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ORIGINAL ARTICLE

Stress ulcer prophylaxis for critically ill children: routine use needs to be re-examined☆

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Abstract
Introduction: Stress ulcer prophylaxis (SUP) is commonly used in Paediatric Intensive Care Units (PICUs). However, strong evidence for this practice is lacking and there is a dire need for paediatric randomized controlled trials (RCTs). Our aim was to assess the usefulness of SUP with omeprazole in critically ill children.
Patients and methods: We conducted a randomized, controlled open-label trial, including 144 children admitted into a PICU with a paediatric Sequential Organ Failure Assessment (pSOFA) score of less than 16. We randomly allocated patients to SUP with omeprazole or no SUP. The primary outcome was development of upper gastrointestinal bleeding or nosocomial infection.
Results: The incidence of gastrointestinal bleeding was 27.1%, but clinically significant bleeding developed in only 5.6% of patients. We did not find a significant difference in the incidence of bleeding between the prophylaxis and control groups (27.8% *vs* 26.4%; *P* = .85). We also did not find a significant difference between the groups in the incidence of ventilator-associated pneumonia (VAP) (9.6% *vs* 8.3%; *P* = .77). The incidence of central line-associated bloodstream infection (CLABSI) was higher in the prophylaxis group compared to the control group (30.6% *vs* 12.5%; *P* = .014). None of the patients developed *Clostridium difficile*-associated diarrhoea. We did not find significant differences in mortality, length of PICU stay or duration of mechanical ventilation. Mechanical ventilation was an independent predictor of bleeding (OR, 6.4; 95%CI, 2.73–14.9).
Conclusion: In PICU patients with mild to moderate organ dysfunction, omeprazole does not seem to be useful for prevention of gastrointestinal bleeding while at the same time increasing the risk of CLABSI. Thus, we recommend restricting SUP to mechanically ventilated children.

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PALABRAS CLAVE
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Profilaxis de las úlceras de estrés en niños críticos: necesidad de replantear su uso rutinario

Resumen
Introducción: La profilaxis de las úlceras por estrés (PUE) se utiliza comúnmente en las Unidades de Cuidados Intensivos Pediátricos (PICU). Sin embargo, no hay pruebas sólidas que apoyen esta práctica y se necesitan urgentemente ensayos clínicos controlados aleatorios (ECCA) pediátricos. Nuestro objetivo era evaluar el valor de la PUE con omeprazol en pacientes críticos pediátricos.
Pacientes y métodos: Ensayo controlado aleatorio abierto, con inclusión de 144 niños ingresados en la UCI con una puntuación en la escala pediátrica de evaluación del fallo multiorgánico secuencial (pSOFA) inferior a 16. Los pacientes fueron asignados al azar a recibir omeprazol para el PUE o a no recibir profilaxis. La variable de resultado principal fue el desarrollo de hemorragia digestiva alta o infecciones nosocomiales.
Resultados: La frecuencia de hemorragia gastrointestinal fue del 27.1%, aunque solo desarrollaron hemorragia clínicamente significativa el 5,6% de los pacientes. No se observaron diferencias significativas en la incidencia de hemorragia entre los grupos de profilaxis y de control (27,8% *vs*. 26,4%; *P* = ,85). Tampoco surgieron diferencias significativas en la incidencia de la neumonía asociada al ventilador (NAV) entre ambos grupos (9,6% *vs*. 8,3%; *P* = ,77). La incidencia de bacteriemia asociada a catéter venoso central (BACVC) fue mayor en el grupo de profilaxis en comparación con el grupo de control (30,6% *vs*. 12,5%; *P* = ,014). Ningún paciente desarrolló diarrea por *Clostridium difficile*. No se encontraron diferencias significativas en la tasa de mortalidad, la duración de la estancia en la UCIP o la duración de la ventilación mecánica. La ventilación mecánica fue un predictor independiente de hemorragia (OR, 6,4; IC 95%: 2,73–14,9).
Conclusión: En pacientes ingresados en la UCIP con disfunción orgánica de leve a moderada, el uso de omeprazol parece ineficaz para la prevención del sangrado gastrointestinal a la vez que aumenta el riesgo de BACVC. Se recomienda restringir el PUE a niños sometidos a ventilación mecánica.

