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Original Article (Pages: 16656-16665)

Evaluation of Proper Prescription of Antacid Agents in a Group of Critically Ill Children Admitted to PICU in 2018-2019

Majid Keivanfar[1,2], Zahara Allameh[3], Peiman Nasri[1,4], *Mohsen Reisi[1,2], Amir Arsalan Korki[4]

[1] Department of Pediatric Pulmonology, Pediatrics Department, Imam Hossein children's hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
[2] Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran.
[3] Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran.
[4] Pediatrics Department, Imam Hossein children's hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract

Background: Critically ill patients, especially those requiring admission to intensive care units (ICU), are at risk for stress-related gastrointestinal mucosal damage. We aimed to evaluate the frequency of proper prescription of antacid agents in a group of critically ill children admitted to PICU.

Methods: In this retrospective study, the medical records of children aged between 1 month and 15 years who were admitted in 2018-2019 to the PICU of Imam Hossein children's hospital, Isfahan, Iran, were reviewed. Demographic data, indications for PICU admission, principal diagnosis, the severity of the disease, incidence of bleeding during hospitalization, indications for stress ulcer prophylaxis, prescription of the antacid agents, type of antacid prescribed, and the patient's final outcome were recorded. All the data were gathered and organized by a medical intern. We calculated the rate of the patients who were indicated for SUP, those who were not indicated for SUP (Stress Ulcer Prophylaxis), those who received SUP (Stress Ulcer Prophylaxis), and those who did not receive SUP. Data analysis was performed with the Statistical Package for the Social Sciences software (SPSS, version 24.0, IBM, Armonk, New York).

Results: We found that 204 (92.7%) of our patients received antacid agents for gastric SUP. Among the patients receiving SUP, 198 (90%) had an indication for SUP, and only 6 (2.7%) cases received unnecessary prophylaxis? In addition, 16 (7.2%) patients had no indication of receiving SUP and did not receive any prophylaxis. We also reviewed the type of antacid medication that was prescribed for SUP and found that 157 (72%) patients had received PPI, and 57 (30%) had received H2Ras.

Conclusions: The findings of the current study revealed that almost all of our study population who had an indication for prophylaxis of stress ulcer appropriately received antacid agents. We suggest that there is a crucial need to conduct large prospective and multicentric studies in pediatric centers to prepare a universally accepted guideline for the prophylaxis of stress ulcers in the pediatric age group.
Key Words: Antacids, intensive care units, pediatrics.

* Please cite this article as: Keivanfar M, Allameh Z, Nasri P, Reisi M, Korki AA. Evaluation of Proper Prescription of Antacid Agents in a Group of Critically Ill Children Admitted to PICU in 2018-2019. Int J Pediatr 2022; 10 (9):16656-16665. DOI: **10.22038/ijp. 2022.62809.4796**

Corresponding Author:

Mohsen Reisi, Department of Pediatric Pulmonology, Pediatrics Department, Imam Hossein children's hospital, Isfahan University of Medical Sciences, Isfahan, Iran. Email: mohsenreisi@yahoo.com

Received date: Jan.09,2022; Accepted date:Apr.13,2022

1- INTRODUCTION

Critically ill patients, especially those requiring admission to intensive care units (ICU), are at risk for stress-related gastrointestinal mucosal damage. The mucosal injury may progress to become mucosal ulceration and might lead to upper gastrointestinal bleeding (GIB) (1, 2, 3, 4). Although the prevalence of stress-related GIB has decreased in the last 25 years, the incidence of stress-related GIB ranges from 6 to 43%; clinically significant bleeding may be presented in up to 5% of children (5-7), and it will increase the health cost and the burden of the disease for both families and healthcare systems. Moreover, it may increase the morbidity and mortality rates of these patients (8). Studies have suggested that respiratory failure, i.e., requiring mechanical ventilation, coagulopathy/thrombocytopenia, and pediatric risk of mortality score (PRISM) of more than ten might be the main risk factors for stress-related GIB and trauma, extensive burn, renal and hepatic failure, hypotension, heart failure/arrhythmia, and drugs may be associated with the development of GIB in critically ill children (7,10,11).

In 2015, the Stanford Health Care (SHC) issued a guideline for prescribing stress ulcer prophylaxis for adults, in which the approved indications for stress ulcer prophylaxis were:

- Patients on mechanical ventilation for greater than 48 hours

- Coagulopathy defined as platelet count <50, INR >1.5 or PTT 2x baseline

- Traumatic head injuries with a Glasgow Coma Score <10 or inability to follow simple commands

- Burns affecting >35% total body surface area

- Major trauma with an Injury Severity Score >16

- Spinal cord injury

- Partial hepatectomy

- Solid-organ transplantation perioperatively in the ICU setting

Use of two antiplatelet agents (i.e., clopidogrel, aspirin, cilostazol, ticagrelor, dipyridamole)

Any TWO of the following:

- Sepsis

- ICU stay >7 days

- Occult bleeding lasting more than six days

High dose steroids with a daily dose greater than:

- 250 mg of hydrocortisone

- 50 mg of methylprednisolone

- 60 mg of prednisone

- 10 mg of dexamethasone (12).

