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ORIGINAL RESEARCH

Implementation of Guideline-Based Use of Proton Pump Inhibitors for Perioperative Stress Ulcer Prophylaxis: A Pre-Post Study Guided by CFIR-ERIC

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Background: The overuse and misuse of proton pump inhibitors (PPIs) in perioperative patients for stress ulcers prophylactic (SUP) is crucial. This study evaluated the impact of a Consolidated Framework for Implementation Research Expert Recommendations for Implementing Change (CFIR-ERIC)-guided intervention on the rational use of PPIs in a perioperative setting.

Methods: A single-center pre-post study was conducted at Beijing Chaoyang Hospital between April and November 2023. All hospitalized patients who used perioperative PPIs for SUP were included. Cases post-intervention were defined as the intervention group and were propensity score-matched with pre-intervention cases, which was defined as the control group. The intervention strategies were developed by following the updated CFIR framework and employing CFIR-ERIC strategies. Outcomes included rational use of PPIs, reasons for irrational use, total hospitalization and drug costs, PPI duration, costs, and average defined daily dose.

Results: 1122 cases were included in the intervention group and control group after propensity score matching, respectively. The intervention group showed significant improved rate of rational PPI use (81.7% vs 42.0%, p<0.001). Rates of non-indication use, inappropriate dosage and administration, drug selection, and administration route were significantly reduced (all p<0.05). Coagulation disorders or anticoagulant/antiplatelet treatment, severe trauma or multiple injuries, severe infection or sepsis were the three most prevalent severe risk factors among patients, with 46.7% and 29.5% of the two groups, respectively. We found no significant differences between the two groups in total hospitalization costs (¥55,672.84 vs ¥57,021.73, p=0.621) and total drug costs (¥3005.38 vs ¥3260.98, p=0.206). Additionally, PPI costs (¥7.44 vs ¥93.70, p<0.001) and defined daily dose (7.00 vs 8.00, p<0.001) were significantly lower in the intervention group. We also observed a downward trend in PPI duration (6.00 days vs 5.00 days, p=0.075).

Conclusion: The CFIR-ERIC-guided intervention effectively improved the rational use of PPIs for perioperative SUP, resulting in significant reductions in both the PPI duration and costs.

Keywords: proton pump inhibitor, CFIR-ERIC, rational drug use, perioperative medication

Introduction

Proton pump inhibitors (PPIs) are widely used in the prevention and treatment of acid-related gastrointestinal diseases for their high efficacy and good tolerability in reducing gastric acid secretion.[1–4] Despite its worldwide adoption, inappropriate use of PPIs is very common, especially in hospitalized patients. Studies have shown that a large proportion of hospital inpatients receive acid-suppressive therapy, including PPIs, without meeting the necessary clinical criteria for treatment.[5] In fact, the inappropriate use of PPIs during hospitalization is prevalent globally, with estimates indicating that 41.0–50.6% of inpatients receive PPIs unnecessarily.[6,7] Moreover, the lack of a date of discontinuation or re-evaluation for de-prescription was also a crucial problem. Evidence showed that half of the

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patients who initiated PPI treatment in the hospital were ongoing with a and continued with it at discharge.[7] In China, inappropriate prophylactic use of PPIs during the perioperative period is common,[8] rating up to over 50% of all PPIs prescriptions.[9]

The overuse of PPIs not only leads to potential adverse effects but also contributes to substantial economic waste. Studies have demonstrated PPI-associated adverse events such as pneumonia, bone fractures, hypomagnesemia, and dementia.[10–12] Furthermore, the financial burden of PPI overuse extends beyond the direct cost of the medication, with additional healthcare expenses arising from managing adverse events associated with unnecessary PPI prescriptions.[13,14] Given the mounting evidence of both clinical and economic consequences, the rational management of PPIs is urgently needed to reduce unnecessary prescriptions and improve patient outcomes.

