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Original Article

Human albumin solution utilization patterns prior and during COVID-19 pandemic in United Arab Emirates: Time to develop and implement national guidelines on prescription and utilization

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Abstract

The human albumin solution (HAS) has limited but important indications in clinical practices. However, the inappropriate use of HAS can be costly. Thus, it is imperative to establish a practical protocol to use albumin products and rationalize its usage. The aim of this study was to identify HAS utilization patterns in a multi-specialty private hospital in Dubai, United Arab Emirates (UAE), before and during the COVID-19 pandemic. In addition, the objective was to demonstrate the importance of reconsidering the prescribing strategies for HAS administration. All data on 20% HAS administration in Mediclinic Welcare Hospital (MWEL) were retrieved between January 2019 and May 2021, including the total quantities administered and data on primary diagnosis. A total of 579 patient admissions with various diagnoses were included in this study. Our data suggested that the percentage of clinically indicated 20% HAS administrations decreased from 13.0% in the pre-COVID-19 phase to 1.5% in the COVID-19 phase ($p<0.001$). An increase in the administration of 20% HAS not backed by agreed clinical evidence followed the increase in new number of COVID-19 cases in the UAE. Our study suggests a large proportion of administered HAS, that drastically increased during COVID-19 with lack of evidence of its benefit. This study can be helpful to refine the institutional guidelines of HAS use, and frequent audits and interactive educational interventions are recommended to tackle this issue. In turn, the refinement of HAS administration guidelines could help to reduce the unjustified cost of inappropriate HAS use.

Keywords: Human albumin, drug utilization, guideline, clinical pharmacy, healthcare

Introduction

In the context of intensive care, fluid resuscitation can be considered as a central and a commonly used intervention in the patient management [1-3]. Human albumin solution (HAS) is among these fluids that is used ubiquitously in the practice of intensive care [4]. In general, HAS has been reported to have a good safety profile in conjunction with rare reports of adverse effects [5, 6]. However, the cost issues, the limited availability and the complexity of manufacture appear as the major limitation of HAS utility, besides the limited body of literature to guide its use [6, 7]. Cost-to-benefit and risk-to-benefit ratios should be considered in the

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guidelines of HAS use due to the costly price of HAS compared to crystalloid solutions [8]. Potential risks of HAS administration range from mild reactions (including hypotension, fever, urticaria, etc.) to severe anaphylactic reaction, albeit with a rare incidence [6, 9]. Thus, the careful consideration and revision of practice guidelines in relation to use of HAS can reduce the unnecessary use of such a high-cost medication [10, 11].

The clinical indication for HAS is based on its role as a plasma expander [12]. Appropriate indications for HAS use include spontaneous bacterial peritonitis, paracentesis, and therapeutic plasmapheresis [7]. The controversial use of HAS administration due to lack of scientific evidence of its benefit includes: long-term treatment of ascites, nephrotic syndrome, pancreatitis, abdominal surgery, acute distress respiratory syndrome, cerebral ischemia, and enteric diseases [13, 14].

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has put enormous strain on health and social systems and resources worldwide [15]. A fraction of COVID-19 patients requires intensive care, and several drugs have been prescribed to manage them, but the scientific evidence is inconclusive regarding the benefits of HAS [16]. The aim of this study was to identify the unitarization pattern of HAS at Mediclinic Welcare Hospital (MWEL) in Dubai, UAE before and during the COVID-19 pandemic. It also aimed to identify the impact of appropriate interventions regarding this expensive drug and the need to revisit the prescribing strategies and guideline implementation for this solution.

Methods

Study design and data collection

The current study was a retrospective observational study evaluating utilization of 20% HAS among patients admitted at Mediclinic Welcare Hospital (MWEL), which is one of the most established healthcare facilities in Dubai, UAE (https://www.mediclinic.ae/en/welcare-hospital/home.html). Eligibility criteria were as follows: patients who were admitted to MWEL and received 20% HAS from January 1st, 2019 to May 31st, 2021. The sole exclusion criterion was the use of other forms of HAS (e.g., 5% HAS). The data were retrieved from MWEL hospital information system (HIS).

