ARTICLE CITATION:

ABSTRACT:

BACKGROUND: Emergency sclerotherapy is still widely used as a first line therapy for variceal bleeding in patients with cirrhosis, particularly when banding ligation is not available or feasible. However, pharmacological treatment may stop bleeding in the majority of these patients.

OBJECTIVES: To assess the benefits and harms of emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis.

SEARCH STRATEGY: Search of trials was based on The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded through January 2010.

SELECTION CRITERIA: Randomised clinical trials comparing sclerotherapy with vasoactive drugs (vasopressin (with or without nitroglycerin), terlipressin, somatostatin, or octreotide) for acute variceal bleeding in cirrhotic patients.

DATA COLLECTION AND ANALYSIS: Outcome measures were failure to control bleeding, five-day treatment failure, rebleeding, mortality, number of blood transfusions, and adverse events. Data were analysed by a random-effects model according to the vasoactive treatment. Sensitivity analyses included combined analysis of all the trials irrespective of the vasoactive drug, type of publication, and risk of bias.

MAIN RESULTS: Seventeen trials including 1817 patients were identified. Vasoactive drugs were vasopressin (one trial), terlipressin (one trial), somatostatin (five trials), and octreotide (ten trials). No significant differences were found comparing sclerotherapy with each vasoactive drug for any outcome. Combining all the trials irrespective of the vasoactive drug, the risk differences (95% confidence intervals) were failure to control bleeding -0.02 (-0.06 to 0.02), five-day failure rate -0.05 (-0.10 to 0.01), rebleeding 0.01 (-0.03 to 0.05), mortality (17 randomised trials, 1817 patients) -0.02 (-0.06 to 0.02), and transfused blood units (8 randomised trials, 849 patients) (weighted mean difference) -0.24 (-0.54 to 0.07). Adverse events 0.08 (0.03 to 0.14) and serious adverse events 0.05 (0.02 to 0.08) were significantly more frequent with sclerotherapy.
AUTHORS' CONCLUSIONS: We found no convincing evidence to support the use of emergency sclerotherapy for variceal bleeding in cirrhosis as the first, single treatment when compared with vasoactive drugs. Vasoactive drugs may be safe and effective whenever endoscopic therapy is not promptly available and seems to be associated with less adverse events than emergency sclerotherapy. Other meta-analyses and guidelines advocate that combined vasoactive drugs and endoscopic therapy is superior to either intervention alone.

DISCUSSION:

This well performed meta-analysis supports the use of vasoactive therapies in the emergency department treatment of acute variceal hemorrhage. Sclerotherapy and/or banding are integral interventions in this population and prompt consultation with gastroenterology remains prudent. However, treatment with vasoactive therapies should begin immediately upon recognition of this highly morbid condition and should not be delayed by consideration for endoscopic therapy. This analysis did not directly compare different pharmacologic treatments, though octreotide remains a mainstay of therapy in this country based on availability.

For instance, we recently cared for an individual in whom octreotide was started at an outside hospital with apparent control of active bleeding. He was then transferred to our referral facility for definitive therapy consisting of emergent endoscopic band ligation. This type of practice appears to be supported by the today’s literature.

ANALYSIS:

Synopsis:

What topic or question did the integrative review address?

The objective of this review was to assess the benefits and harms of emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis. An important question as variceal bleeds carry a 10-20% mortality with each bleed. Currently banding ligation is considered the optimal treatment, but when not available the authors estimate that sclerotherapy is used 30-50% of the time. The authors suspect that pharmacology alone may stop most of these bleeds. Notably the goal of therapy is to stop bleeding and prevent bleeds from reoccurring in the next 6 weeks. Re-bleeds in the 1st 6 wks are associated with a greatly increased risk of death.

How were potential relevant research reports identified?

The search strategy included a search of trials based on the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, and Science Citation Index, Expanded through January, 2010. A manual search of the reference lists of pertinent
English language studies, articles, reviews, and editorials was conducted. Proceedings from relevant international congresses were searched by hand.

What determined if a research report was included in the analysis or not?

Selection criteria for the trials included: randomized clinical trials that compared sclerotherapy with vasoactive drugs (vasopressin [with or without nitroglycerine], terlipressin, somatostatin, or octreotide) for acute variceal bleeding in cirrhotic patients. Studies that used quasi-randomization methods (e.g. date of birth or admission) were excluded. Studies were not excluded based upon the language of the report. Both abstracts and full research reports were included.

How many studies were included in the analysis?

Seventeen trials were included (1817 patients).

What research methods were used in the studies included in the analysis?

The included studies were randomized clinical trials evaluating emergency sclerotherapy versus pharmacological treatments (vasopressin ± nitroglycerin, terlipressin, somatostatin, or octreotide). Studies with additional interventions were included if the intervention was given to both study groups.

8 Outcomes included: failure to control bleeding, five-day treatment failure, rebleeding within 42 days or while in hospital, mortality within 42 days or while in hospital, mortality before additional treatments to prevent rebleeding, transfusions, adverse events, and serious adverse events. Not all 17 trials reported on the same 8 outcome measures. 10 reported on 5 day treatment failure, only 8 reported on need for transfusions.