Although numerous high-quality guidelines on PPIs for stress ulcer prophylaxis (SUP) have been issued, their implementation in clinical practice remains inadequate and lacks long-term sustainability. Moreover, the central government of China issued an official guiding principle for the clinical utilization of PPIs as an action plan.[15] However, there is limited research on effective strategies for the systematic reduction of inappropriate PPI prescriptions in perioperative care. The Consolidated Framework for Implementation Research (CFIR) and the Expert Recommendations for Implementing Change (ERIC) are complementary frameworks widely used in healthcare implementation science.[16,17] In clinical settings, CFIR-ERIC helps to identify barriers and facilitators to the successful implementation of evidence-based practices, making it particularly valuable in translating research into routine care.[18,19] This study seeks to evaluate the effectiveness of a structured intervention based on the CFIR-ERIC framework to promote the guideline-based, rational use of PPIs for perioperative stress ulcer prophylaxis. We conducted a pre-post study using the CFIR-ERIC Strategy to manage guideline-based rational use of PPIs for perioperative SUP.

Methods

Study Design

This multi-phase single-center pre-post study was conducted at Beijing Chaoyang Hospital between April and November 2023. We evaluated the rational use of PPIs before (using the order review data from January to June 2022) for pre-evaluation, conducted CFIR-guided qualitative research, matched into strategies guided by CFIR-ERIC (April to June 2023), and implemented the strategies through an initial-intervention phase (July 2023) and a post-intervention phase (August to November 2023). The implementation program is shown in Figure 1. We followed the STROBE statement for cohort studies to report our findings.[20] The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee of the hospital (grant number 2023-ke-753).

Participants

All hospitalized patients were included in the selection. Inclusion criteria were as follows: a) Patients used prophylaxis PPIs for stress ulcer prophylaxis; b) Patients who underwent surgeries; c) Cases with complete medical records. Exclusion criteria: a) Patients used PPIs for therapeutic use, such as gastroesophageal reflux disease, peptic ulcer, upper gastrointestinal bleeding, and *Helicobacter pylori* infection; b) Patients receiving chemotherapy or sleeve gastrectomy surgery.

Cases during the post-intervention phase were classified as the intervention group, while those in the pre-evaluation phase were classified as the control group.

Intervention

We followed the updated CFIR[16] to conduct interviews and identified barriers and facilitators for the issue. The barriers and facilitators were inductively mapped to the Consolidated Framework for Implementation Research Expert Recommendations for Implementing Change (CFIR-ERIC) Strategy Matching Tool,[21] and organized into categories by hierarchical cluster analysis.[22] Subsequently, the strategies were implemented through several practical approaches for clinical interventions, aimed at training healthcare professionals across the hospital. The strategies were as follows:

