Colloids Versus Albumin in Large Volume Paracentesis to Prevent Circulatory Dysfunction: Evidence-based Case Report

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ABSTRACT

Parasentesis dalam jumlah besar dapat menyebabkan disfungsi sirkulasi akibat parasentesis. Albumin dikatakan dapat mencegah terjadinya disfungsi ini. Tetapi, sayangnya dari segi harga cukup mahal dan diperlukan alternatif lain yang dapat digunakan untuk menggantikannya. Laporan ini membandingkan albumin dengan koloid dalam mencegah terjadinya disfungsi sirkulasi akibat parasentesis.


Didapatkan satu meta-analisis dan empat uji klinis dengan randomisasi. Meta analisis tersebut menyatakan albumin sangat superior dengan odds ratio 0.34 (0.23-0.51). Tiga uji klinis menyatakan hasil yang sama dan satu uji klinis menunjukkan hasil yang sama dan satu uji klinis memperlihatkan albumin tidak lebih superior dibandingkan koloid. Dari hasil kajian pada semua artikel, memang koloid belum bisa dipakai untuk menggantikan albumin dalam mencegah disfungsi sirkulasi akibat parasentesis, tetapi koloid dapat tetap digunakan terutama pada pasien yang dilakukan dengan parasentesis kurang dari lima liter.

Kata kunci: parasentesis volume besar, albumin, koloid, disfungsi sirkulasi akibat parasentesis.

ABSTRACT

Large volume paracentesis may cause paracentesis induced circulatory dysfunction (PICD). Albumin is recommended to prevent this abnormality. Meanwhile, the price of albumin is too expensive and there should be another alternative that may prevent PICD. This report aimed to compare albumin to colloids in preventing PICD.

Search strategy was done using PubMed, Scopus, Proquest, dan Academic Health Complete from EBSCO with keywords of “ascites”, “albumin”, “colloid”, “dextran”, “hydroxyethyl starch”, “gelatin”, and “paracentesis induced circulatory dysfunction”. Articles was limited to randomized clinical trial and meta-analysis with clinical question of “In hepatic cirrhotic patient undergone large volume paracentesis, whether colloids were similar to albumin to prevent PICD”.

We found one meta-analysis and four randomized clinical trials (RCT). A meta analysis showed that albumin was still superior of which odds ratio 0.34 (0.23-0.51). Three RCTs showed the same results and one RCT showed...
albumin was not superior than colloids. We conclude that colloids could not constitute albumin to prevent PICD, but colloids still have a role in patient who underwent paracentesis less than five liters.

**Keywords:** large volume paracentesis, albumin, colloids, paracentesis induced circulatory dysfunction.

INTRODUCTION

Large-volume paracentesis (LVP) is defined as single paracentesis of volume more than 5 liters/day.1,2 This procedure is indicated when patient has refractory ascites. This kind of ascites has some criteria, such as: diuretic-resistant ascites, diuretic-intractable ascites, early recurrent ascites, at least one-week duration of diuretic treatment.3 The American Association for the Study of Liver Diseases4 defined more easily that refractory ascites is unresponsive to sodium-restricted diet and high-dose diuretic treatment (400 mg/day spironolactone and 160 mg/day furosemide) or the ascites recurs rapidly after paracentesis.

LVP becomes the main treatment in refractory ascites, besides transjugular intrahepatic portosystemic shunt, liver transplantation, and peritoneovenous shunt5 that are still limited in Indonesia. LVP may cause an impairment of circulatory system that is called paracentesis-induced circulatory dysfunction (PICD). Paracentesis directly increases cardiac output, reduces cardiac filling pressure, suppresses renin-angiotensin, and deactivates sympathetic nervous systems for approximately 12 hours.6 There are big changes in circulation, including cardiac output inversely reduces to baseline and begins to activate renin angiotensin, and activates the sympathetic nervous system. Renal function is also better in the first hour and will worsen 24 to 48 hours after paracentesis. The circulatory dysfunction does not happened because of the decrease of circulatory blood volume secondary from rapid accumulation of ascites, but because of the accentuation of arterial vasodilatation which will form “new” ascites.6 PICD is recognized by an increase of plasma renin activity of >50% of the pretreatment value on day 4-6 after paracentesis to a level >4 ng/ml hours.1

