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# DRUG UTILISATION EVALUATION OF HUMAN ALBUMIN SOLUTION IN TAWAU HOSPITAL, SABAH, MALAYSIA

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## ABSTRACT

*Human albumin solution (HAS) which is available in government hospitals in Malaysia, mostly are supplied by the National Blood Centre, Ministry of Health (MOH) Malaysia. Due to the high usage of HAS, it is a strain to meet the demands nationwide. Moreover, HAS is very expensive. This study was a retrospective observational study evaluating drug utilisation of HAS in Hospital Tawau, Sabah. A name list of 61 patients who had received HAS between 6 months from 1 January to 30 June 2019 was sent for medical records tracing. Forty-eight prescriptions of HAS were evaluated and later categorised as 'proven indications' or 'unproven indications' with the aid of an internally prepared guideline. The result of this study indicates that 12 (25%) out of 48 prescriptions were for 'unproven indications'. Possible wastage due to 'unproven indications' was 29 vials which were 20% of the total HAS usage in this study, estimated to cost RM7,804 (USD1,880). Major surgery with a serum albumin level of 20 g/L and above (55.2%), paracentesis with ascitic fluid removed of less than 5 L (24.1%) and hypoalbuminemia without justified comorbid or diagnosis (20.6%) being reasons for possible wastage of HAS in this study. The percentage of possible wastage of HAS reflected in this study was not as high as other published research done in other countries, mainly due to additional steps required for prescribing HAS in our facility (filling Blood Plasma Product Request Form) and also the need to obtain approval from the Director-General of MOH Malaysia if it was prescribed for other than the approved indications.*

***Keywords*:** Drug utilisation evaluation, Drug use evaluation, Human albumin solution, Drug utilisation review, Albumin

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## INTRODUCTION

Drug use evaluation (DUE), sometimes referred to as drug utilisation review, is a system of continuous, systematic and criteria-based drug evaluation that ensures the appropriate use of drugs (World Health Organization 2003). The objectives of DUE include ensuring that drug therapy meets current standards of care, controlling drug cost, preventing problems related to medication, evaluating the effectiveness of drug therapy and identification of areas of practice that require further education of practitioners (World Health Organization 2003).

Human albumin solution (HAS) is an expensive colloidal preparation which is commonly used in clinical practice. Albumin is the most abundant protein in blood plasma and is responsible for many important physiological functions. Both HAS and albumin maintain the colloidal osmotic pressure and the transportation of the endogenous compounds such as fatty acids, unconjugated bilirubin, hormones, bile acids, amino acids, metals and toxic metabolites as well as various drugs (Fanali *et al*. 2012).

HAS which is available in government hospitals in Malaysia is mostly supplied by the National Blood Centre, Ministry of Health (MOH) Malaysia and came in with 20% strength. Some were still obtained via procurement from drug companies. Due to the high usage of HAS, it is a strain to meet the demands of supply nationwide, moreover, it is very expensive. Wastages due to unproven use of HAS have also been reported all over the world (Farasatinasab *et al*. 2018; Farsad *et al.* 2016; Foroughinia and Mazraie 2017; Jahangard-Rafsanjani *et al.* 2011; Tanzi *et al*. 2003).

In MOH Malaysia Drug Formulary, the approved indications for the use of HAS are for acute hypovolemic shock, hypoproteinaemia and neonatal hyperbilirubinaemia (Ministry of Health Malaysia 2020). Other indications for use in an adult will require special approval by the Director-General of MOH Malaysia. There is many of new strong evidence of other uses of HAS apart from the few listed in the MOH Malaysia Drug Formulary. Thus, this DUE of HAS will include all justified uses of HAS based on the current evidence available, not restricted to the few listed in the MOH Drug Medicines Formulary. To do this, an internal guideline was developed from several evidence-based literature and it was also verified by a medical specialist (Table 1).

The objective of this study is to evaluate HAS utilisation patterns in Tawau Hospital, Sabah, Malaysia. Specific objectives include calculating the percentage of use of HAS for 'proven indication' and 'unproven indication' in Tawau Hospital, to calculate the total cost of HAS used for 'unproven indication' in Tawau Hospital for the study period and to classify the indications that HAS usually prescribed for, for the study period in Tawau Hospital.