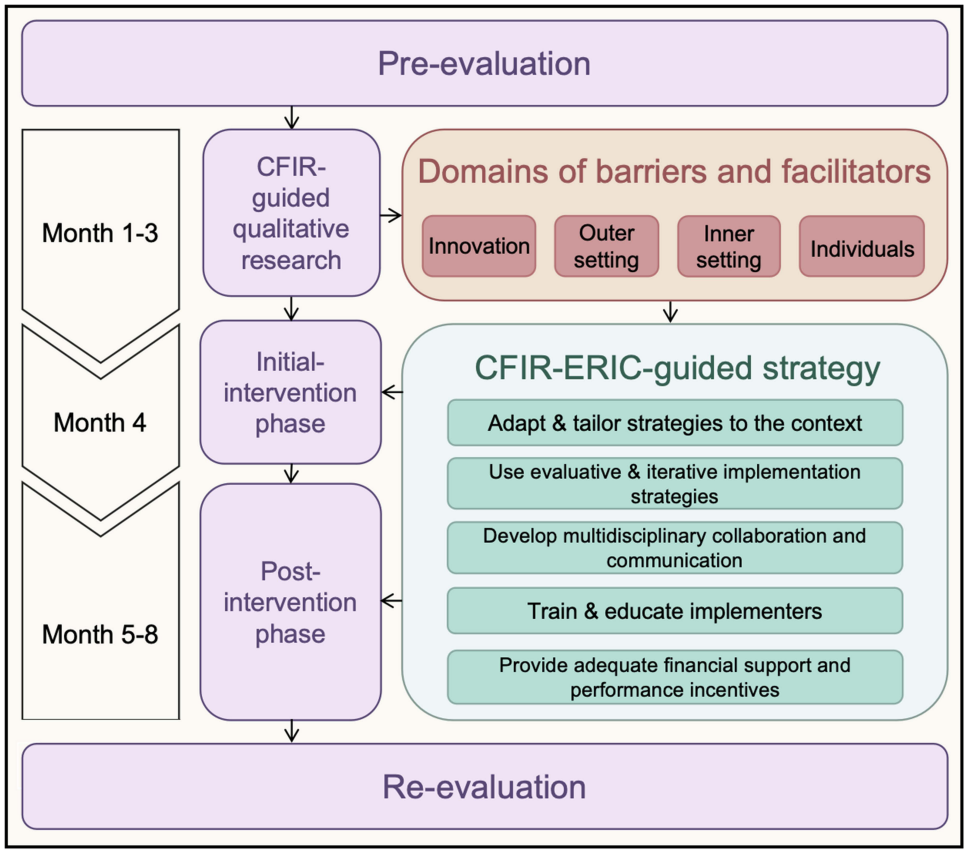

Figure 1 Overview of the study design.

A. Adapt & tailor strategies to the context: streamlined the clinical medication process through pathway management; embedded a rational PPI use management system within the electronic medical record system
B. Use evaluative & iterative implementation strategies: conducted daily specialized focus rounds by clinical pharmacists; provided monthly specialized medical order reviews and feedback on the rational use of PPIs
C. Develop multidisciplinary collaboration and communication: established connections between clinical staff and clinical pharmacists to address questions on rational medication use
D. Train & educate implementers: conducted hospital-wide training on the rational use of PPIs covering 36 medical departments
E. Provide adequate financial support and performance incentives: implemented a hospital reward and penalty project

Data Collection

Baseline characteristics including age, sex, ethnicity, insurance information, admission department, length of stay, surgery duration, admission to intensive care unit (ICU), and length of stay in ICU, costs, and PPI information were collected through the routine electronic health record of the hospital information system.

Outcomes

The main outcome was the rational use of PPIs for perioperative stress ulcer prophylaxis, by conducting a medical order review of the pre-evaluation phase and post-intervention phase (Supplemental material S1). The criteria we used for evaluating rational use were based on the Guidelines for the Clinical Application of Proton Pump Inhibitors issued by the central government of China.[15] Secondary outcomes included the individualized outcomes of rational use (non-indication use, inappropriate dosage and administration, inappropriate drug selection, therapeutic duplication, inappropriate solvent

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selection), total hospitalization costs, total drug cost, PPI duration, PPI costs, and average use density (AUD) for PPI. AUD was calculated using the following formula: Total amount of PPI daily dose for the case*100/defined daily dose (DDD)*PPI duration for the case. DDD was defined by referring to the World Health Organization standardized value.[15]

Statistical Analysis

Continuous variables were presented as the mean (standard deviation) for normal distribution or mean (interquartile range) for non-normal distribution. The two-sample *t*-test was used for normally distributed data. The Wilcoxon rank-sum test and Mann–Whitney *U*-test were used for uniform and non-uniform data to check the homogeneity between the two groups, respectively. Categorical variables were presented as the number and frequency. Chi-squared test or Fisher's exact test was used for analysis. Propensity score matching (PSM) was performed using the greedy nearest-neighbor matching algorithm in a 1:1 ratio with a caliper of 0.02 and no replacements to address potential confounding. The standardized differences between the intervention group and the control group were estimated to measure the balance of the covariate. A standardized difference (SD) of below 10% was considered to represent good matching. The potential confounders included sex, age, ethnicity, insurance, department, length of stay, surgery duration, admission to ICU, and length of stay in ICU. Differences with p values of <0.05 were considered statistically significant. Statistical analysis was performed using R Studio (version 4.1.2).

Results

1196 and 1783 patients were involved in the intervention group and the control group, respectively (Figures 1 and 2). Mean (SD) age is 61.64 (14.51) and 61.73 (15.12) for the intervention group and control group, with the female proportion of 44.0% and 45.7% (Table 1). The intervention group showed an increased proportion of Han ethnicity, lower patients receiving health insurance, and different distribution of admission departments. After PSM, baseline characteristics between the two groups were well balanced with a standardized difference of 0.05 or less (Table 1, Supplemental material S2).