PICD may occur till six days after paracentesis and will activate renin-angiotensin system which is related to a rapid return of ascites, renal failure, and worsened prognosis.7 International Ascites Club2 and American Association for the Study of Liver Diseases4 recommended infusion of albumin 6-8 gram/liter of ascites removed when large volume paracentesis is performed in hepatic cirrhotic patient. This was based on different incidence of PICD treated with albumin and synthetic plasma expanders that only happened in patients whom had paracentesis more than 5 liters.6 Moreover, PICD happens in 80% patients not receiving any infusion.7 Unfortunately the cost of albumin is too high. There are many trials that try to replace albumin with more cost-effective fluids. In this evidence-based case report, we want to look for new evidence to find good alternative (colloids) to replace albumin in large volume paracentesis.

CLINICAL QUESTION

A-49 year old patient with tense ascites was planned to undergo large volume paracentesis. She was hospitalized for paracentesis three months ago and came again due to the ascites. The physical examination showed normal hemodynamic with blood pressure 110/70 mmHg. Laboratory examination revealed albumin of 2.65 g/dL. In Indonesia national insurance, albumin transfusion will not be covered if albumin serum is more than 2.5 g/dL. Meanwhile, albumin transfusion is recommended when large volume paracentesis is performed. We would like to know whether colloids can replace albumin in large volume paracentesis in preventing paracentesis-induced circulatory dysfunction.

In hepatic cirrhotic patients with ascites that underwent large volume paracentesis, are colloids not inferior to albumin to prevent paracentesis-induced circulatory dysfunction?

METHODS

The article searching was conducted in PubMed, Proquest, Academic Search Complete (EBSCO), and Scopus in June 14th 2015
related to the PICO (Table 1), using search tools containing keywords of ascites, colloids, albumin, paracentesis-induced circulatory dysfunction with synonyms and related terms. (Table 2) Search strategy in each search engine is described in Figure 1 including the inclusion and exclusion criteria.

**Selection**

After doing the searching, five articles were obtained. No duplicate article in four search engines and all articles were available and taken to be appraised. There were one meta-analysis and four randomized clinical trials.

**RESULTS**

Bernardi et al. did a meta-analysis and they found from 8 studies performed from 1990-2010 that albumin has OR 0.34 (CI 95%: 0.23-0.51), favorable than other volume expanders in preventing post-paracentesis circulatory dysfunction. They also found that hyponatremia can be prevented with albumin better than colloids (OR: 0.61; CI 95%: 0.4-0.93). It seemed that it may reduce mortality (OR: 0.65; CI 95%: 0.42-1.01). Ascites recurrence, renal impairment, hepatic encephalopathy, portal hypertensive bleeding, and hospital readmission cannot be reduced with albumin.

Alsebaey did not find significant difference comparing terlipressin, HES 130/0.4, midodrine, albumin 2 grams/liter, and albumin 6 grams/liter in preventing incidence of PICD (8%, 8%, 20%, 12%, 12%, respectively). HES 6% was given at dose of 8 grams/liter ascites removed and given half dose within 2 hours and the rest 6 hours after procedure. Albumin was administered at dose mentioned above with the same way of administration. Plasma renin activity was checked at baseline and 6 days after paracentesis. Unfortunately each group only consisted of 25 patients. The study was done in Egypt and