Treatment of stress ulcers mainly focuses on increasing gastric PH and reducing the damage from the secreted acid. Stress ulcer prophylaxis was introduced more than four decades ago (13). The primary agents for prophylaxis are histamine-2-receptor antagonists (H2RAs), Proton pump inhibitors (PPIs), and sucralfate, with PPIs being the most frequent drug for any age since their discovery (14-16). Despite the frequent use of these agents, previous randomized clinical trials (RCTs), systematic reviews, and Meta analyzes are not consistent about the efficacy and benefits of stress ulcer prophylaxis (17).

In 2018, Krag et al. conducted a large RCT that did not confirm the efficacy of omeprazole in reducing the mortality or a composite of the secondary outcome of "clinically important events"; they, thus, questioned the routine use of PPIs in critically ill adults (17, 18). Likewise, some studies have indicated that there may be significant harms and side effects using

antacid prophylaxis. Ventilator-Associated Pneumonia (VAP) and C. Difficile-Associated Disease (CDAD) are shown to be the most dangerous side effects, and unfortunately, limited experience exists in this regard (19, 20). There are no universally accepted guidelines for beginning, continuing, and discontinuing stress ulcer prophylaxis, but increasing the knowledge about the risk factors of stress ulcers may help physicians in decision making.

Given that the critically ill patients, especially those requiring admission to intensive care units (ICU), are at risk for stress-related gastrointestinal mucosal damage, and considering the importance of the stress ulcers and GIB and the risks of stress ulcer prophylaxis, we aimed to evaluate the frequency of proper prescription of antacid agents in a group of critically ill children admitted to PICU.

2- Material and methods:

In this retrospective study, the medical records of children aged between 1 month and 15 years who were admitted in 2018-2019 to the PICU of Imam Hossein children's hospital, Isfahan, Iran, were reviewed. Demographic data, indications for PICU admission, principal diagnosis, the severity of the disease, incidence of bleeding during hospitalization, indications for stress ulcer prophylaxis, prescription of the antacid agents, type of antacid prescribed, and the patient's final outcome were recorded. We identified all patients who were admitted to the PICU in our specified date range; so the medical records of all children admitted to PICU during the study period were reviewed. Then, the patients whose GIB clinically predated their admission to the ICU were excluded. All the remaining patients that did not meet any of the exclusion criteria were included in the study. The acid-suppressive therapy (AST) was considered appropriate if the patient had one of the major criteria and/or two or more than 2 of the minor criteria.

As there are no universally accepted criteria for stress ulcer prophylaxis, indications for stress ulcer prophylaxis were considered as having one of the major criteria or two or more than two of the minor criteria as described below:

Major criteria:

a) Coagulopathy defined as platelet count <50, INR >1.5 or PTT 2x baseline

b) Mechanical ventilation for more than 48 hours

c) History of GI ulcer and/or GIB in the past year

d) Traumatic head injuries with a Glasgow Coma Score <10 or inability to follow simple commands and spinal cord injuries

e) Burns affecting >35% total body surface area

Minor criteria:

a) ICU stay >7 days

b) Sepsis

c) Occult bleeding lasting more than 6 days

d) High dose steroids with a daily dose greater than:

- 250 mg of hydrocortisone
- 50 mg of methylprednisolone
- 60 mg of prednisone
- 10 mg of dexamethasone (12).

2-1. Inclusion and exclusion criteria

The inclusion criteria consisted of hospitalization in the PICU and the absence of active GIB at the time of admission. Exclusion criteria were as follows: discharge or death of the patient before 24 hours from admission in PICU; evidence of previous upper gastrointestinal bleeding; a current history of epistaxis, facial trauma, or other confounding factors

with bleeding of digestive origin; diagnosis of brain death at admission; prolonged hospitalization (> 1 year); use of prophylactic medications for UE prior to admission to the PICU; lack of authorization to participate in the study (in the service where it was requested)(12).

2-2. Data analysis

All the data were gathered and organized by a medical intern. We calculated the rate of the patients who were indicated for SUP, those who were not indicated for SUP; those who received SUP; and those who did not receive SUP.

Data analysis was performed with the Statistical Package for the Social Sciences software (SPSS, version 24.0, IBM, Armonk, New York). Descriptive statistics are used to report the data, and the normally distributed data are presented as mean ± standard deviation.