## METHODS

### Study Design and Study Population

This retrospective observational study was conducted at Tawau Hospital, Sabah, Malaysia. List of patients (12 years old and above) who had received HAS between 1 January 2019 and 30 June 2019 was obtained from the Inpatient Pharmacy supply record. Patients who had fulfilled the inclusion and exclusion criteria were identified. Only patient with the age of 12 years old and above were included in this study. This cut-off age is because indicated uses of HAS for pediatrics are different from that of adult. In Malaysia, usage of HAS for paediatric patients approved are beyond the indications listed in MOH Blue Book. All uses stated in the Paediatric Protocols for Malaysian Hospitals (currently in its 4th edition published in the year 2018) are exempted from obtaining special approval from the Director-

General of MOH Malaysia. Thus, in this research, we excluded paediatrics. We included all warded in-patients as well as day cases in the Heamodialysis Unit (including visit for heamodialysis sessions).

Patient's individual hardcopy medical records were traced from the Medical Record Unit to obtain more information on the prescription of HAS. Simple sampling was done as only hardcopy medical records which were traceable by Medical Record Unit were included in this study.

## Data Collection

Data collection was done using a data collection form. The data extracted includes patients' age and gender, serum albumin and protein level (pre-HAS prescription), the indication behind each HAS prescription, strength and number of vial(s) administered, duration of treatment etc. The data was then evaluated with the internal guideline as reference (Table 1) to classify whether it is for 'proven indication' or 'unproven indication'.

The development of the internal guideline in this study (Table 1), like other similar studies (Farasatinasab *et al.* 2018; Foroughinia and Mazraie 2017), developed by means of evaluating latest evidence-based studies and guidelines. Indications for the use of HAS for heart surgery and organ transplantation was excluded in this internal guideline, as the service is not offered in this facility. The guideline was then verified by a medical specialist.

**Table 1:** Summary of internal guideline used for this study.

| | |
|---|---|
| **Proven indications (for which there is widespread consensus)** | |
| Spontaneous bacterial peritonitis | In association with antibiotics.<br>Day 1: 1.5 g/kg<br>Day 3: 1 g/kg |
| Paracentesis | 6 g–8 g of albumin/L ascitic fluid removed, after paracentesis of volumes > 5 L. |
| Therapeutic plasmapheresis | For exchanges of > 20 mL/kg in one session or > 20 mL/kg/week in more than one session. |
| **Occasionally proven indications (when other criteria are fulfilled)** | |
| Major surgery | Albumin should not be used in the immediate post-operative period.<br>Only indication for use: serum albumin < 20 g/L after normalisation of circulatory volume. |
| Cirrhosis of the liver with refractory ascites | Generally ineffective, except in patients with serum albumin < 20 g/L. |
| Hepatorenal syndrome | In association with vasoconstricting drugs.<br>1 g/kg per day (100g maximum) for 2 days<br>Followed by 25 g/day–50 g/day until vasocontricting drugs is discontinued. |
| Nephrotic syndrome | Only in patients with albumin < 20 g/dL with hypovolaemia and/or pulmonary oedema. |
| Burns | In the case of burns of > 30% body surface area, after the first 24 h. |
| Contraindications to the use of non-protein colloids | Reason for contraindications to the use of non-protein colloids.<br>• pregnancy and breastfeeding<br>• acute liver failure<br>• moderate-severe renal failure (particularly when anuria/oligouria)<br>• dialysis treatment in the presence of severe abnormalities of haemostasis and baseline albumin < 20–25 g/L<br>• coagulation defects/severe bleeding risk<br>• severe congestive heart failure<br>• intracranial haemorrhage<br>• hypersensitivity |

*(continued on next page)*

**Table 1:** (*continued*)

| **Occasionally proven indications (when other criteria are fulfilled)** | |
|---|---|
| Haemorrhagic shock | Only in the case of:<br>- lack of response to crystalloids or colloids;<br>- contraindication to the use of non-protein colloids. |

### Analysis

All data were then transferred to SPSS software version 25.0. For continuous variables which includes age, serum albumin and protein level, mean and standard deviation were provided. Patient's gender was presented in the form of percentages. The usage of HAS and indications for prescriptions of HAS were reported in numbers and percentages. Percentages of total prescription for 'proven indication' and 'unproven indication' were also calculated. Total possible wastage from HAS use for 'unproven Indication' was also calculated in term of number and price, by multiplying the total number of unnecessary vials with estimated price of one albumin vial. The cost of one vial of HAS (20 g in 100 mL) was estimated to be RM269.10.

### Ethical Approval

This research has obtained ethical approval from Medical Research and Ethics Committee, MOH Malaysia on 3 June 2019 with NMRR ID: NMRR-19-484-47075.

## RESULTS

A total of 61 patients were recorded to use HAS but only 32 of them with complete medical records traced. Interestingly, seven of them were prescribed with HAS multiple times (ranges from 2 to 5 times) in the 6-months duration. For this study, a total of 48 prescriptions were obtained from 32 patients for the study duration.