<table>
<thead>
<tr>
<th>Problem</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic cirrhotic patients with ascites that undergone large volume paracentesis</td>
<td>Colloids</td>
<td>Albumin</td>
<td>Paracentesis-induced circulatory dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Search engine</th>
<th>Terms</th>
<th>Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proquest</td>
<td>ascites AND paracentesis AND (colloids OR hydroxyethyl starch OR dextran OR gelatin) AND albumin AND &quot;paracentesis induced circulatory dysfunction&quot; (limits: scholarly journal)</td>
<td>17</td>
</tr>
<tr>
<td>PubMed</td>
<td>(((&quot;ascites&quot;[MeSH Terms] OR &quot;ascites&quot;[All Fields]) AND (&quot;paracentesis&quot;[MeSH Terms] OR &quot;paracentesis&quot;[All Fields])) AND (&quot;albumins&quot;[MeSH Terms] OR &quot;albumins&quot;[All Fields] OR &quot;albumin&quot;[All Fields])) AND (paracentesis-induced[All Fields]) AND (&quot;blood circulation&quot;[MeSH Terms] OR &quot;blood&quot;[All Fields] AND &quot;circulation&quot;[All Fields]) OR &quot;blood circulation&quot;[All Fields] OR &quot;circulatory&quot;[All Fields] AND (&quot;physiopathology&quot;[Subheading] OR &quot;physiopathology&quot;[All Fields] OR &quot;dysfunction&quot;[All Fields])) AND (&quot;(colloids&quot;[Pharmacological Action] OR &quot;colloids&quot;[MeSH Terms] OR &quot;colloids&quot;[All Fields]) OR &quot;colloid&quot;[All Fields]) OR (&quot;hydroxyethyl starch derivatives&quot;[MeSH Terms] OR (&quot;hydroxyethyl&quot;[All Fields] AND &quot;starch&quot;[All Fields] AND &quot;derivatives&quot;[All Fields]) OR (&quot;hydroxyethyl starch derivatives&quot;[All Fields]) OR (&quot;hydroxyethyl&quot;[All Fields] AND &quot;starch&quot;[All Fields]) OR (&quot;hydroxyethyl starch&quot;[All Fields]) OR (&quot;dextrans&quot;[MeSH Terms] OR &quot;dextrans&quot;[All Fields]) OR (&quot;dextrans&quot;[All Fields]) OR (&quot;gelatin&quot;[MeSH Terms] OR &quot;gelatin&quot;[All Fields]))</td>
<td>4</td>
</tr>
<tr>
<td>Academic Search Complete (EBSCO)</td>
<td>ascites AND albumin AND ( colloid OR dextran OR hydroxyethyl starch OR gelatin ) AND paracentesis induced circulatory dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Scopus</td>
<td>ascites AND albumin AND ( colloid OR dextran OR hydroxyethyl starch OR gelatin ) AND paracentesis induced circulatory dysfunction AND ( LIMIT-TO (DOCTYPE , &quot;re&quot;) OR LIMIT-TO (DOCTYPE , &quot;ar&quot;) ) AND ( LIMIT-TO (LANGUAGE , &quot;English&quot;) )</td>
<td>56</td>
</tr>
</tbody>
</table>
albumin 6 grams/liter costs seven times than HES 130/0.4. Further analysis showed that the baseline of MELD score was lower in HES and albumin (11.76 versus 15.28), but not so different in CTP score (9.48 versus 9.88). It is quite hard to compare equally between HES and albumin in this study.

Abdel-Khalek also did a randomized controlled trial by comparing 68 patients with albumin 8 grams/liter and 67 patients with HES 6%. The incidences of PICD were 8.8% and 23.9%, respectively. They used albumin with dose 8 grams/liter and half dose was given during paracentesis and the other was given 6-8 hours after paracentesis in order to prevent volume overload. Meanwhile, for HES 6% the dose and the way in administering of the colloid was the same with albumin.

Garcia-Compean did a randomized controlled trial were performed in 69 patients and did 96 LVP of which 48 with dextran-40 and 48 with albumin. Dextran-40 or albumin was given for one or two hours as soon as the LVP started. They found that PICD happened in 42% patients given dextran-40 and in 20% given albumin at 48-hour post-paracentesis. These percentages were counted only from 19 patients in dextran group and 16 patients in albumin group because not all patients were checked for plasma renin activity.

Ginès, et al compared dextran 70, polygeline, and albumin. Albumin was given in 97 patients with dose of 8 grams/liter with half dose within the first 2 hours and the other 6-8 hours after paracentesis. Dextran-70 was administered to 93 patients with the same dose and schedule with albumin. Next, there were 99 patients treated with polygeline also using the same dose and schedule as for albumin. Plasma renin activity was checked at baseline and day-6 after paracentesis. PICD in albumin, dextran-70, and polygeline group were 18.5%, 34.4%, and 37.8%, respectively.

Critical Appraisal

A meta-analysis by Bernardi were appraised using meta-analysis review form, meanwhile there were four clinical trials that were appraised. Three of them, Abdel-Khalek, Garcia-Compean, Ginès, had been included in the meta-analysis mentioned above. Meanwhile, Alsebaey had not been included in the meta-analysis. The appraisal forms for each type of study were obtained from EBM toolkit in http://clinicalevidence.bmj.com/ and presented in Table 3 and Table 4.
### Table 3. Critical appraisal of the meta-analysis

<table>
<thead>
<tr>
<th>Article (years)</th>
<th>Patient Intervention</th>
<th>Relevance</th>
<th>Validity</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernardi(^a) (2012)</td>
<td>+/- 6% dextran-70, 3.5% gelatin, 6% HES, 10% dextran-40</td>
<td>+ + + + + + Aggregate</td>
<td>0.34 (0.23-0.51)</td>
<td>15 34.5 0.8 5</td>
</tr>
</tbody>
</table>

+/- in patient means not only patient undergone large volume paracentesis.