3- Results

Records of 220 patients were evaluated; the mean age of the study population was 25.5 months, ranging from 1month to 15 years, with 106 boys (48%) and 114 girls (52%). The median PICU stay was 5 (2-12 days) and the median hospital stay was 10 (6-23) days (**Table 1**).

Table-1: Patients' characteristics

Variable		N=220
Age, Mean (range)		25.5 month (2m - 15y)
Gender	Male, n (%) Female, n (%)	106 (48%) 114 (52%)
ICU stay, Mean (range)		5 (2-12)
Hospital stay, Mean (range)		10 (6-23)
Outcome	Discharge, n (%) Death, n (%)	161 (73%) 59 (27%)

Overall, 139 patients (63.1%) received mechanical ventilation for more than 48 hours, 34 (15.4%) had a history of gastric ulceration regardless of the pathology, 28 (12.7%) had coagulopathy or impaired coagulation, 46 (20.9%) had major trauma (traumatic head injuries with a Glasgow Coma Score <10 or inability to follow simple commands and spinal cord injuries) or major burn,i.e., burns affecting >35% of the total body surface area. In total, 117 patients (53.1%) had one or more of the minor criteria that 23 of these patients (10.4% of all patients) had only minor criteria for receiving SUP (two or more of the minor criteria) that were mostly sepsis or ICU stay >7 days. 4 of our patients had four major criteria, ten patients had three major criteria, and 18 patients had two major criteria at once (**Table 2**).

We found that 204 (92.7%) of our patients received any kind of antacid agent for gastric SUP. Among the patients receiving SUP, 198 (90%) had an indication for SUP, and only 6 (2.7%) patients received unnecessary prophylaxis. In addition, 16 (7.2%) patients had no indication of receiving SUP and did not receive any prophylaxis. There was no patient with indications who did not receive SUP.

We also reviewed the type of antacid medication that was prescribed for SUP and found that 157 (72%) patients had received PPI, and 57 (30%) had received H2Ras (Ranitidine). Overall, 161 (73%) of the patients were discharged from the hospital, and 59 (27%) were deceased either in PICU or in the ward.

Table-2: Patient's indications for receiving SUP

Indication	N=220, (%)
mechanical ventilation for more than 48 hours	139 (63.3%)
Coagulopathy or impaired coagulation	28 (12.7%)
history of GI ulcer and/or GIB in the past year	34 (15.4%)
Major trauma and/or major burn	46 (20.9%)
one or more than one of the minor criteria	117 (53.1%)
Patients that only had minor criteria as an indication	23 (10.4%)
Two major indications at once	18 (8.1%)
Three major indications at one	10 (4.5%)
Four major indications at once	4 (1.2%)

4- DISCUSSION

Stress-related gastric damage is usually one of the complications of the main reason for ICU admission, and prevention of any further damages is very important in critically ill children; since SUP has its own risks, there should be strong data regarding the prevention. Our findings showed that almost all patients with an indication for stress ulcer prophylaxis (90%) had received an antacid agent. The high rate of appropriateness we confirmed in our findings might be associated with the vast spectrum of our considered indications. Moreover, in the studied PICU, we used a protocol for stress ulcer prophylaxis similar to the Stanford university guideline (12). Although the indications for SUP are ill-defined, Stanford Health Care (SHC) and the American Society of Health-System Pharmacists (ASHP) are among the few health organizations that have put forth comprehensive guidelines for the use of acid-suppressing medications in the setting of ICU (12, 21). In 2014, Sahin et al. demonstrated that mechanical ventilation is the only risk factor that is significantly associated with stress-induced GIB. In addition, mechanical ventilation and trauma were enormously significant, and coagulopathy/thrombocytopenia, PRISM III ≥10, renal and hepatic failure, hypotension, and heart failure/arrhythmia were found to be associated with the development of GIB in critically ill children (11).

Interestingly, 92.7 % of our population received stress ulcer prophylaxis, and 97% of these patients had a reason to receive prophylaxis. However, in a large study population of about 336000 patients in Denmark, only 60 % of them received an antacid medication (15). In a recent multicenter study conducted in Canada, the frequency of children receiving acid-suppressive medication varied from 36% to 100%, with a total of 70% of all the study population who received SUP (22). Our high rate of patients receiving SUP may be associated with the fact that our institution is the referral center for pediatric diseases, and our PICU beds are limited, so we have to admit the most critically ill children.