The study period was divided into two phases: 1) January 1st, 2019 - January 31st, 2020 defined as the pre-COVID-19 phase, and 2) February 1st, 2020 - May 31st, 2021 defined as the COVID-19 phase [17]. Statistics on new cases of COVID-19 recorded in the UAE was retrieved from "Our World in Data" [18].

Indications for 20% HAS

Regarding the approach to identification of appropriate use of 20% HAS, the current study relied on the guidelines of "albumin therapy in clinical practice" as issued by Roberts *et al.*, Caraceni *et al.* and Mendez *et al.* [12, 19, 20]. Specifically, the administration of 20% HAS was considered appropriate for the following clinical indications based on the patients' primary diagnosis: (1) advanced liver disease (cirrhosis), (2) ascites, (3) hepatorenal syndrome, (4) post-paracentesis circulatory dysfunction, (5) acute renal failure induced by spontaneous bacterial peritonitis, and (6) conditions characterized by extreme effective hypovolemia [12, 19, 20]. The diagnosis of COVID-19 was not considered as an indication for the administration of 20% HAS as evidenced by recent literature [21, 22].

Repeated administration of 20% HAS for the same patient and the same diagnosis was considered as a single entry, whereas repeated administration for the same patient for two or more different diagnoses at different admission episodes were considered as separate entries.

Statistical analysis

The statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Potential association between categorical variables was evaluated through chi-squared test (χ^2). Temporal trend was assessed using linear-by-linear test for association (LBL). The $p<0.050$ was considered as the cut-off for statistical significance.

Results

Characteristisc of the study sample

A total of 579 patient admissions with unique diagnoses were included in the study. The administration of 20% HAS was found in a total of 123 admitted cases, with a total of 3356 vials during the pre-COVID-19 phase. In the COVID-19 phase, a total of 456 admissions were included in the study, with a total of 19996 vials of 20% HAS being administered to the patients.

We found that the percentage of clinically indicated 20% HAS administration decreased from 13.0% in the pre-COVID-19 phase to only 1.5% in the COVID-19 phase (16/123 vs. 7/456; $p<0.001$, χ^2 test, **Figure 1**). Overall, the most common primary diagnosis associated with 20% HAS administration was COVID-19 (n=259, 44.7%), followed by sepsis (n=60, 10.4%), respiratory conditions other than COVID-19 (n=51, 8.8%), and gastrointestinal conditions other than ascites or peritonitis (n=32, 5.5%, **Table 1**).

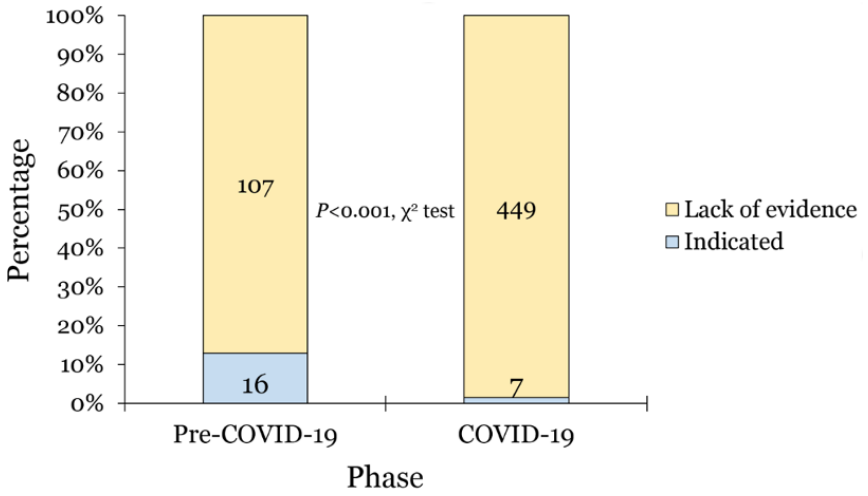

Figure 1. The administration of 20% human albumin solution in the two phases of the study stratified by the presence of a clinical indication or lack thereof.