### Table 4. Critical appraisal of the randomized controlled trials

<table>
<thead>
<tr>
<th>Article (years)</th>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
<th>Random</th>
<th>Long follow-up</th>
<th>All patients analyzed</th>
<th>Blind</th>
<th>Treated equally</th>
<th>Similar at start</th>
<th>CER (%)</th>
<th>EER (%)</th>
<th>RRR (%)</th>
<th>ARR (%)</th>
<th>NNT (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alsebaey(^a) (2013)</td>
<td>+</td>
<td>HES 6%</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>12</td>
<td>8</td>
<td>33.3</td>
<td>4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Abdel-Khalek(^10) (2010)</td>
<td>+</td>
<td>HES 6%</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>8.8</td>
<td>23.9</td>
<td>-171</td>
<td>-15.1</td>
<td>7 (3.7-35.4)</td>
<td></td>
</tr>
<tr>
<td>Gines(^12) (1996)</td>
<td>+/-</td>
<td>Dextran-70</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
<td>18.5</td>
<td>34.4</td>
<td>-86</td>
<td>-15.9</td>
<td>6 (3.5-29.9)</td>
<td></td>
</tr>
<tr>
<td>Polglyeline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.5</td>
<td>37.8</td>
<td>-104</td>
<td>-19.3</td>
<td>5 (3.2-14.6)</td>
<td></td>
</tr>
</tbody>
</table>

P: patient, +/- in P: not all patients were performed large volume paracentesis. I: intervention, HES: hydroethylstarch. C: comparison, +: albumin. O: outcome, +: paracentesis induced circulatory dysfunction. In validity, +: yes, -: no. CER: control event rate, event=outcome. EER: experimental event rate, event=outcome. RRR: relative risk reduction, minus (-):relative risk increase. ARR: absolute risk reduction, minus (-):absolute risk increase. NNT: number needed to treat, if the ARR in minus, so it becomes number needed to harm. *95% CI of NNT can not be counted because no available data.

### DISCUSSION

PICD may occur as hypotension caused by arteriolar vasodilatation and hypervolemic hyponatremia, and if severe it may lead to hepatorenal syndrome and death.\(^13\),\(^14\) It can also induce a rapid return of ascites and renal failure that is not easily reversible and will reduce survival rate.\(^7\) Increased plasma renin activity may reduce survival to 6 months from 57 months in normal plasma renin activity.\(^15\)

According to several studies (Gines, et al\(^12\) and Abdel-Khalek, et al\(^10\)) found in this report, albumin was found to prevent PICD when given 8 grams/liter ascites removed given half dose at the first 2 hours and the other 6-8 hours after paracentesis better than colloids (dextran 70, polglyeline, and HES 6%). Garcia-Compean, et al\(^11\) also showed that dextran 40 was not better than albumin. The way of albumin administration they did was as soon as the LVP done for 1-2
hours. Unfortunately, they did not check renin activity in all patients, they only did in 36% of patients. Stronger evidence from the meta analysis with good validity by Bernardi, et al also showed that including in 8 trials, albumin is better than other plasma expanders in preventing PICD (OR: 0.34), only one study showed albumin is no better than colloid, but the evidence is weak because of small sample size (n=25 in each group).

The different results from each trial as mentioned above may be caused by different baseline characteristics of the patients in each trial. Some of baseline characteristics are shown in Table 5. PICD happened in patients receiving any colloid ranging from 8% to 42% and in patients receiving albumin in 8.8-20%. Moreover, in our opinion, the result from meta analysis should be interpreted carefully since the baseline characteristics of each trial were varied, particularly the amount of ascitic fluid removed was varied from 5.5 to 15.9 liters.

When compared with crystalloid, albumin is also better in reducing PICD. Sola-Vera, et al compared albumin with saline 3.5% in LVP. They began the infusion 3 hours after paracentesis. The dose of albumin and 3.5% saline were 8 gr/L and 170 mL/L of ascites removed, respectively.