The intervention group demonstrated a significantly higher rate of rational PPI use compared to the control group (81.7% vs 42.0%, p<0.001, Table 2). Rates of non-indication use were significantly reduced in the intervention group (11.9% vs 16.5%, p=0.002). Coagulation disorders or anticoagulant/antiplatelet treatment, severe trauma or multiple

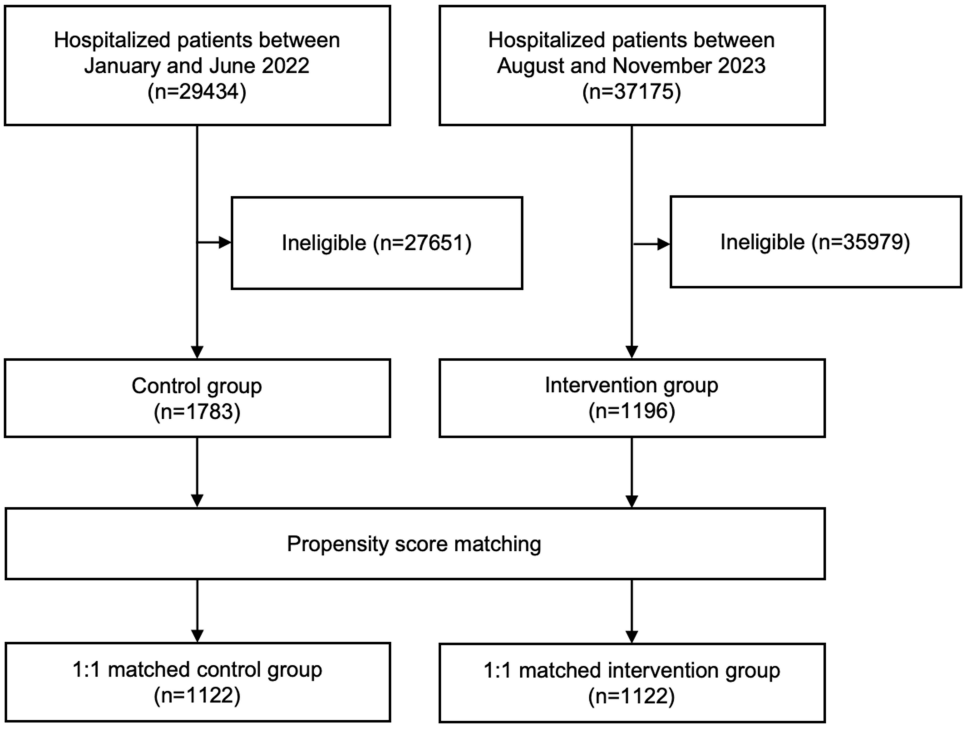

Figure 2 Identification of intervention and control group among hospitalized patients used perioperative PPIs.

Table 1 Baseline Characteristic of the Crude and Propensity-Matched Groups

	Crude Group			**PSM Group**		
	Intervention Group (n=1196)	**Control Group (n=1783)**	**P-value**	**Intervention Group (n=1122)**	**Control Group (n=1122)**	**P-value**
Age [years, mean (SD)]	61.64 (14.51)	61.73 (15.12)	0.866	61.56 (14.56)	61.84 (14.65)	0.650
Sex (%)			0.388			0.898
Male	670 (56.0)	969 (54.3)		635 (56.6)	631 (56.2)	
Female	526 (44.0)	814 (45.7)		487 (43.4)	491 (43.8)	
Ethnicity (%)			0.006			0.441
Han	1157 (96.7)	1685 (94.5)		1083 (96.5)	1075 (95.8)	
Others	39 (3.3)	98 (5.4)		39 (3.5)	47 (4.2)	
Insurance (%)			<0.001			0.128
Health insurance	694 (58.0)	1202 (67.4)		674 (60.1)	674 (60.1)	
Publicly funded healthcare	17 (1.4)	44 (2.5)		17 (1.5)	28 (2.5)	
Self-pay	32 (2.7)	55 (3.1)		31 (2.8)	44 (3.9)	
Other	453 (37.9)	482 (27.0)		400 (35.7)	376 (33.5)	
Department (%)			<0.001			0.971
Cardiology	421 (35.2)	570 (32.0)		413 (36.8)	395 (35.2)	
Neurosurgery	150 (12.5)	152 (8.5)		135 (12.0)	132 (11.8)	
General Surgery	102 (8.5)	266 (14.9)		102 (9.1)	104 (9.3)	
Cardiac Surgery	110 (9.2)	125 (7.0)		101 (9.0)	101 (9.0)	
Orthopedics	98 (8.2)	183 (10.3)		97 (8.6)	104 (9.3)	
Gynecology	81 (6.8)	95 (5.3)		76 (6.8)	77 (6.9)	
Hepatobiliary and Pancreatic Surgery	66 (5.5)	98 (5.5)		60 (5.3)	59 (5.3)	
Urology	33 (2.8)	90 (5.0)		33 (2.9)	31 (2.8)	
Thoracic Surgery	26 (2.2)	55 (3.1)		26 (2.3)	29 (2.6)	
General Department	20 (1.7)	24 (1.3)		20 (1.8)	21 (1.9)	
Breast Surgery	11 (0.9)	21 (1.2)		11 (1.0)	15 (1.3)	
Vascular Surgery	34 (2.8)	16 (0.9)		10 (0.9)	15 (1.3)	
Otolaryngology	13 (1.1)	10 (0.6)		8 (0.7)	9 (0.8)	
Others	30 (2.7)	78 (4.4)		30 (2.7)	30 (2.7)	