Introduction

Upper gastrointestinal bleeding is common in critically ill children, with an incidence of approximately 10% that increases to approximately 51% with mechanical ventilation. The risk factors include coagulopathy, organ failure, respiratory failure, high-pressure ventilator settings, and a high Paediatric Risk of Mortality (PRISM) score of 10 or greater.[1,2] Some of these episodes are clinically significant, causing shock or requiring blood transfusion.

Although not fully understood, the pathophysiology of stress ulcers is thought to be different from that of peptic ulcers, involving factors such as mucosal ischemia and reperfusion injury. Acid-suppressive drugs have the potential to prevent stress ulcers, and an intragastric pH of more than 4 was been shown to be protective.[3] Consequently, stress ulcer prophylaxis (SUP) has gained popularity in adult and paediatric intensive care units, with mechanical ventilation being the most frequent indication. However, the routine use of SUP in all critically ill patients is also very common.[4,5]

Several agents have been used for SUP, including proton-pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs) and sucralfate, with the former exhibiting the greatest efficacy in adult studies.[6] Omeprazole is the PPI most frequently used for SUP, although this is not one of the licensed indications for this drug.

Stress ulcer prophylaxis is not without risk: the increase of gastric pH achieved by PPIs or H2RAs may favour gastric colonization by pathogens. Subsequent regurgitation or retrograde colonization to the pharynx and trachea may increase the risk of ventilator-associated pneumonia (VAP).[7,8] In addition, it has been proposed that the loss of the bacteriostatic effect of the acidic gastric juice, combined with the frequent use of antibiotics in critically ill patients could increase the risk of *Clostridium difficile*-associated diarrhoea.[9]

The previous literature on the usefulness of SUP in critically ill children is limited, and data from randomized controlled trials (RCTs) are scarce. Therefore, the aim of our trial was to evaluate the safety and efficacy of SUP with omeprazole, the agent used most commonly for SUP in critically ill children.

Patients and methods

We conducted a randomized controlled open-label trial in the paediatric intensive care unit (PICU) of Menoufia Uni-

versity Hospital between January 2019 and September 2020. The study protocol was approved by the Medical Research Ethics Committee of the Menoufia School of Medicine, and we obtained written informed consent from the parents of participants.

Critically ill children admitted to the PICU were eligible for the study. The exclusion criteria included age less than 1 month or greater than 16 years; presence of upper gastrointestinal bleeding at the time of PICU admission; underlying haemorrhagic disorders (eg, haemophilia or purpura) and administration of SUP before PICU admission. We also excluded patients with paediatric Sequential Organ Failure Assessment (pSOFA) scores of 16 or greater, as there is evidence suggesting that they are at higher risk of gastrointestinal bleeding and therefore all of them received SUP.

At admission, patients were randomly assigned to the prophylaxis group or the control group. We used block randomization to achieve a homogeneous allocation of participants in the 2 study groups using the website https://www.graphpad.com/quickcalcs/randMenu/.

We calculated that a sample size of 72 patients in each group would offer a power of 84% with a type I error probability (alpha level) of 0.05 and an expected proportion of gastrointestinal bleeding of 1/2.5.

Patients in the prophylaxis group received omeprazole within 4 h of PICU admission at a dose of 1 mg/kg/day delivered intravenously. Patients in the control group were not given anything for SUP. Participants were not blinded to treatment allocation.

If a patient in the control group developed gastrointestinal bleeding during the PICU stay, omeprazole was given to treat it. If a patient in the prophylaxis group developed gastrointestinal bleeding while taking omeprazole, the dose was increased up to 3.5 mg/kg/day.

Treatment with omeprazole was discontinued when patients improved, as evinced by no longer needing vasoactive medications, weaning to low levels of ventilatory support and progression of enteral feeding to two thirds of the required energy intake.

