

**SUPPLEMENTARY MATERIAL 1**

**Supplementary Table 1. Search Strategy for PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL)**

| <b>Database or virtual library</b> | <b>Search strategy</b>   | <b>Results up to June 2019</b> | <b>Results up to March 2020</b> |
|------------------------------------|--|--------------------------------|---------------------------------|
| Pubmed                             | <p>((("Esophageal and Gastric Varices"[Mesh] or "Gastrointestinal hemorrhage"[Mesh] OR varix[tiab] OR varic*[tiab] OR hemorrhage[tiab] OR haemorrhage[tiab] OR bleed*[tiab] OR esophageal[tiab] OR oesophageal[tiab] OR gastrointestinal[tiab] OR upper GI[tiab]))) AND ("Terlipressin"[Mesh] OR terlipress*[tiab] OR terlypressin[tiab] OR vasopressin[tiab] OR "Octreotide"[Mesh] OR octreotide*[tiab] OR "Somatostatin"[Mesh] OR "somatotropin release inhibiting factor"[tiab])) AND (("Randomized Controlled Trial"[PT] or "Randomized Controlled Trials as Topic"[Mesh] OR "Clinical Trial"[PT] OR "Clinical Trials as Topic"[Mesh] OR "Clinical Trial, Phase III"[PT] OR "Clinical Trial, Phase II"[PT] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh] OR "Single-Blind Method"[Mesh] OR (random*[tiab]) OR ((randomized[tiab] OR randomized[tiab] OR clinical[tiab] OR control*[tiab]) AND trial[tiab]) OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("Placebos"[Mesh] OR placebo*[tiab]) OR ("Cross-Over Studies"[Mesh]) OR ((crossover[tiab] OR cross-over[tiab] OR "cross over"[tiab]) AND (design*[tiab] OR study[tiab] OR studies[tiab] OR procedure*[tiab] OR trial*[tiab])))</p> | 854                            | 868                             |
| Scopus                             | <p>TITLE-ABS-KEY ( "Esophageal gastric Varices" OR ( varix OR varic* ) AND ( hemorrhage OR haemorrhage OR bleed* OR esophageal OR oesophageal OR upper OR gastrointestinal ) ) ) AND TITLE-ABS-KEY ( terlipressin OR terlipress* OR terlypressin OR vasopressin OR octreotide OR octreotide* OR somatostatin ) AND TITLE-ABS-KEY ( "Randomized Controlled Trial" OR "Clinical Trial" OR "Clinical Trial III" OR "Clinical Trial II" OR "Double-Blind" OR "Random Allocation" OR "Single-Blind" OR random* OR ( ( randomized OR randomised OR clinical OR control* OR placebo* ) AND ( trial ) ) OR ( ( singl* OR doubl* OR trebl* OR tripl* ) AND ( blind* OR mask ) ) OR ( ( "Cross-</p>  | 791                            | 802                             |

|         |   |     |     |
|---------|---|-----|-----|
|         | Over" OR crossover OR "cross over" ) AND ( trial* ) ) )   |     |     |
| CENTRAL | <p>#1 MeSH descriptor: (Esophageal and Gastric Varices) explode all trees</p> <p>#2 MeSH descriptor: (Gastrointestinal Hemorrhage) explode all trees</p> <p>#3 varix:ti,ab OR varic*:ti,ab OR hemorrhage:ti,ab OR haemorrhage:ti,ab OR bleed*:ti,ab OR esophageal:ti,ab OR oesophageal:ti,ab OR upper gastrointestinal:ti,ab</p> <p>#4 #1 OR #2 OR #3</p> <p>#5 MeSH descriptor: (Terlipressin) explode all trees</p> <p>#6 terlipress*:ti,ab OR terlypressin:ti,ab OR vasopressin:ti,ab OR octreotide*:ti,ab OR somatostatin:ti,ab</p> <p>#7 MeSH descriptor: (Octreotide) explode all trees</p> <p>#8 MeSH descriptor: (Somatostatin) explode all trees</p> <p>#9 #5 OR #6 OR #7 OR #8</p> <p>#10 #4 AND #9</p> | 715 | 720 |