(*Continued*)

Table 1 (Continued).

	Crude Group			PSM Group		
	Intervention Group (n=1196)	**Control Group (n=1783)**	**P-value**	**Intervention Group (n=1122)**	**Control Group (n=1122)**	**P-value**
Length of stay [days, median (IQR)]	10.00 (10.00)	10.00 (12.00)	0.330	10.00 (10.25)	10.00 (11.00)	0.713
Surgery duration [min, median (IQR)]	120.00 (165.00)	120.00 (180.00)	0.339	120.00 (170.00)	120.00 (160.00)	0.130
Admission to ICU (%)	627 (52.4)	886 (49.7)	0.154	583 (52.0)	595 (53.0)	0.642
Length of stay in ICU [days, median (IQR)]	1.00 (3.00)	1.00 (3.00)	0.688	3.00 (3.00)	3.00 (3.00)	0.423

Abbreviations: IQR, interquartile range; ICU, intensive care unit.

Table 2 Outcomes of the Intervention Group and Control Group

Outcome	**Intervention Group (n=1122)**	**Control Group (n=1122)**	**P-value**
Rational use	917 (81.7)	471 (42.0)	**<0.001**
Reasons for irrational use			
Non-indication use	133 (11.9)	185 (16.5)	**0.002**
Inappropriate dosage and administration	2 (0.2)	418 (37.3)	**<0.001**
Inappropriate drug selection	83 (7.4)	256 (22.8)	**<0.001**
Inappropriate route of drug administration	1 (0.1)	44 (3.9)	**<0.001**
Therapeutic duplication	3 (0.3)	9 (0.8)	0.148
Inappropriate solvent selection	0 (0.0)	1 (0.1)	1.000
Total hospitalization costs (¥)	55,672.84 (68,771.63)	57,021.73 (68,387.45)	0.621
Total drugs cost (¥)	3005.38 (7061.96)	3260.98 (7519.88)	0.206
PPI duration (days)	6.00 (8.00)	5.00 (7.00)	0.075
PPI costs (¥)	7.44 (75.10)	93.70 (228.82)	**<0.001**
Average PPI DDD	7.00 (9.92)	8.00 (12.00)	**<0.001**

Abbreviations: PPI, proton pump inhibitor; DDD, defined daily dose; data shown as mean (SD).

injuries, severe infection or sepsis were the three most prevalent severe risk factors among patients, with over 46.7%, 29.5%, 22.2% of the total group with these risks, respectively (Table 3). 133 cases in the intervention group had no indications for SUP, of which none were evaluated to have severe risk factors, 17 had only one potential risk factor, and 116 had no risk factor. For the control group, 185 cases had no indications, with none having severe risk factors, 25 had only one potential risk factor, and 160 had no risk factor. Rates of inappropriate dosage and administration (0.2% vs 37.3%, $p<0.001$), drug selection (7.4% vs 22.8%, $p<0.001$), and route of drug administration (0.1% vs 3.9%, $p<0.001$) were all significantly lower in the intervention group. However, therapeutic duplication and inappropriate solvent selection did not differ significantly between groups.