Patients underwent a thorough evaluation, and the diagnosis of sepsis was based on the criteria of the International Paediatric Sepsis Consensus Conference.[10] We assessed the severity of illness severity at admission by means of the pSOFA score (possible value range, 0–24 points)[11] at the end of the first 24 h. The follow-up for each patient ended at the discharge from the PICU, and the primary outcome was the development of upper gastrointestinal bleeding during SUP or of infections such as hospital-acquired pneumonia (HAP), VAP, central line-associated bloodstream infection (CLABSI), and *C. difficile*-associated diarrhoea. The secondary outcomes were PICU mortality, length of PICU stay, and duration of mechanical ventilation.

Overt upper gastrointestinal bleeding was defined as the presence of haematemesis, melena or flecks of blood in nasogastric aspirates (coffee ground vomitus). Clinically significant gastrointestinal bleeding was defined as bleeding causing development or worsening of shock or requiring non-elective transfusion of packed red blood cells.

We defined VAP according to the criteria established by the Centers for Disease Control and Prevention (CDC)[12] as pneumonia occurring more than 2 calendar days after initiation of invasive mechanical ventilation and the ventilator being in place on the date of the event or the day before. We considered pneumonia that developed 2 days after hospital admission in the absence of endotracheal intubation healthcare-associated pneumonia (HAP).

We defined CLABSI as presence of a primary bloodstream infection in patients that had a central line within the 48-h period before the development of the infection and was not bloodstream-related to an infection at another site.[13] We diagnosed *C. difficile*-associated diarrhoea by means of stool toxin testing.

Statistical methods

We have expressed qualitative data as absolute frequencies and percentages. We expressed non-normally distributed quantitative data as median and interquartile range. The association between qualitative variables was assessed by means of the chi square test or the Fisher exact test. We used the Mann-Whitney *U* test to compare two non-normally distributed quantitative variables. Variables found to differ significantly in patients that developd bleeding *versus* patients that did not using these tests were tested further through univariate logistic regression analysis. We used multivariate logistic regression analysis to adjust for confounding variables. Statistical significance was defined as a 2-tailed *P*-value of less than .05. The data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, USA).

Results

Sample characteristics

We recruited 144 patients: 72 allocated to SUP with omeprazole (prophylaxis group) and 72 allocated to no SUP (control group).

We matched the patients included in both groups (Table 1). We did not find significant differences between groups in the frequency of complex chronic conditions, sepsis, coagulopathy, invasive mechanical ventilation or steroid administration. There were also no significant differences in the pSOFA scores. Most patients had been admitted due to respiratory and neurological disorders. Only 2 patients were admitted for surgical diseases (1 in each group). The sample did not include any patients with COVID-19, since they were not allowed to be treated in our hospital. The median duration of SUP was 6 days.

A total of 8 patients in the sample received steroids, 3 of them in the control group.

Efficacy of stress ulcer prophylaxis

The incidence of overt upper gastrointestinal bleeding was 27.1%, although only 5.6% of patients developed clinically significant bleeding. We found no significant differences between the prophylaxis and the control groups in the frequency of gastrointestinal bleeding or blood transfusion (Table 2).

Table 1 Demographic, clinical, and laboratory characteristics of the study sample.