What were the important and consistent findings?

When comparing sclerotherapy with each vasoactive drug, no significant differences were noted on any outcome measure.

• This analysis amounted to separate meta-analyses for each drug – this was done because the authors report that no definitive evidence suggesting the drugs are equivalent exists.

Outcome measures were reported as “pooled risk differences” The only outcomes measures which had a statistically significant differences comparing sclerotherapy vs pharmacology treatment were: 1) adverse events 2) serious adverse events. Sclerotherapy carried a higher risk of both outcomes. Of note, “adverse” and “serious adverse” events were not further differentiated.

When combining all of the trials (regardless of the vasoactive drug used) the risk differences* were:
• Failure to control bleeding: -0.02 (-0.06 to 0.02) (Non-statistically significant)
• Five-day failure rate: -0.05 (-0.10 to 0.01) (Non-statistically significant)
• Rebleeding: 0.01 (-0.03 to 0.05) (Non-statistically significant)
• Mortality: -0.02 (-0.06 to 0.02) (Non-statistically significant)
• Transfused blood units (included eight trials and 849 patients): -0.24 (-0.54 to 0.07) weighted mean difference. (Non-statistically significant)
• Adverse events: 0.08 (0.03 to 0.14) (Statistically significant, more in sclerotherapy group)
• Serious adverse events: 0.05 (0.02 to 0.08) (Statistically significant, more in sclerotherapy group)

*Risk difference: the incidence of a disease (or outcome) that can be attributed to a particular exposure (e.g. exposure to a particular treatment). It is useful in understanding differences in risk due to differences in exposures. The risk difference (or absolute risk difference) is not the same as relative risk – relative risks identify the risk factors for particular outcomes, but they cannot tell you how likely an outcome is to occur, only how much more likely the outcome is to occur in one group than the other.

What were the analyst’s conclusions?

The authors conclude that there was no convincing evidence to support the use of emergency sclerotherapy for variceal bleeding in cirrhosis as the first, single treatment when compared to vasoactive drugs. They also concluded that vasoactive drugs may be safe and effective when endoscopic therapy is not readily available and that vasoactive drugs were associated with fewer adverse events than emergency sclerotherapy. They do note, however, that other meta-analyses and guidelines report that combined therapy (vasoactive drugs + endoscopic therapy) seems to be superior to either intervention alone.

Credibility Profile:
Was the topic clearly defined and clinically meaningful?

Yes, the purpose of the review was clearly defined and the study groups were clearly defined. The topic is of clinical importance due to the mortality associated with variceal bleeding in cirrhosis, the resources necessary to perform emergency sclerotherapy, and the costs associated with sclerotherapy when compared to the administration of vasoactive drugs.

Was the search for potential reports broad and unbiased?

Yes, the search strategy was clearly described and was considerably broad. The authors provided an adequate description of the methods used to decide on trial inclusion (e.g. independent decisions on inclusion of each trial by two authors, disagreement resolution). Reasons for trial exclusion were provided.

Were the characteristics of the studies displayed or discussed in sufficient detail?
Yes. A list of the reasons for trial exclusion is provided. Descriptions of the included trials were provided, including tables of the study characteristics, outcome measures, treatments, and methodological quality.

Is there truly and integration/synthesis of findings or merely a reporting of separate findings?

Yes, study findings were integrated and synthesized. Statistical methods included the use of hierarchical linear modeling (random effects model), with findings presented as risk differences. In addition, several sensitivity analyses were conducted to further investigate the robustness of the findings. These included re-analysis excluding a trial that included patients only after their initial bleeding had been controlled (mortality outcome), re-analysis including only trials reported as full papers (excluding abstracts only), re-analysis including only the six trials judged by the authors as adequately controlling bias, and re-analysis including only trials of sclerotherapy vs. somatostatin and excluding the trial that included patients only after their initial bleeding was controlled.

Do the overall findings accurately reflect the findings from all the individual studies?

Yes. However, there were some inconsistencies, which may have been due to the way the individual trials reported their results. Here are the details by outcome measure:

*Sclerotherapy versus vasopressin (one trial):* failure to control bleeding significantly reduced by sclerotherapy (inconsistent w/overall findings); rebleeding and mortality no significant difference (consistent w/overall findings); transfusions no significant difference (consistent w/overall); adverse events no significant difference (inconsistent w/overall).

*Sclerotherapy versus terlipressin (one trial):* failure to control bleeding no significant difference (consistent w/overall findings); five-day treatment failure no significant difference (consistent w/overall findings); rebleeding no significant difference (consistent w/overall); mortality 42-days no significant difference (consistent w/overall); transfusions no significant difference (consistent w/overall); adverse events no significant difference (inconsistent w/overall); serious adverse events no significant difference (inconsistent w/overall).