Table 3 Indications for Proton Pump Inhibitors Use in Perioperative Patients

Risk factors	Intervention Group (n=1122)	Control Group (n=1122)	P-value
Severe risk factors			
Coagulation disorders (International Normalized Ratio>1.5, platelets<50×10^9/L or partial thromboplastin time>2 times the normal value) or taking anticoagulant or antiplatelet drugs	565 (50.4%)	484 (43.1%)	0.001
Severe trauma, multiple injuries	304 (27.1%)	359 (32%)	0.012
Severe infection, sepsis	191 (17%)	307 (27.4%)	<0.001
Mechanical ventilation or receiving extracorporeal life support (eg, ECMO or hemopurification)	138 (12.3%)	39 (3.5%)	<0.001
Severe psychological stress, such as psychological trauma	15 (1.3%)	44 (3.9%)	<0.001
Shock or persistent low blood pressure	17 (1.5%)	39 (3.5%)	0.004
Acute renal failure or undergoing renal replacement therapy	33 (2.9%)	22 (2%)	0.172
Severe cranial, cervical, or spinal trauma	13 (1.2%)	21 (1.9%)	0.226
Various difficult, complex surgeries (surgery time>3h)	10 (0.9%)	10 (0.9%)	1.000
Severe burns (adult burn area>30%, child burn area>15%)	4 (0.4%)	9 (0.8%)	0.266
Acute respiratory distress syndrome	6 (0.5%)	6 (0.5%)	1.000
Cardiovascular accidents	5 (0.4%)	7 (0.6%)	0.772
Chronic liver disease or acute liver failure	1 (0.1%)	1 (0.1%)	1.000
Potential risk factors			
Routine use of NSAIDs before admission	43 (3.8%)	92 (8.2%)	<0.001
Long-term fasting or parenteral nutrition	27 (2.4%)	66 (5.9%)	<0.001
ICU stay>1 week	35 (3.1%)	25 (2.2%)	0.239
High-dose use of corticosteroids (dose> Hydrocortisone 250mg/d or equivalent doses of other drugs)	12 (1.1%)	27 (2.4%)	0.024
Existing history of peptic ulcer or bleeding	21 (1.9%)	18 (1.6%)	0.747
Routine use of immunosuppressants before admission	9 (0.8%)	9 (0.8%)	1.000
Persistent fecal occult blood>3 days (excluding hemorrhoids)	10 (0.9%)	2 (0.2%)	0.043
Age>60 years, history of Helicobacter pylori infection, and persistent H. pylori positivity	2 (0.2%)	3 (0.3%)	1.000

Abbreviations: ECMO, Extracorporeal Membrane Oxygenation; NSAIDs, Nonsteroidal Antiinflammatory Drugs; ICU, intensive care center.

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We found no significant differences between the two groups in total hospitalization costs (¥55,672.84 vs ¥57,021.73, p=0.621), total drug costs (¥3005.38 vs ¥3260.98, p=0.206), and PPI duration (6.00 days vs 5.00 days, p=0.075), whereas PPI costs (¥7.44 vs ¥93.70, p<0.001) and DDD (7.00 vs 8.00, p<0.001) were significantly lower in the intervention group.

Discussion

This before-after study was the first to use the CFIR-ERIC-guided management of guideline-based rational use of PPIs for perioperative SUP. The implementation of this strategy improved the rational use of PPIs, with significant reductions in non-indication use, inappropriate dosage and administration, inappropriate drug selection, inappropriate route of drug administration, as well as the PPI costs and DDD.

In current clinical guidelines and recommendations, the use of PPIs for SUP in perioperative patients underscores the importance of individual risk assessment.[23,24] The recommendations advise that PPI prophylaxis should be considered only in patients with clearly defined risk factors. Such risk factors include the need for mechanical ventilation, coagulation disorders, difficult or complex surgeries, and other pathological states that increase the risk of bleeding (Supplemental Material S1). For most patients without these risk factors, the routine use of PPIs for SUP is not supported. Through the qualitative research phase, we found out that most doctors supported the rational use of PPIs while the actual implementation was not good, especially when it came to perioperative cases. Risk assessment of bleeding for indication use of PPIs, appropriate dosage, drug selection, time of initiation, and de-prescription of PPIs needed to be strengthened in the routine treatment. Furthermore, since more than half of the cases in our study would transfer to the ICU after surgery, they may be more susceptible due to the severity of their condition, mechanical ventilation, coagulopathy, or other risk enhancers. For these patients, guidelines recommend the use of PPIs for prophylaxis for patients at high risk of clinically important bleeding.[25] It is imperative that these guidelines be integrated into practice with a dynamic precision medicine approach, tailoring care to the individual patient's risk profile to avoid both underuse and overuse of PPIs.