Variable	Prophylaxis group ($n = 72$)	Control group ($n = 72$)	Total sample ($N = 144$)	P
Age, months	24 (7–106.5)	24 (6–72)	24 (6–84)	.87
Male sex	34 (47.2%)	40 (55.6%)	74 (51.4%)	.4
Weight, kg	11.5 (7.1–21.1)	10.9 (6–20.8)	11 (7–20.4)	.57
Malnutrition	20 (27.8%)	25 (34.7%)	45 (31.3%)	.37
Category on admission				
Sepsis	16 (22.2%)	14 (19.4%)	30 (20.8%)	.46
Non-infectious SIRS	17 (23.6%)	12 (16.7%)	29 (20.1%)	
Non-SIRS	39 (54.2%)	46 (63.9%)	85 (59%)	
Complex chronic condition [a]	28 (38.9%)	33 (45.8%)	61 (42.4%)	.39
Primary reason for PICU admission				
Respiratory	24 (33.3%)	25 (34.7%)	49 (34%)	.84
Neurologic	24 (33.3%)	20 (27.8%)	44 (30.6%)	
Cardiac	8 (11.1%)	12 (16.7%)	20 (13.9%)	
Metabolic	5 (6.9%)	5 (6.9%)	10 (6.9%)	
Renal	2 (2.8%)	1 (1.4%)	3 (2.1%)	
Gastrointestinal	2 (2.8%)	1 (1.4%)	3 (2.1%)	
Infectious	3 (4.2%)	4 (5.6%)	7 (4.9%)	
Other [b]	4 (5.6%)	4 (5.6%)	8 (5.6%)	
Steroid therapy [c]	5 (6.9%)	3 (4.2%)	8 (5.6%)	.72
pSOFA	4 (2–5)	4 (2–5)	4 (2–5)	.94
Invasive MV	28 (38.9%)	23 (31.9%)	51 (35.4%)	.38
Coagulopathy	13 (18.1%)	10 (13.9%)	23 (16%)	.49
Duration of SUP, days	6 (4–10.8)	NA	NA	NA
CRP, mg/dL	5 (4–24.8)	12 (5–48)	7.2 (4–44.5)	.14
Haemoglobin, g/dL	10.4 (9.3–11.9)	10.6 (9.3–11.7)	10 (9.3–11.9)	.79
WBC, 1000/μL	10.85 (8.03–16.11)	10.55 (5.5–14.78)	10.65 (7.22–15.3)	.28
Platelets, 1000/μL	268 (191.8–374.3)	321.5 (191.5–451)	298 (191.5–398.8)	.19
Creatinine, mg/dL	0.4 (0.3–0.6)	0.4 (0.3–0.7)	0.4 (0.3–0.62)	.65
ALT, U/L	23 (15.5–41.5)	27 (17–49.5)	25 (16.8–45.3)	.52
Albumin, g/dL	3.7 (2.9–4)	3.8 (3.3–4)	3.7 (3.1–4.2)	.46

Data is expressed as median (interquartile range); or absolute frequency (percentage).
ALT, alanine aminotransferase; CRP, C-reactive protein; MV, mechanical ventilation; NA, not applicable; PICU, paediatric intensive care unit; pSOFA, paediatric Sequential Organ Failure Assessment score; SIRS, systemic inflammatory response syndrome; SUP, stress ulcer prophylaxis; WBC, white blood cell count.
[a] Includes cancer, cardiomyopathies, cerebral palsy, epilepsy, cystic fibrosis, immunodeficiencies and other.
[b] Includes trauma, surgical, toxicological, allergic, connective tissue and vascular disorders.
[c] Steroid administration does not include dexamethasone given for 24 h to prevent post-extubation stridor.

Safety of stress ulcer prophylaxis

As can be seen in Table 2, there were no significant differences in the incidence of VAP or HAP between the prophylaxis and control groups. None of the patients transferred to the PICU from the paediatric ward developed HAP within 48 h of PICU admission.

The incidence of CLABSI was significantly higher in the prophylaxis group. None of the patients developed *C. difficile*-associated diarrhoea.

We did not find significant differences in mortality, length of PICU stay (in survivors), length of hospital stay or duration of mechanical ventilation duration between the prophylaxis and control groups.

Risk factors for upper gastrointestinal bleeding

The median pSOFA score, incidence of sepsis, and proportion of patients requiring mechanical ventilation were significantly higher in the group of patients that developed gastrointestinal bleeding (Table 3), associations confirmed by univariate logistic regression analysis. In the multivariate analysis, only mechanical ventilation remained an independent predictor of bleeding (Table 4).

Discussion

Stress ulcer prophylaxis is a common intervention in critically ill children, and its use varies considerably between PICUs, which reflects the uncertainty about its risks and benefits.[14]

Ours is one of the few paediatric RCTs that addresses this issue, and the only one to our knowledge assessing the usefulness of omeprazole.[15]

In our study, we found that SUP with omeprazole failed to reduce the incidence of gastrointestinal bleeding, while a systematic review that pooled data from 2 small paediatric RCTs found that SUP was significan-

Table 2 Efficacy and safety of stress ulcer prophylaxis.