Table 1. The diagnosis of the patients who were administered with 20% human albumin solution in the two phases of the study.

Category of patient diagnosis	Total n (%)	Pre-COVID-19 phase n (%)	COVID-19 phase n (%)
COVID-19	259 (44.7)	0 (0)	259 (56.8)
Sepsis	60 (10.4)	23 (18.7)	37 (8.1)
Respiratory disease	51 (8.8)	16 (13)	35 (7.7)
Gastrointestinal disease	32 (5.5)	15 (12.2)	17 (3.7)
Cardiac disease	22 (3.8)	10 (8.1)	12 (2.6)
Urinary tract infection	19 (3.3)	6 (4.9)	13 (2.9)
Obstetric or gynaecologic	15 (2.6)	3 (2.4)	12 (2.6)
Renal disease	15 (2.6)	6 (4.9)	9 (2)
Cancer	11 (1.9)	3 (2.4)	8 (1.8)
Pneumonia	11 (1.9)	4 (3.3)	7 (1.5)
Skin disease	10 (1.7)	6 (4.9)	4 (0.9)
Fever	9 (1.6)	0 (0)	9 (2)
Others [a]	9 (1.6)	7 (5.7)	2 (0.4)
Peritonitis	9 (1.6)	5 (4.1)	4 (0.9)
Viral disease	9 (1.6)	0 (0)	9 (2)
Multi-organ disease	8 (1.4)	2 (1.6)	6 (1.3)
Hepatic disease	7 (1.2)	6 (4.9)	1 (0.2)
Endocrine disease	6 (1)	2 (1.6)	4 (0.9)
Orthopedic conditions	6 (1)	1 (0.8)	5 (1.1)
Ascites	5 (0.9)	4 (3.3)	1 (0.2)
Central nervous system disease [5]	5 (0.9)	3 (2.4)	2 (0.4)
Post plastic surgery	1 (0.2)	1 (0.8)	0 (0)

[a] Included cases not yet diagnosed, inguinal hernia; osteoarthritis; postprocedural fever and hemothorax

Temporal trends of inappropriate use of 20% HAS over the study period

In order to assess the time trend of inappropriate use of 20% HAS over time, we divided the study period into five quantiles as follows: 01-01-2019 to 30-06-2019; 01-07-2019 to 31-12-2019; 01-01-2020 to 30-06-2020; 01-07-2020 to 31-12-2020; and 01-01-2021 to 31-05-2021. The percentage of administration of 20% HAS with lack of proper indication increased from 85.5% during 01-01-2019 to 30-06-2019, to 86.3% during 01-07-2019 to 31-12-2019, 95.2% during 01-01-2020 to 30-06-2020, 98.4% during 01-07-2020 to 31-12-2020, and reached 100% during 01-01-2021 to 31-05-2021 (p<0.001, LBL, **Figure 2**).