Out of these 48 prescriptions, 28 (58.3%) were for male patients whilst 20 (41.7%) were from female patients. The mean age was 52 ± 16 years old, mean serum albumin pre-level was 20.2 ± 7.3 g/L and mean serum protein pre-level was 53 ± 5.1 g/L. In this study, 27 (56.3%) had serum albumin pre-level of less than 20 g/L whilst 21 (43.7%) had serum albumin level of 20 g/L and above. All 48 prescriptions used HAS in vial of 100 mL with 20% strength. The mean vials used per prescription is 3.02 ± 1.973. Patients' demographic is in Table 2.

**Table 2:** Patient's demographics.

| **Variable (*N* = 48)** | **Results*** |
|---|---|
| Age, years old | 52 ± 16 (18–89) |
| Gender | 58.3%: Male<br>41.7%: Female |
| Vials used per prescription | 3.02 ± 1.973 (1–10) |
| Serum albumin pre-level | 20.2 ± 7.3 |
| Serum protein pre-level | 53.0 ± 5.0 |

*Notes:* *mean ± SD (range) for continues variables; Frequency (%) for nominal variables.

Thirty-six (75%) of the prescriptions were for 'proven indications' and 12 (25%) prescriptions were for 'unproven indications'. Thirty-six prescriptions for 'proven indications' were from 29 patients whilst the 12 prescriptions for 'unproven indications' were from nine patients. From the 12 prescriptions categorised as 'unproven indications', three prescriptions were prescribed for the same patient.

In term of vial usage, only 29 vials (20%) of HAS were used for 'unproven indications' and the remaining 116 vials (80%) were for 'proven indications'.

Total HAS used was 145 vials. Estimated price per vial is RM269.10. This estimate came from extrapolation of price of 50 mL vial (20%) which is available widely in the market which was priced at RM134.55. HAS in vials of 100 mL (20%) are supplied by the National Blood Centre to government facilities for free. One hundred and sixteen vials of HAS for 'proven indications' estimated to cost RM31,215.60 (USD7,520.30) whilst 29 vials of HAS used for 'unproven indications' is estimated to cost RM7,804 (USD1,880).

In this study, top three indications for prescription of HAS were for contraindication to non-protein colloids in septic shock (27%), paracentesis (22.9%) and major surgery (18.7%). Indications arranged from highest to lowest in Table 3.

In this study, all 13 prescriptions for contraindications to non-protein colloids in septic shocks are deemed as 'proven indications'. This is because, all patients had at least one reason that contraindicated them to receive non-protein colloid. All 13 patients have moderate to severe renal failure. One of the 13 patients had acute liver failure prior to HAS initiation and another one had to undergo dialysis treatment in the presence of severe abnormalities of haemostasis and baseline albumin of less than 20 g/L.

**Table 3:** Summary of HAS usage by indications.

| Indications | Proven indications | | Cost of HAS for proven indications (USD) | Unproven indications | | Cost of HAS for unproven indications (USD) |
|---|---|---|---|---|---|---|
| | Number of prescriptions (%) | Number of vials (%) | | Number of prescriptions (%) | Number of vials (%) | |
| Spontaneous Bacterial Peritonitis | 6 (12.5) | 35 (24.1) | 2,269.00 | 0 | 0 | 0 |
| Paracentesis | 7 (14.6) | 15 (10.3) | 972.50 | 4 (8.3) | 7 (4.8) | 453.80 |
| Major Surgery | 4 (8.3) | 12 (8.3) | 778.00 | 5 (10.4) | 16 (11.0) | 1,037.20 |
| Hepatorenal Syndrome | 2 (4.2) | 16 (11.0) | 1,037.30 | 0 | 0 | 0 |
| Septic shock contraindicated to non-protein colloid | 12 (25.0) | 26 (18.0) | 1,815.20 | 0 | 0 | 0 |
| Hypoalbuminemia | 0 | 0 | 0 | 2 (4.2) | 3 (2.1) | 194.50 |
| Unindentified | 0 | 0 | 0 | 1 (2.1) | 3 (2.1) | 194.50 |
| Haemorrhagic shock contraindicated with crystalloid and colloid | 3 (6.3) | 9 (6.2) | 583.50 | 0 | 0 | 0 |
| Volume expansion (hypovolemia) contraindicated to non-protein colloid | 2 (4.2) | 3 (2.1) | 64.80 | 0 | 0 | 0 |
| Total | 36 (75) | 116 (80) | 7,520.30 | 12 (25) | 29 (20) | 1,880.00 |

In this study, major surgery with serum albumin level of 20 g/L and above contributed to 55.2% from total possible HAS wastage. Next highest contributor of possible HAS wastage was 'paracentesis with ascitic fluid removed of less than 5 L' which accounted for 24.1% and hypoalbuminemia without justified comorbid or diagnosis, were accounted for 20.6%.

