerging that NSBB may also have other beneficial therapeutic effects in patients with cirrhosis, for example by reducing the risk of spontaneous bacterial peritonitis [30]. Improved survival with NSBB

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Table 1. Randomised controlled trials of banding ligation versus non-selective beta-blockers.

Study	No. of patients	Variceal bleeding ligation	Variceal bleeding β-blockers	Mortality ligation	Mortality β-blockers
Chen	54	1/26	2/28	3/26	3/28
Sarin	99	4/45	12/44	5/45	5/44
De	30	2/15	1/15	NR	NR
De la Mora	24	1/12	2/12	0/12	1/12
Song	61	6/31	7/30	5/31	8/30
Lui	100	3/44	9/66	11/44	18/66
Gheorge	53	3/25	13/28	1/25	5/28
Drastich	77	4/40	7/33	2/40	3/33
Schepke	152	19/75	22/77	34/75	33/75
Lo	100	8/50	13/50	12/50	11/50
Jutabha	62	0/31	6/31	0/31	4/31
Thuluvath	31	2/16	1/15	6/16	3/15
Psilopoulos	60	2/30	9/30	12/30	10/30
Abdelfattah	156	4/51	13/52	4/51	5/52
Lay	100	11/50	12/50	14/50	12/50
Norberto	62	2/31	3/31	3/31	3/31

compared to EBL has been shown in a long term follow up of a randomised trial of secondary prophylaxis [31,32] leading to less decompensation (other than bleeding), as well as in haemodynamic responders in another secondary prophylaxis randomised trial [33], and in pre-primary prophylaxis [34]. These potential outcomes mean that NSBB could be the "aspirin" of hepatologists [35,36]. Carvedilol may be more effective than propranolol – it resulted in reduced rates of bleeding compared to EBL [37,38].

Compliance with NSBB and dealing with intolerance or side effects is a problem encountered in clinical practice but is not addressed in the randomised studies; increased compliance could improve efficacy, as in therapy for chronic hepatitis C. With improved compliance, outcomes with NSBB might become even better than reported at present.

We believe that NSBB should be first line therapy for primary prophylaxis of portal hypertensive bleeding in patients in cirrhosis, rather than EBL, as the reduction in bleeding risk is insufficient given the considerations discussed above. EBL should be reserved for patients who have contraindications or true intolerance to NSBB.

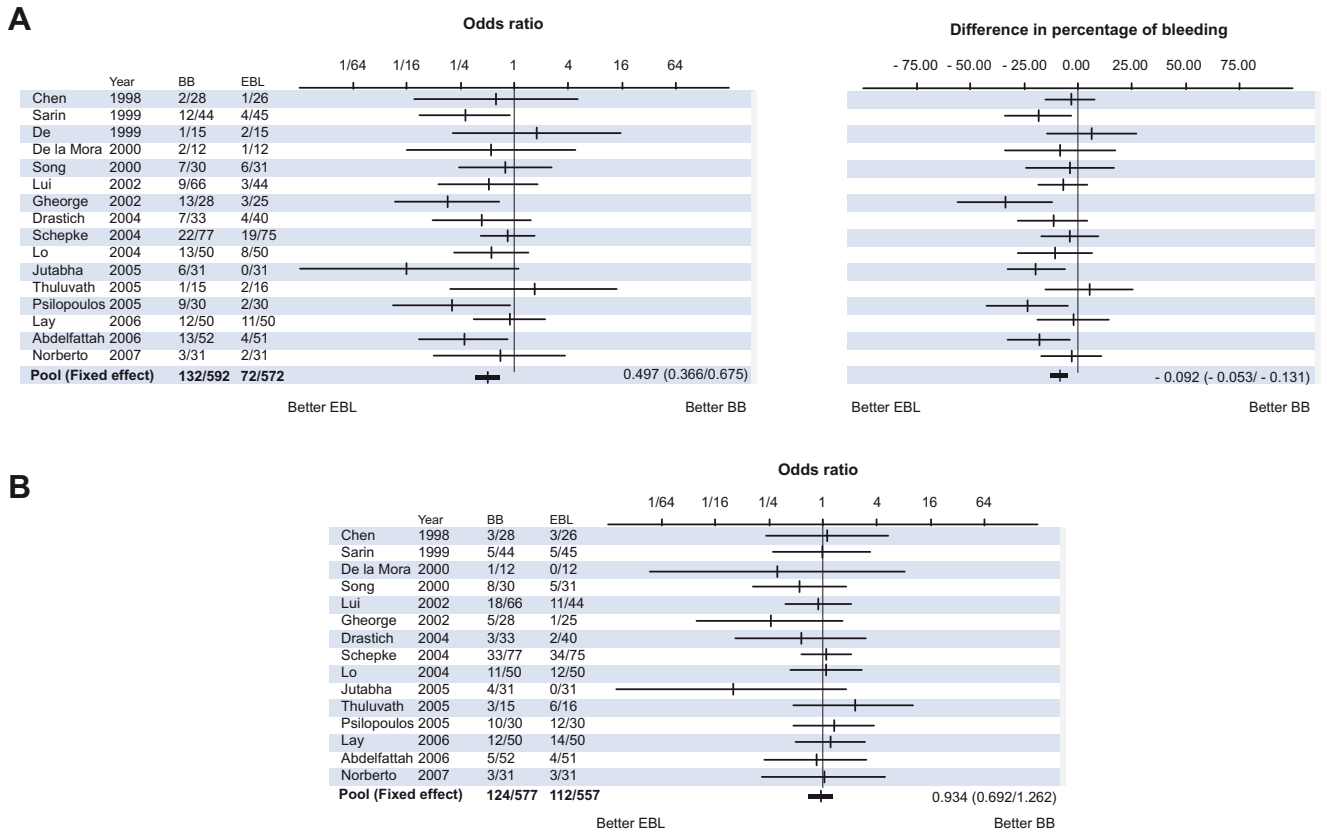

Fig. 1. Forest plots for (A) first bleeding (B) mortality in patients with cirrhosis and varices receiving either endoscopic banding ligation or non-selective beta-blockers in randomised clinical trials (BB: beta-blockers, EBL: endoscopic band ligation).

Why is this strategy not universally applied? Some reasons have been already discussed, but an additional explanation could be the remuneration in health care systems. EBL is paid for, on a per procedure basis, whereas NSBB does not have a specific cost code. If it does, the cost of propranolol 80 mg twice a day, for 12 months is only £21.46 (less than 25 Euros), so even including dispensing costs, this is likely to be one of the cheapest and cost effective therapeutic strategies in any branch of Medicine!

Conflicts of interest

The Authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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