*Sclerotherapy versus somatostatin (four trials):* failure to control bleeding no significant difference (consistent w/overall findings); five-day treatment failure no significant difference (consistent w/overall); rebleeding no significant difference (consistent w/overall); rebleeding before other elective treatments no significant difference (consistent w/overall); mortality no significant difference (consistent w/overall); mortality before other elective treatments no significant difference (consistent w/overall); transfusions no significant difference (consistent w/overall); adverse events significantly increased in sclerotherapy group (consistent w/overall); serious adverse events significantly increased in sclerotherapy group (consistent w/overall findings).
Sclerotherapy versus octreotide (ten trials): failure to control bleeding no significant difference (consistent w/ overall findings); five-day treatment failure no significant difference (consistent w/overall); rebleeding no significant difference (consistent w/overall); rebleeding before other elective treatments no significant difference (consistent w/overall); mortality no significant difference (consistent w/overall); mortality prior to other elective treatments no significant difference (consistent w/overall); transfusions no significant difference (consistent w/overall); adverse events – incomplete reporting of these data in these trials, but for the six trials reporting complete data, there were no significant differences (inconsistent w/overall). Adverse events in these trials were not reported by their severity; however, one trial reported four “major” complications in the sclerotherapy group and none in the octreotide group.

What overall findings were consistently well-supported and which were less well supported?

As above, the failure to control bleeding, 5-day treatment failure, rebleeding, rebleeding before additional treatment, mortality, mortality before additional treatment and transfusion outcomes/findings were more consistent than the adverse event and serious adverse event findings. This seems to have been a result of the ways in which the individual papers defined and reported these outcome measures.

What, if anything, could explain differences in results from study to study?

Failures to adequately control potential biases could have impacted the results of some of the studies. The authors reported “unclear” reporting of control bias in 11/17 studies. Examples of this include failure to use intention-to-treat analysis in some trials, failure to report blinded outcome assessment in all trials (all 17 trials were found to be unblinded), failure to report information on patients lost to follow-up in some trials, protocol violations, and insufficient methods used to observe and record information on adverse events. Also, not all studies reported on the same outcome measures.

ARE THE CONCLUSIONS OF THE INTEGRATION CREDIBLE? Yes

Clinical Significance:
Do the conclusions resonate with what I see in everyday practice?

Yes. This is an uncommon entity, but is something that every emergency physician will encounter and we should be familiar with management.

Are the majority of the findings sizable enough, consistent enough, and well enough supported that the conclusions are likely to hold up in everyday practice?

While this analysis was conducted in a rigorous and methodologically strong manner, the authors accurately report that the methodological quality of many of the trials was less than ideal. This may have affected the findings of this review; however, bias would be
unlikely in some of the hard outcomes such as mortality, rebleeding, etc. In general, the findings do seem to be consistent and well-supported.

**Applicability Profile:**

*Are my patients similar to any of those studied? Are they similar to those in a particular study? Was there anything of note in the results for samples or subsamples that are most like my patients?*

Yes, our patients are similar to the patients in these trial and these trials represent a broad subset of the population in question.

*Are the outcomes achieved of value to me or my patients?*

Yes, the key outcomes evaluated (failure to control bleeding, 5-day treatment failure, rebleeding, rebleeding prior to additional treatment, mortality, mortality prior to additional treatment, transfusions, adverse events, and serious adverse events) are very important to patients, families, and clinicians.

*What were the key features of the approach or intervention?*

Intravenous administration of the pharmacologic agent, often over an extended period (important consideration for placement on appropriate nursing units).

*Am I able to safely and effectively use the approach or intervention described?*

Yes, we have appropriate resources to administer vasoactive medications in this patient population.

*Are the findings and conclusions impressive enough to warrant trying them in any practice?*

While these findings seem to indicate that sclerotherapy is not better than treatment with vasoactive drugs AND that adverse outcomes occur more frequently with sclerotherapy, it is important to note that current evidence, guidelines, and consensus conference statements indicate that combination therapy (sclerotherapy + vasoactive drug treatment) is the first line, preferred, and most effective treatment for acute variceal bleeding. In addition, band therapy is considered to be superior to sclerotherapy.

With this in mind, if one were in an institution where band therapy and combination therapy were not available options, treatment with vasoactive drugs would seem a safe, effective option. It has also been demonstrated that endoscopic treatment is easier and safer when performed following vasoactive drug administration, so that drug therapy can begin immediately with endoscopy to follow.
Are there any organizational, logistical, cost, or time barriers to incorporating this approach into my practice? Could they be overcome?

Collaboration with and buy-in from consultants. Development of an evidence-based guideline for this patient population might be of use.

What changes, additions, training, or purchases would be needed to start using this approach?

No additional purchases, training, etc. required. In general, nursing training and appropriate inpatient placement is required for use of these medications. Transfer to a higher level of care would likely be required for smaller institutions and these patients should ideally be treated in an intensive care setting.

SHOULD I CONSIDER CHANGING MY PRACTICE BASED ON THESE FINDINGS?

Maybe. Clearly pharmacologic management is a valuable treatment adjunct in acute variceal bleeding, with the advantage of the ability to initiate this therapy immediately in the ED. However most will likely also receive sclerotherapy in combination or banding if available. GI service should be involved regardless.