In this study, five out of nine prescriptions for major surgery were found to be for 'unproven indications'. The five prescriptions were classified as 'unproven indication' due to patient's serum albumin level were 20 g/L or above. Major surgery is listed as one of the occasionally appropriate indications for the use of HAS by Liumbruno *et al.* (2009) in their article titled 'Recommendations for the use of albumin and immunoglobulins' provided that HAS is given after normalisation of circulatory volume and the serum albumin is < 20 g/L (grade of recommendation 2C+). Liumbruno *et al.* (2009) in their paper only listed two examples of surgery to fall under major surgery which is > 40% resection of the liver and extensive intestinal resection. In our study, we classify indications as major surgery when the surgery involves a risk to the life of the patient specifically an operation upon an organ within the cranium, chest, abdomen or pelvic cavity, following the definition by Merriam-Webster Medical Dictionary (2020). In this study, eight out of nine surgeries involved are laparotomy procedures, only one laparoscopic procedure.

Hypoalbuminemia without justified comorbid or diagnosis had caused possible wastage of six vials of HAS solution in this study. This came from three prescriptions. The first prescription of HAS was with diagnosis of liver cirrhosis secondary to autoimmune disease, in which patient has no ascites and not diagnosed as having spontaneous bacterial peritonitis or hepatorenal syndrome at time of HAS initiation. The second prescription of HAS was for patient with a diagnosis of anasarca secondary to hypoalbuminemia. For the third prescription, the patient had pre-serum albumin level of 27 g/L and was diagnosed with gall bladder cancer with liver and peritoneal metastases.

In term of price, these possible wastage of 29 vials of HAS 20 g in 100 mL is estimated to cost RM7,804 (USD1,880).

## DISCUSSION

Surprisingly, contraindications to non-protein colloids in septic shocks was the top indication (*N* = 13, 27.1%) for prescription of HAS in this study. Non-proteins colloids such as dextran and hydroxyethyl starch solution has been associated with detrimental effects on renal function. Thus, non-proteins colloids are contraindicated in patient with moderate to severe renal impairments (Vincent 2007). One of the major focus in the treatment of septic shock is haemodynamic support which involves volume resuscitation (Rhodes *at al*. 2017). It can be achieved with either crystalloid or colloid solutions. Although most clinical trials have not shown either type of resuscitation fluid to be superior in septic shock, a meta-analysis by Delaney *et al.* (2011) and several other studies found out that albumin-containing solutions have been linked to a considerable drop in mortality when compared to other fluid resuscitation regimens (Finfer *et al.* 2004; Caironi *et al*. 2014; Delaney *et al*. 2011). Despite the finding, crystalloids are still recommended as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (Rhodes *et al*. 2017). This is mainly due to availability and cost. The use of colloids will come into place in septic shock when patient is unresponsive to fluid resuscitations with crystalloids.

Possible wastage due to uses for 'unproven indications' was 29 vials of HAS which accounts for only 20% of the total HAS usage in this study which is far lower than other published research all over the world. A study done by Tarín Remohí *et al*. (2000) reported that unproven use of HAS was 77% of the total cost of HAS usage in 22 public hospitals in Spain for a study duration of 5 months. Foroughinia and Mazraie (2017) reported that the additional expenses of HAS misuse were about 88.6% of the total cost in the studied year. Several other published research on HAS use also showed high percentage of unproven use of HAS as compared to our study (Farasatinasab *et al*. 2018; Farsad *et al.* 2016). The possible explanation behind this low percentage from this study is because since 2018, the Inpatient Pharmacy Unit of Tawau Hospital has introduced compulsory filling of Blood Plasma Product Request Form before supplying HAS to the ward. This form is created for the ease of filling in Fractionated Plasma Product Usage Record for HAS as per National Blood Centre (PDN) requirement. This form required signature by specialist for HAS to be supplied. If the indication for prescriptions of HAS is not listed in MOH Medicines Formulary or Paediatric Protocols for Malaysian Hospitals (for uses in paediatrics), the specialist will then require to fill in another form to obtain approval of use from the Director-General of MOH Malaysia. In a way, all these processes somehow controlled the prescribing of HAS.