**Supplementary Table 2. Table of excluded studies**

| <b>First author - year of publication</b> | <b>Name of study</b>  | <b>Reason for exclusion</b>  |
|---|---|--|
| Asad 2014                                 | A Comparison of Terlipressin and Octreotide for the Control of Esophageal Variceal Bleeding in Patients of Liver Cirrhosis  | The study was an abstract with incoherence in the results.   |
| Zhang 2002                                | Effects of somatostatin, octreotide and pitressin plus nitroglycerine on systemic and portal hemodynamics in the control of acute variceal bleeding.                                | The outcomes assessed are different. Not all the patients were cirrhotics.                                 |
| Zhou 2002                                 | Comparison of octreotide, vasopressin, and omeprazole in patients with acute bleeding portal hypertensive gastropathy: a controlled study   | The participants were all patients with upper gastrointestinal hemorrhage not just patients with cirrhosis |
| Li 2016                                   | Effects of terlipressin and high-dose octreotide on portal and systemic hemodynamics of cirrhosis patients with gastroesophageal varices: a multicenter randomized controlled trail | The outcome assessed was different. Just abstract available  |

|                   |   |  |
|-------------------|---|--|
| Freeman 1982      | Controlled trial of terlipressin ('Glypressin') versus vasopressin in the early treatment of esophageal varices                                     | Did not compare vasopressin analog vs. somatostatin analog   |
| Yang 1998         | Effect of vasopressin (Pitressin) on esophageal variceal bleeding in patients with cirrhosis, A multicenter, randomized controlled trial.           | Did not compare vasopressin analog vs. somatostatin analog   |
| Silvain 1993      | Terlipressin plus transdermal nitroglycerin vs. octreotide in the control of acute bleeding from esophageal varices: a multicenter randomized trial | The intervention (terlipressin) was in combination with another drug                                       |
| Walker 1992       | Terlipressin vs. Somatostatin in bleeding esophageal varices: A controlled, double-blind study  | Pre-elimination study of another included in the revision.   |
| Burroughs 1996    | Therapeutic benefit of vaso-active drugs for acute variceal bleeding: A real pharmacological effect, or a side-effect of definitions in trials?     | Did not compare vasopressin analog vs. somatostatin analog   |
| Signorelli 1996   | Sclerotherapy with or without somatostatin or octreotide in the treatment of acute variceal haemorrhage: our experience. Gastroenterology           | Did not compare vasopressin analog vs. somatostatin analog   |
| Rguez-Moreno 1991 | A randomized trial of somatostatin (S) versus vasopressin plus nitroglycerin (V/N) in the treatment of acute variceal bleeding (AVB)                | The intervention (terlipressin) was in combination with another drug                                       |
| Tricerri 1995     | Octreotide versus terlipressin in association with endoscopic sclerosis in treatment of esophageal varices in patient with cirrhosis                | No abstract nor full text found  |
| Avgerinos 1995    | Somatostatin and octreotide in the management of acute variceal hemorrhage  | It was a systematic review and meta-analysis.  |
| Campisi 1993      | Upper digestive hemorrhage. Comparison of terlipressin and octreotide   | The participants were all patients with upper gastrointestinal hemorrhage not just patients with cirrhosis |
| Law 1997          | Octreotide or vasopressin for bleeding esophageal varices   | It was a review. Not a RCT   |
| Hung 2016         | No mortality difference following treatment with terlipressin or somatostatin in cirrhotic patients with gastric variceal hemorrhage                | It was an observational study. Not a RCT   |
| Chelarescu 2001   | Terlipressin vs. somatostatin in acute variceal bleeding a prospective, randomized trial.   | The intervention (terlipressin) was in combination with another drug                                       |
| Imperiale 1995    | A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage  | It was a systematic review   |