Variable	Prophylaxis group ($n = 72$)	Control group ($n = 72$)	Total sample ($N = 144$)	P
GI bleeding	20 (27.8%)	19 (26.4%)	39 (27.1%)	.85
GI bleeding type				
Clinically significant	5 (6.9%)	3 (2.8%)	8 (5.6%)	.54
Not clinically significant	15 (20.8%)	16 (22.2%)	31 (21.5%)	
No bleeding	52 (72.2%)	53 (73.6%)	105 (72.9%)	
HAP	8 (11.1%)	8 (11.1%)	16 (11.1%)	1
VAP	7 (9.6%)	6 (8.3%)	13 (9%)	.77
CLABSI	22 (30.6%)	9 (12.5%)	31 (21.5%)	.014*
C. difficile-diarrhoea	0 (0%)	0 (0%)	0 (0%)	NA
ARDS	4 (5.6%)	1 (1.4%)	5 (3.5%)	.37
Blood transfusion	25 (34.7%)	21 (29.2%)	46 (31.9%)	.47
Mechanical ventilation duration, days	0 (0–3)	0 (0–3)	3 (0–3)	.64
PICU Mortality	9 (12.5%)	10 (13.9%)	19 (13.2%)	.81
PICU stay, days	6 (4–13)	6 (4–10)	6 (4–13)	.61
Hospital stay, days	9 (6–15)	8 (6–14)	9 (6–14.8)	.39

Data expressed as median (interquartile range) or absolute frequency (percentage).
ARDS, acute respiratory distress syndrome; CLABSI, central line-associated bloodstream infection; GI, gastrointestinal; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.
* Statistically significant.

Table 3 Characteristics of patients with and without gastrointestinal bleeding.

Variable	With GI bleeding ($n = 39$)	Without GI bleeding ($n = 105$)	P
Age, months	18 (9–102)	24 (5.3–84)	.84
Male sex	19 (48.7%)	55 (52.4%)	.70
Weight, kg	10.5 (6.5–20.5)	11 (7–21.1)	.76
Category on admission			
Non-SIRS	17 (43.6%)	68 (64.8%)	.041*
Non-infectious SIRS	9 (23.1%)	20 (19%)	
Sepsis	13 (33.3%)	17 (16.2%)	
Primary reason for PICU admission			
Respiratory	13 (33.3%)	36 (34.3%)	
Neurologic	11 (28.2%)	33 (31.4%)	
Cardiac	5 (12.8%)	15 (14.3%)	
Metabolic	3 (7.7%)	7 (6.7%)	.27
Gastrointestinal	0 (0%)	3 (2.9%)	
Infectious	0 (0%)	3 (2.9%)	
Renal	4 (10.3%)	3 (2.9%)	
Other**	3 (7.7%)	5 (4.8%)	
SUP	20 (51.3%)	52 (49.5%)	.85
Invasive mechanical ventilation	27 (69.2%)	24 (22.9%)	<.001*
Coagulopathy	8 (20.5%)	15 (14.3%)	.37
pSOFA	5 (3–6)	4 (2–5)	.024*

GI, gastrointestinal; PICU, paediatric intensive care unit; pSOFA, paediatric Sequential Organ Failure Assessment score; SIRS, systemic inflammatory response syndrome; SUP, stress ulcer prophylaxis.
* Statistically significant.
** Includes trauma, surgical, toxicological, allergic, connective tissue and vascular disorders.

tly more effective in preventing gastrointestinal bleeding compared with ''no treatment''. However, when these 2 studies were pooled with an additional small RCT comparing ''treatment'' *vs* ''placebo'', the authors did not find a significant difference.[16]

We ought to highlight that we only included children with mild to moderate organ dysfunction (pSOFA score < 16), so it is possible that more severely ill children may in fact benefit from SUP. Furthermore, the sample under study was heterogeneous, and it is likely that the usefulness of SUP varies between patient subsets, as demonstrated by a recent observational study that found no instances of clinically important bleeding in children admitted for status asthmaticus that did and did not receive SUP.[17]

Ventilator-associated pneumonia has been a major concern discouraging SUP based on the findings of observational