Contributors for possible wastage of HAS in this study includes major surgery with serum albumin level of 20 g/L and above (55.2%), paracentesis with ascitic fluid removed of less than 5 L (24.1%) and hypoalbuminemia without justified comorbid or diagnosis (20.6%). The top contributors for wastage in this study is different from other published studies. Tanzi *et al*. (2003) reported most wastage is for the indications as follows: intradialytic blood pressure support, general indication of serum albumin values of < 20 g/L and acute respiratory distress syndrome. In separate study, Farasatinasab *et al*. (2018) reported that the indication of hypoalbuminemia was with the most numbers of HAS wastage. The research by Farasatinasab *et al.* (2018) was done in hospital in which it is also a referral centre for cancer surgery and a main cause of severe hypoalbuminemia might be a consequence of malnutrition due to cancer.

Top indications behind possible wastage of HAS also largely dependent on the service offered in the facility. This study was done in Hospital Tawau which is a public specialist hospital made up by multiple disciplines including general surgery, ophthalmology, internal medicine etc. This hospital does not offer services for cardiac surgery or organ transplantations. Hence, there is no prescriptions of HAS for any of these two indications.

The main indications that cause possible wastage of HAS in this study is major surgery. In this study, five out of nine prescriptions for major surgery were found to be of 'unproven indications' due to pre-HAS initiation serum albumin level of 20 g/L and above. It is typical for patients undergoing major surgery to see a decrease in serum albumin levels, primarily as a result of extravascular albumin leakage brought on by a systemic inflammatory response (Mahkovic-Hergouth and Kompan 2007). It has been established that a post-operative drop in serum albumin is an early indicator of unfavourable outcomes, such as post-surgery problems and longer hospital stays (Hübner *et al.* 2016; Labgaa *et al.* 2007). However, the use of albumin in the immediate post-operative period is never advised for any other type of operation (Liumbruno *et al.* 2009)

Paracentesis became second top contributors (24.1%) for possible HAS wastage. Four out of 11 prescriptions had ascitic fluid removed of less than 5 L. According to Peltekian *et al*. (1997), the systemic and renal hemodynamics are unaffected 48 h following a single large volume 5 L paracentesis without albumin replacement. The American Association for the Study of Liver Diseases (AASLD) practice guideline by Runyon (2013) recommends supplementing 6 g–8 g of HAS per litre of fluid when more than 5 L of ascitic fluid are removed post-paracentesis. This is done in order to lessen the adverse effects of significant

intravascular volume changes, such as electrolyte imbalances and serum creatinine levels (Shah and Fields 2017).

Similar to other studies, hypoalbuminemia without justified comorbid or diagnosis had also contributed to HAS wastage in this study (Tanzi *et al*. 2003); Farasatinasab *et al*. 2018). Three prescriptions for hypoalbuminemia had used six vials of HAS. The first prescription is for hypoalbuminemia in liver cirrhosis secondary to autoimmune disease. Albumin may play a dual role in liver failure. The ability of albumin to bind to excess plasma bilirubin may make it useful for the treatment of hyperbilirubinemia; other than that, albumin may also able to maintain plasma oncotic pressure (Farasatinasab *et al.* 2018). However, there is still lack of consensus on the role of albumin in the treatment of hypoalbuminemia due to liver failure (Liumbruno *et al.* 2009). The second prescription was for anasarca secondary to hypoalbuminemia. HAS use for the treatment of oedema remain controversial. Albumin serves as the primary regulator of fluid transport across bodily compartments and the primary determinant of plasma oncotic pressure. (Fanali *et al*. 2012). According to the Starling model, hypoalbuminaemia is frequently linked to increased inflammation and vascular permeability and the development of oedema, particularly in cases of severe malnutrition (Gonzales *et al.* 2022). However, the benefits of albumin in removing fluid from the interstitial to intravascular space are only momentary; shortly after albumin delivery, it seeps back from the capillary into the interstitium and may exacerbate the oedema (Margarson and Soni 1998).

Unproven uses of HAS had led to government funding wastage for the procurement or production of HAS. Strategies should be planned to prevent wastage due to unproven drug uses in the future.

### Limitations

As patient's medical records in Hospital Tawau were kept manually, the sampling done was convenience sampling as we can only include prescriptions of HAS from medical records traceable by the Medical Record Unit. This limitation also limited our sample size.

This study is only a small-scale study. Sampling time frame should be widened in the future to increase sample size in order to increase the significance. Multicentre studies can also be done as a mean of increasing the sample size in the future.

## CONCLUSION

The percentage of possible wastage of HAS reflected in this study was not as high as other published research done in other countries, mainly due additional steps required for prescribing HAS in our facility (filling in the Blood Plasma Product Request Form) and also the need to obtain approval from the Director-General of MOH Malaysia if it was prescribed for other than the approved indications, in all other MOH facilities.

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