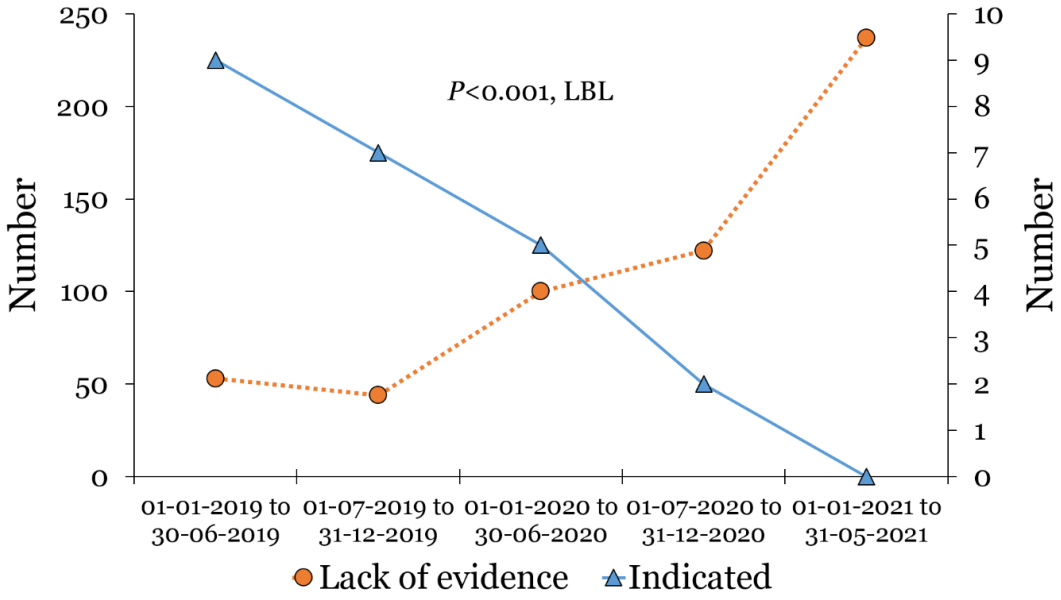

Figure 2. Temporal trend of inappropriate use of 20% human albumin solution over the study period. LBL: Linear-by-linear test for association. Number of unique patients who received 20% HAS with lack of proper evidence are plotted on the Y-axis, while the number of unique patients who received clinically indicated 20% HAS are plotted on the secondary Y-axis.

An increase in the number of HAS use with lack of evidence followed the new number of COVID-19 cases in the UAE

To evaluate the effect of COVID-19 on the inappropriate use of 20% HAS, we retrieved data on new cases of COVID-19 in the country from Our World in Data (https://ourworldindata.org/coronavirus/country/united-arab-emirates). Stratified per month, the number of unique patients that received HAS without proper evidence followed by the number of new COVID-19 cases in the UAE as shown in (**Figure 3**).

A significant increase in the total number of HAS vials dispended during COVID-19 phase

The total number of 20% HAS vials administered in the pre-COVID-19 phase that were clinically indicated was 319 compared to only 99 vials in the COVID-19 phase, while the number of vials administered with absence of clear evidence of indication was 3037 in the pre-COVID-19 phase which ascended to 19897 vials in the COVID-19 phase (**Figure 4**). The increase in quantity of 20% HAS vials administered with lack of evidence over the two study phases was statistically significant (p<0.001, χ^2, **Figure 4**).