Table 4 Risk factors for gastrointestinal bleeding.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Non-infectious SIRS	1.8 (0.70–4.65)	.22	1.1 (0.38–3.19)	.86
Sepsis	3.05 (1.25–7.49)	.015*	1.93 (0.71–5.3)	.20
pSOFA	1.22 (1.03–1.43)	.022*	1.15 (0.96–1.39)	.13
Invasive mechanical ventilation	7.59 (3.35–17.2)	<.001*	6.4 (2.73–14.9)	<.001*

CI, confidence interval; OR, odds ratio; pSOFA, paediatric Sequential Organ Failure Assessment score; SIRS, systemic inflammatory response syndrome.
* Statistically significant.

studies.[18] However, in our study, SUP was not associated with a significant increase in the incidence of VAP or HAP, which was consistent with a retrospective paediatric study that compared ranitidine and sucralfate with no prophylaxis.[7] In another paediatric trial, none of the patients that underwent SUP developed pneumonia caused by an organism previously isolated from the stomach.[19] Similarly, another paediatric RCT failed to find significant differences in the incidence of VAP in groups that received ranitidine, omeprazole, sucralfate or no treatment.[15]

Likewise, a meta-analysis of adult RCTs did not find an increased risk of pneumonia in critically ill patients associated with the use of PPIs,[6] but a larger meta-analysis concluded that PPIs may be associated with higher risk of pneumonia (OR, 1.39; 95% CI, 0.98–2.10).[20]

The findings of the latter studies suggest a non-existent or, at most, weak association of SUP with VAP. Nevertheless, strong concerns linger, and the issue can only be settled with the performance of larger paediatric RCTs. It important to keep in mind that SUP is not the sole risk factor implicated in VAP, with more important factors including prior antibiotic therapy, steroid therapy, bloodstream infections, genetic syndromes and reintubation,[21] and therefore large trials would need to be conducted to establish the small contribution of SUP, assuming it exists.

Another concern related to PPIs is the risk of *C. difficile*-associated diarrhoea suggested by previous observational studies.[22] In our study, however, none of the patients developed *C. difficile*-associated diarrhoea, in agreement with a recent paediatric multicentre observational study that found a very low incidence of *C. difficile*-associated diarrhoea (1%) in mechanically ventilated children that received SUP.[14] Furthermore, a meta-analysis of RCTs in critically ill adult patients found no association of PPI or H2RA with *C. difficile* infection.[20]

While our study did not find an association of omeprazole with VAP or *C. difficile*-associated diarrhoea, it did find a significantly higher incidence of CLABSI in children that underwent SUP. This is of utmost importance, as it suggests that the use of SUP in children with non-severe critical illness is morally questionable, as it puts them at risk of a serious form of nosocomial infection associated with an increased morbidity and mortality, in addition to increasing health care costs.

The association of bloodstream infections with SUP could result from bacterial overgrowth in the stomach and duodenum made possible by gastric acid suppression, followed by bacterial translocation through the damaged intestinal epithelial barrier under conditions of mucosal ischemia.[23] However, this cannot explain the development of CLABSI in our study. One explanation worth considering is that PPIs also have anti-inflammatory effects, including inhibition of production of pro-inflammatory cytokines. Furthermore, PPIs inhibit neutrophil proton pumps and therefore interfere with neutrophil function. The clinical consequences of these anti-inflammatory effects are not clear. Theoretically, they may promote healing of acid peptic disorders, but they might also predispose to the development of infections, especially in patients with liver disease.[24] A multicentre point-prevalence study in the general ICU population found that SUP was associated with ICU-acquired infections, such as bloodstream and urinary tract infections.[25] On the other hand, a recent multicentre retrospective study did not find a similar association.[26]

In addition, PPIs have an antimicrobial effect on the gut flora through the blocking of H^+-ATPase in some bacteria and fungi, which may be beneficial if they destroy pathogens but detrimental if they destroy useful organisms.[24]

The net impact of these effects on the risk of bloodstream infections needs to be addressed in larger paediatric trials.