**Supplementary Table 3. Table of sponsorship by a drug company in RCTs**

| <b>First author</b> | <b>Year</b> | <b>Sponsorship</b> |
|---------------------|-------------|--------------------|
|---------------------|-------------|--------------------|

|          |      |   |
|----------|------|---|
| Kravetz  | 1984 | This study obtained somatostatin from Dr. J. M. Cuatrecasas (Kabi-Fides, Barcelona, Spain) and Dr. B. Strindberg (Kabi-Vitrum AB, Stockholm, Sweden). |
| Jenkins  | 1985 | Not reported  |
| Bagarani | 1987 | Not reported  |
| Saari    | 1990 | Not reported  |
| Hwang    | 1992 | This study was supported by a grant (NSC80-0412-B075-117) from the National Science Council, Republic of China.                                       |
| Huang    | 1992 | Not reported  |
| Pauwels  | 1994 | Not reported  |
| Pedretti | 1994 | This study was supported in part by the Italian Ministry University and Scientific Research, Project on Liver Cirrhosis.                              |
| Feu      | 1996 | This study was supported in part by grants 94/0757, 94/7434 and 94/0068 from de Fondo de Investigaciones Sanitarias by Ferring AB (Malmo, Sweden)     |
| Walker   | 1996 | Not reported  |
| Brunati  | 1996 | Not reported  |
| Chon     | 2000 | Not reported  |
| Ali      | 2001 | Not reported  |
| Lee      | 2003 | Not reported  |
| Kim      | 2005 | Not reported  |
| Cho      | 2006 | Not reported  |
| Seo      | 2006 | Not reported  |
| Abid     | 2009 | This study was supported by a research fund from the Department of Medicine.  |
| Adarsh   | 2011 | Not reported  |
| Seo      | 2014 | This study was supported by a grant from the Ministry of Health, Welfare and Family Affairs, Republic of Korea  |
| Fatima   | 2017 | This study was supported by the hospital Zakat fund.  |