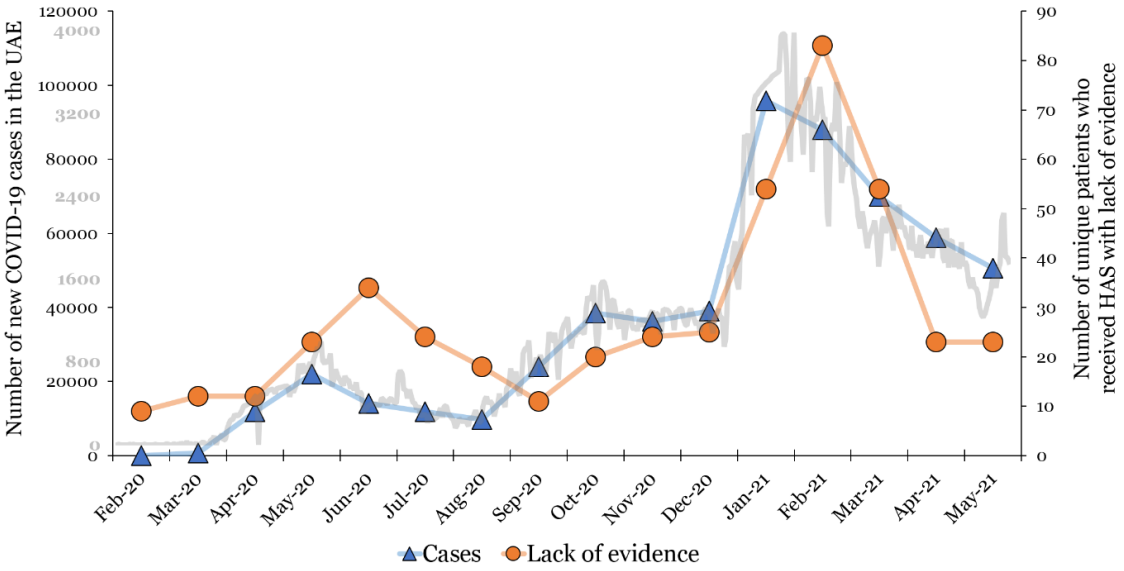

Figure 3. The number of unique patients who received human albumin solution (HAS) with lack of evidence compared to new number of COVID-19 cases in the United Arab Emirates UAE (daily (shown in grey color) and stratified per month). The number of monthly COVID-19 cases in UAE are plotted on the left Y-axis with numbers in black color; the number of daily cases COVID-19 cases in UAE are plotted on the left Y-axis with numbers in grey color; the number of unique patients who received 20% HAS with lack of proper evidence are plotted on the right Y-axis (secondary axis). Data on new cases of COVID-19 in the UAE were retrieved from Our World in Data [18], while the data on 20% HAS use represented those from Mediclinic Welcare Hospital (MWEL).

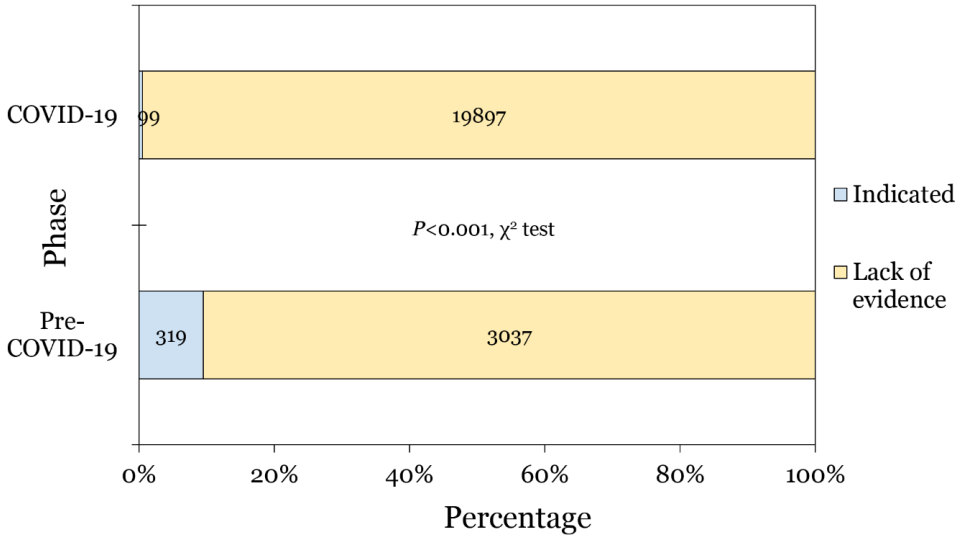

Figure 4. The total quantity of 20% human albumin solution vials administered in the two phases of the study stratified by the presence of a clinical indication or lack thereof.

Discussion

Human albumin is a high cost colloidal blood derivative preparation [23]. There are often difficulties in its manufacturing and supply, yet it is frequently considered for clinical use in the management of critically ill patients despite the lack of scientific evidence justifying its use in a plethora of diagnoses [24-26]. Therefore, the inappropriate use of HAS can consume a significant part of hospital budgets [27]. The role of clinical pharmacist can be prominent in the introduction and implementation of evidence-based guidelines that can result in significant reduction of inappropriate albumin use and costs without compromising clinical outcomes [11].