We ought to clarify that the term ''CLABSI'' used in this study differs from the term ''catheter-related bloodstream infection'', as the latter denotes that the catheter is the source of bloodstream infection; and we cannot exclude the possibility that some of the bloodstream infections in our sample originated from sources other than catheters, including the gastrointestinal tract on account of acid suppression. In any case, our data revealed an association of SUP with bloodstream infections and showed that VAP and *C. difficile*-associated diarrhoea are not the only types of infections that may occur with SUP.

It is fair to assume that the safety and efficacy of SUP will be reflected on the general PICU outcome measures. In agreement with the findings of a meta-analysis of adult RCTs, we found did not find significant differences in mortality, length of PICU stay, length of hospital stay and duration of mechanical ventilation between the prophylaxis and control groups.[20] Similarly, a paediatric RCT did not find an association between acid-suppressive drugs or sucralfate with mortality.[15]

Until the controversy surrounding the safety of SUP is resolved, it would be more prudent to consider nonpharmacological strategies to prevent bleeding secondary to stress ulcers, such as prompt resuscitation of patients with shock

and early initiation of enteral feeding, both of which contribute to maintaining splanchnic blood flow.[27,28]

Furthermore, there is evidence that while upper gastrointestinal bleeding is common in critically ill children, clinically significant bleeding is rare. Therefore, it has been suggested that SUP be restricted to patients with at least 2 risk factors for significant bleeding.[1] In this regard, in our study we found that gastrointestinal bleeding was more likely to develop in patients with higher pSOFA scores, that required mechanical ventilation or with a diagnosis of sepsis. The pSOFA score is a measure of organ failure, a factor found to be associated with an increased risk of gastrointestinal bleeding in previous studies,[2,29] although these studies did not quantify the level of organ dysfunction using the pSOFA or similar scores.

However, in the multivariate analysis we found that mechanical ventilation was the only independent predictor of bleeding, which corroborated the findings of a previous retrospective study.[30] We ought to highlight that the proportion of patients that required mechanical ventilation did not differ significantly in the prophylaxis and control groups, which suggests that this variable did not affect our findings regarding SUP safety and efficacy.

Other paediatric observational studies have reported a higher incidence of gastrointestinal bleeding associated with high PRISM scores, coagulopathy, respiratory failure, pneumonia and polytrauma.[1,31]

The notion that SUP is not justified except in children with certain risk factors is supported by the findings of a meta-analysis of RCTs in critically ill adults, which concluded that SUP with PPIs and H2RAs likely achieves important reductions in gastrointestinal bleeding in patients at increased risk of bleeding, but not in patients at low risk of bleeding.[20] As a consequence, some authors have proposed the development of guidelines and educational programs aimed at PICU providers as a valuable tool to achieve a more rational use of acid-suppressive medications.[32]

The main limitation of our study is that the treatment was not masked, which could be a source of ascertainment bias. However, the same limitation applies to the vast majority of paediatric SUP trials in the previous literature.[16] In addition, we only included patients with mild to moderate degrees of organ dysfunction at admission, so our findings cannot be generalized. However, this does not make them worthless, as non-severely ill patients, to whom the findings do apply, constitute the largest group of patients admitted to many PICUs, from which we can glean a clear message: routine SUP should be avoided in non-severely ill children.

Another limitation is that we did not compare omeprazole with other drugs used for SUP. In addition, the sample was heterogeneous and not large enough to reliably assess the useful of omeprazole in different subsets of patients. Nevertheless, this heterogeneity is what characterizes most PICU admissions in the real world. Lastly, we did not evaluate the influence of some factors, like enteral nutrition, on the study results.

Conclusion

In children with mild-to-moderate organ dysfunction at the time of PICU admission, SUP with omeprazole was not effective in preventing upper gastrointestinal bleeding. Furthermore, it was associated with bloodstream infection. Our findings speak strongly against the common practice of routinely administering PPIs to all critically ill children. It seems prudent to narrow down the indications for SUP exclusively to patients requiring mechanical ventilation. At the same time, it is clear that larger RCTs are needed to assess the usefulness of SUP in critically ill children more rigorously.

Conflicts of interest

The authors have no conflicts of interest to declare.

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