**Supplementary Table 4. Table of the number of events for main outcomes**

| <b>First author<br/>Year of<br/>publication</b> | <b>Number<br/>of patients</b> | <b>Intervention</b>                         | <b>Mortality RR<br/>(95% CI)</b> | <b>Bleeding<br/>control RR<br/>(95% CI)</b> | <b>Early<br/>rebleeding RR<br/>(95% CI)</b> | <b>Adverse events<br/>RR (95% CI)</b> |
|---|-------------------------------|---|----------------------------------|---|---|---------------------------------------|
| Kravetz<br>1984                                 | 31<br>30                      | Vasopressin<br>Somatostatin                 | 0.97<br>(0.56 to 1.67)           | 0.86<br>(0.67 to 1.10)                      | 0.57<br>(0.23 to 1.41)                      | 7.42<br>(2.49 to 22.14)               |
| Jenkins<br>1985                                 | 12<br>10                      | Vasopressin<br>Somatostatin                 | 1.67<br>(0.38 to 7.29)           | 0.36<br>(0.17 to 0.77)                      | NR  | 4.23<br>(0.23 to 79.10)               |
| Bagarani<br>1987                                | 25<br>24                      | Vasopressin<br>Somatostatin                 | 6.72<br>(0.89 to 50.61)          | 0.42<br>(0.21 to 0.84)                      | NR  | N/E                                   |
| Saari<br>1990                                   | 22<br>32                      | Vasopressin<br>Somatostatin                 | 1.06<br>(0.51 to 2.20)           | 0.70<br>(0.48 to 1.02)                      | 0.35<br>(0.05 to 2.59)                      | 10.04<br>(0.54 to 185.28)             |
| Hwang<br>1992                                   | 24<br>24                      | Vasopressin<br>Octreotide                   | 1.09<br>(0.60 to 1.97)           | 0.62<br>(0.42 to 0.92)                      | 0.54<br>(0.13 to 2.28)                      | 3.67<br>(1.17 to 11.52)               |
| Huang<br>1992                                   | 21<br>20                      | Vasopressin<br>Octreotide                   | 1.71<br>(0.69 to 4.24)           | 0.83<br>(0.54 to 1.26)                      | 2.31<br>(0.72 to 7.44)                      | N/E                                   |
| Pedretti<br>1994                                | 30<br>30                      | Terlipressin<br>Octreotide                  | 1.33<br>(0.33 to 5.45)           | 0.70<br>(0.47 to 1.03)                      | N/E   | 2.57<br>(1.26 to 5.24)                |
| Pauwels<br>1994                                 | 17<br>18                      | Terlipressin<br>Somatostatin                | 0.91<br>(0.38 to 2.16)           | 0.71<br>(0.45 to 1.11)                      | 0.75<br>(0.08 to 7.21) <sup>a</sup>         | 9.50<br>(0.55 to 1644.19)             |
| Feu<br>1996                                     | 80<br>81                      | Terlipressin<br>Somatostatin                | 1.01<br>(0.50 to 2.05)           | 0.95<br>(0.82 to 1.10)                      | 1.00<br>(0.58 to 1.74)                      | 1.65<br>(1.02 to 2.67)                |
| Walker<br>1996                                  | 53<br>53                      | Terlipressin<br>Somatostatin                | 0.92<br>(0.44 to 1.89)           | 1.16<br>(0.94 to 1.43)                      | 1.60<br>(0.71 to 3.60) <sup>a</sup>         | 0.14<br>(0.01 to 2.70)                |
| Brunati<br>1996                                 | 28<br>28                      | Terlipressin<br>Octreotide                  | 1.00<br>(0.28 to 3.61)           | 1.05<br>(0.79 to 1.40)                      | NR  | NR                                    |
| Chon<br>2000                                    | 13<br>15                      | Vasopressin<br>Somatostatin                 | 0.16<br>(0.01 to 2.89)           | 0.89<br>(0.62 to 1.27)                      | 1.30<br>(0.22 to 7.69)                      | 4.62<br>(0.59 to 36.27)               |
| Ali Hafta<br>2001                               | 17<br>17                      | Terlipressin<br>Somatostatin                | 0.60<br>(0.17 to 2.12)           | 1.17<br>(0.80 to 1.70)                      | NR  | NR                                    |
| Lee<br>2003                                     | 23<br>20                      | Vasopressin<br>Somatostatin                 | 2.61<br>(0.29, 23.13)            | 0.92<br>(0.76 to 1.10)                      | 0.47<br>(0.10 to 2.30)                      | 1.45<br>(0.64 to 3.28)                |
| Kim<br>2005                                     | 36<br>37                      | Terlipressin<br>Octreotide                  | 0.51<br>(0.05 to 5.42)           | 0.97<br>(0.86 to 1.10)                      | 0.71<br>(0.13 to 3.97)                      | 1.27<br>(0.90 to 1.80)                |
| Cho<br>2006                                     | 43<br>45                      | Terlipressin<br>Octreotide                  | 0.78<br>(0.30 to 2.08)           | 1.02<br>(0.95 to 1.11)                      | 1.28<br>(0.37 to 4.44)                      | NR                                    |
| Seo<br>2006                                     | 48<br>50                      | Terlipressin<br>Somatostatin                | 1.74<br>(0.44 to 6.87)           | 0.98<br>(0.87 to 1.09)                      | 2.14<br>(0.57 to 8.03)                      | 2.17<br>(0.20 to 23.18)               |
| Abid<br>2009                                    | 163<br>161                    | Terlipressin<br>Octreotide                  | 1.27<br>(0.48 to 3.33)           | 0.97<br>(0.92 to 1.02)                      | NR  | NR                                    |
| Adarsh<br>2011                                  | 69<br>141                     | Terlipressin<br>Somatostatin-<br>Octreotide | 0.65<br>(0.29 to 1.45)           | 1.01<br>(0.88 to 1.17)                      | NR  | NR                                    |
| Seo<br>2014                                     | 261<br>519                    | Terlipressin<br>Somatostatin-<br>Octreotide | 0.91<br>(0.55 to 1.49)           | 1.02<br>(0.97 to 1.08)                      | 0.74<br>(0.33 to 1.65)                      | 3.41<br>(2.03 to 5.72)                |

|                |          |                            |                        |                        |                        |    |
|----------------|----------|----------------------------|------------------------|------------------------|------------------------|----|
| Fatima<br>2017 | 30<br>30 | Terlipressin<br>Octreotide | 0.33<br>(0.01 to 7.87) | 1.29<br>(0.99 to 1.67) | 0.39<br>(0.04 to 4.00) | NR |
|----------------|----------|----------------------------|------------------------|------------------------|------------------------|----|

RR: Risk Ratio, NR: Not Reported; N/E: Not estimable

<sup>a</sup>Not included in the meta-analysis