Findings from several previous publication have shown the scope of unsuitable use of HAS and the results of the current study were in line with literature. Specifically, we found that only 4% of the cases included in this study over a period of about two and a half years were based on agreed clinical indications. However, the results of this study also showed an increasing trend of using HAS in the absence of clinical indication. Unjustified HAS administration based on controversial antiquated recommendations is not unique to this study and is commonplace worldwide as shown by various studies. For example, a study from Spain showed that 77% costs of albumin use were related to its improper use [28]. Another study from Belgium highlighted the importance of internally developed criteria to guide the indications for HAS use [29]. A more recent study from Italy showed that 41% of albumin orders were based on occasionally appropriate indication, and 18% had inappropriate indications compared to slightly more than a third of orders that had appropriate indications [30]. Likewise, a recent study from the US showed that albumin was used for an appropriate indication in 68% of the patients, which underline that such practice is commonplace worldwide [31].

The results of the current study can be viewed as an initial warning signal that warrants a revision for the current practice of HAS administration. This can be followed by guideline implementation and order-sheet consideration to minimize the improper use of HAS. Such an approach was shown by Laki *et al*, in a recent study from Iran [32]. The previous study was conducted over three phases spanning 45 days, and the frequency of inappropriate albumin orders reduced significantly from 58% to 27% in the last phase of the study. This decrease can be attributed to proper baseline evaluation of the practices, which was done in this study, followed by comprehensive implementation of improved HAS administration guideline, frequent audits, feedback and interactive educational approaches. The annual cost savings through clinical pharmacist intervention was shown in a recent study by Dastan *et al*, by saving of more than $200,000 [11]. Similarly, the clinical pharmacist interventions in two studies from the US, which targeted inappropriate albumin in the ICU, showed an annual cost-savings of $355,393 in the ICUs, and $341,930 in general ward patients in a 755-bed university medical center. These findings highlight the central role of such strategy [33, 34].

Another important finding of this study was the aggravated inappropriate use of HAS amid the COVID-19 pandemic. Specifically, the administration of 20% HAS lacking proper evidence was noticed among more than 95% of the cases during COVID-19 pandemic [21, 35].

Additionally, we discovered that sepsis was the second most common diagnosis associated with 20% HAS administration. Despite the presence of few studies and clinical trials showing an improvement following albumin administration in sepsis [36-38], its use is still controversial since the benefit of administration of HAS in sepsis has not proven yet in large-scale randomized control trials [4]. Other conditions in which 20% HAS was used despite the lack of proper scientific evidence included respiratory, gastrointestinal and cardiac disease, which should be tackled in the implementation of more proper guidelines for judicious use of HAS in the future [13, 39].

Study limitations

There are some limitations of this study. The study included relatively small sample size considering the study design which involved one institution rather than being a multi-center study. Therefore, generalizability of our results can be limited. Certain diagnoses can be included in the “appropriate use of HAS” group; however, we believe that such issue would minimally affect the conclusions of the study based on the adoption of the most recent guidelines of HAS utilization [12, 13, 19, 20, 40].

Conclusion

The direct role of HAS for a range of applications frequently observed in the critically ill and other conditions remains controversial. The current study can be viewed as a baseline evaluation of the current practice of HAS administration. Our results pointed to the importance of implementing comprehensive evidence-based guidelines for 20% HAS administration. It is recommended that this approach is followed by frequent audits and interactive educational

approaches, which can help to improve the cost-to-benefit value of HAS in patient management. Such interventional measures involving a stricter guideline with continuous educational and administrative interventions can be helpful in cost saving. Hospitals should also consider clinical pharmacists as an important component of a multidisciplinary team and improvement plan to promote optimal treatment.

Ethics approval

This study was conducted according to the declaration of Helsinki guidelines. Ethical permission was issued by the Research and Ethics Committee at MWEL (No. MCME.ADM.224.0, issued on 30/06/2021). In addition, the study was approved by Dubai Scientific and Research Ethics Committee (DSREC) at Dubai Health Authority (DHA) (Ref. No. DSREC-08/2021_6, issued on 13/09/2021).

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Conflict of interest

The authors declare that they have no competing interests.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding authors on request.

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