Prescription of SUP has been seen to be more inappropriate in non-critical patients; as stated in a similar study in Saudi Arabia conducted in 2019, only 23.7 % of the patients received appropriate SUP according to the ASHP guidelines (23). We can see similar results for unnecessary SUP in other studies like a study in Saudi Arabia, which showed that approximately 58% of the patients received unnecessary SUP (24). Furthermore, prior studies have shown that in most hospitals, the routine use of SUP for non-ICU patients is often unnecessary and sometimes inappropriate (25, 26, 38). It is an important finding,

since despite prescription of SUP in high-risk patients might decrease the incidence of GIB, unnecessary use may increase drug reactions, potential drug interactions, polypharmacy problems, unnecessary hospital costs, and personal economic burden (27, 28).

The more important problems associated with the use of antacid agents are shown to be hospital-acquired pneumonia and clostridium difficile colitis (30, 31). It has been estimated that daily PPI use in the inpatient setting resulted in a greater than 70% increase in the odds of developing C. difficile colitis (32).

Moreover, a systematic review and meta-analysis in 2011 revealed that acid-suppressive therapy resulted in an estimated additional one case of pneumonia for every 200 patients treated (33). In a strictly medical ICU population, PPIs were independently associated with an increased risk of C. difficile infections. Additionally, this study found no difference in GIB despite the use of acid-suppressing medications (34). In a strictly cardiothoracic population, PPI use was found to be an independent risk factor for nosocomial pneumonia (35). Studies have also found that acid-suppressive therapies do not affect the GIB rate in patients without risk factors. Researchers have noted that 72% of hospitalized patients who developed a bleed had received some forms of bleeding prophylaxis (36).

This low rate of appropriate prescription of SUP is also seen in PICU-based studies. A study conducted in 2016 on PICU patients in Sari,Iran, showed that only 42% of the patients received SUP properly (29).

In our study, only 2.7% of the patients received unnecessary SUP. Considering that we use a protocol for SUP in our PICU, the low rate of unnecessary SUP can be reasonable. But unfortunately, with the lack of a protocol for the pediatric age group and little data on the matter, our protocol is mainly based on the data from adult populations, and it is necessary to prepare an age-specific guideline for the pediatric populations.

Unfortunately, the available studies on the effects of antacid agents in stress ulcer prophylaxis did not strongly demonstrate that antacid agents would decrease the mortality and morbidity rate of critically ill children. Moreover, data on the complications of antacid agents are scarce. A recent systematic review and network meta-analysis on 72 trials, including 12 660 patients, had interestingly concluded that for higher risk critically ill patients, PPIs and H2RAs are likely to result in significant reductions in GIB compared with not providing prophylaxis. Moreover, for low-risk patients, the reduction in GIB might not be important. Both PPIs and H2RAs may result in considerable increases in the frequency of pneumonia. A systematic review and network meta-analysis on studies with data of various qualities suggested no important effects of interventions on mortality or other in-hospital morbidity outcomes (17).

Studies suggest that educating practitioners on stress ulcers and its prophylaxis costs and benefits can reduce the unnecessary use of SUP; thus, it might reduce the adverse complications and economic burden of the SUP (37).

Since its discovery, there has been a concern about stress-related mucosal damage, especially in critically ill patients. In spite of the valuable evidence from the clinical trials, descriptive studies, and systematic reviews, the prophylaxis for stress ulcers has remained to be determined. Our study, along with the other studies in this field, shows that stress ulcer prophylaxis is considered as a routine management in intensive care. SUP may decrease the risk of developing stress-related gastric ulcers, as discussed above, but there are complications associated with SUP agents in addition to its cost and

burden on both patients and society. The current controversies might be because of the differences between studies on the indication for prophylaxis, the rate of patients receiving prophylaxis, and the appropriate prescription rates. However, according to our literature review, it is mandatory to provide a reliable and universally accepted guideline for the pediatric age group that would discuss the indications, drug of choice, dosage, and time of discontinuing prophylaxis.

It is also essential to notice that most of the studies on this topic have been conducted on adults, and the data available for pediatrics are scarce.

4-1. Limitations and strengths of the study

Considering that our PICU is a referral PICU with limited beds, our population is limited to the worst cases, and it might have affected our results. But by evaluating the unnecessary prescription of SUP, we also showed that our in-hospital protocol was practical, and with some edits and improvements, it can be extended to other PICUs until a well-established universal protocol is available.

5- CONCLUSION

The findings of the current study revealed that almost all of our study population who had an indication for prophylaxis of stress ulcer had appropriately received antacid agents. Only 2.7 % of the patients received unnecessary SUP. We suggest that there is a crucial need to conduct large prospective and multicentric studies in pediatric centers to prepare a universally accepted guideline for the prophylaxis of stress ulcers in the pediatric age group.

6- ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of the Isfahan University of medical sciences (IR.MUI.MED.REC.1397.167). As it is an observational study, the ethics committees agreed that there was no need for a free and informed consent form (ICF), with the authors' commitment to signing the confidentiality and privacy terms regarding identity and patient data.

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