Although there is no data concerning colloid versus placebo, we also suggest colloid infusion if albumin is not possible. Other trial compared paracentesis alone with paracentesis plus albumin (dose 10 gram/L of ascitic fluid removed), there was significant less PICD in albumin group (16%) compared with paracentesis alone (30%). Albumin may look superior in terms of preventing PICD, but there is lack of data comparing saline with colloid. Repeated paracentesis (<5L) may lessen the need for albumin, but there is also no sufficient data that showed significant advantage of total paracentesis compared with repeated smaller-volume paracentesis.

We should note that in patients undergoing smaller volume paracentesis (less than 5 liter), colloid infusion is needed with dose as given of 8 grams/liter ascites removed. From the original trial, Gines, et al compared albumin with colloids (dextran 70 or polygeline) infusion and found no significant difference in PICD incidence (4 of 24 patients versus 1 of 7 patients) for smaller volume paracentesis, hence colloid may be useful in patients undergone smaller volume paracentesis. The International Ascites Club also recommends the use of colloid if the ascitic fluid is removed less than 5 liters, although this is only basis on consensus.

Further study showed as long as the ascites removed is less than 8 liters, and the albumin of 6-8 gram/liters of ascites removed is given,

<table>
<thead>
<tr>
<th>Table 5. Baseline characteristic from RCTs</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Alsebaey</td>
</tr>
<tr>
<td>Abdel-Khalek</td>
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<tr>
<td>Garcia-Compean</td>
</tr>
<tr>
<td>Gines (dextran)</td>
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<tr>
<td>Gines (polygeline)</td>
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</tbody>
</table>

* mean (SD); RCT: randomized clinical trial; MAP: mean arterial pressure.
the development of PICD is not associated with renal dysfunction.\textsuperscript{15}

Besides, preventing PICD post-LVP, albumin also protects patient having hyponatremia and reduces mortality post-LVP.\textsuperscript{8} Meanwhile, another meta-analysis showed that albumin was not significantly better than other colloids in terms of death, encephalopathy, hyponatremia, gastrointestinal bleeding, readmission, renal impairment, and sepsis/severe infection.\textsuperscript{18}

With regard to adverse effects, human albumin is considered to be safe. In the period 1990 to 2000 with a total of 112 million albumin doses distributed worldwide, no death related to albumin was documented. Anaphylactoid reactions are very rare following albumin infusion and found to be higher in patients with athapoglobinemia, but much lower than gelatins and dextrans, similar to starches.\textsuperscript{6} Other events include: heart failure, increase risk of variceal bleeding, lung oedema, increase of nitrogen bodies, and viral transmission.\textsuperscript{19}

Patient with refractory ascites may produce ascites depending on patient’s sodium intake. If patient with normal renal function adheres to sodium restriction of 88 mmol/day, the production of ascites should be <4 liters a week.\textsuperscript{15} Education to restrict the consumption of sodium is needed in all patient with ascites in order to slower the production of ascitic fluid.

The main problem of using albumin is the cost. The price of albumin 20% per 100 mL in Indonesia is approximately 150 USD. To reduce the cost, there was a study that compared standard dose (8 gr/L of ascites removed) with half dose (4 gr/L of ascites removed) of albumin. The subjects were 35 patients in each group and they found no significant difference in incidence of PICD, 20% in standard dose versus 14% in half dose.\textsuperscript{20} Alsebaey et al\textsuperscript{9} also supported that incidence of PICD was not different in patients receiving albumin infusion of 2 gr/L of ascites removed with albumin 6 gr/L of ascites removed, although in this study the sample size was small.

Besides LVP, evidence of albumin use in cirrhotic patient is also established in spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome, but not enough in ascites, bacterial infections beside SBP, hypervolemic hyponatremia, and hepatic encephalopathy.\textsuperscript{14} Alternative treatment for refractory ascites is insertion of transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation as indicated.\textsuperscript{15}

**CONCLUSION**

Up to day albumin is still superior to colloids and can reduce the incidence of paracentesis induced circulatory dysfunction in patients undergoing large volume paracentesis. It is recommended to use albumin with dose 8 grams/liters ascites removed if it is more than five liters/day in liver cirrhotic patients. Considering the high cost of albumin, half dose of albumin may give the same benefit although the evidence is weak. Colloids are still needed when paracentesis is done less than five liters per day.

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