While our study primarily addresses inappropriate PPI use in terms of indications, other important factors such as selection, dosage and administration route also play significant roles in the overall rational use of PPIs. There was an enhancement in drug selection, particularly with the use of omeprazole or esomeprazole being the only two options for prophylactic indications, which aligned with the guideline.[15] Furthermore, the issue of unsuitable drug formulations was also improved. Recent studies have highlighted the substantial economic burden of unnecessary PPI prescriptions, particularly when inappropriate dosage forms (eg, intravenous formulations when oral options are suitable).[26,27] This can lead to significant hospital expenditures and increased healthcare costs. Our study confirms these findings, showing that inappropriate use of PPI is not only prevalent in terms of indications but also in terms of dosage form, which often deviates from evidence-based guidelines. We observed a significant shift toward oral PPI use, contributing to reduced PPI costs. Prioritizing oral administration wherever appropriate could be the reason for the significant reduction in PPI cost.

The challenge of non-indication use of PPIs was the most resistant to change and thus became a focal point of our intervention. This included addressing the continuation of PPIs in patients who had either only one potential risk factor or no clear indications for use, as well as the persistence of therapy beyond the resolution of risk factors. The prevailing belief of PPIs' effectiveness on SUP and underestimation of their adverse outcomes were the widespread perceptions among healthcare providers.[28] This underscores a significant gap in education and practice, where the routine use of PPIs has overshadowed the need for stringent indication-based prescriptions. We targeted these misconceptions by conducting educational sessions that addressed the importance of evidence-based use of PPIs, provided clear guidelines on when to initiate and discontinue therapy, and disseminated updated knowledge about the potential risks associated with unnecessary PPI use (including drug-drug interactions, cost implications, and the risk of adverse effects with long-term use).

Prior studies have explored various strategies to optimize the use of PPIs due to the increasing awareness of the risks associated with their overuse and inappropriate prescribing. The strategies predominantly fall into three categories: educational programs, electronic health record-based decision support, and multifaceted approaches combining various strategies.[29] For example, Agee et al[30] and Herzig et al[31] implemented educational seminars and EHR alerts, respectively, achieving some reduction in PPI overuse. Belfield et al[32] and Del Giorno et al[33] took a multifaceted approach, which included educational components, guideline implementation, and audit and feedback mechanisms. These interventions

resulted in reductions in inappropriate PPI use but varied in their sustainability and extent, with a lack of generalizability. Our study diverges from these precedents primarily in the application of the CFIR-ERIC method, which not only synthesizes multiple strategies but also heavily focuses on adapting interventions to the context by analyzing barriers and facilitators to change. This method allowed for a nuanced approach, tailoring the interventions to specific institutional needs, rather than applying a one-size-fits-all strategy.

Our study was primarily centered on the perioperative population, where the majority of interventions were targeted from the healthcare provider's perspective. For long-term adherence to appropriate PPI use, managing patient aspects could also be crucial. Nguyen-Soenen et al[34] tested a multi-faceted intervention, which combined patient education brochures and deprescribing algorithms sent to both patients and general practitioners, in a pragmatic cluster-randomized controlled trial. Interventions like this could help push forward the importance of engaging patients and practitioners in the process of rational use of PPIs.

Our study possesses several strengths that contribute to the existing literature on the rational use of PPIs. We used the CFIR-ERIC framework to guide our intervention program, which could help develop a comprehensive approach to guide the implementation of evidence-based strategies. Furthermore, our integration of the electronic medical record system, multidisciplinary collaboration, and targeted strategies provided a robust platform for promoting change in clinical behavior. However, there were also some limitations of this study. The single-center study design might restrict the generalizability of our results to other settings with different patient demographics or institutional policies. However, we confirmed the effectiveness of the CFIR-ERIC framework guidance on this issue, which could help develop individualized strategies in other settings. Additionally, the potential for residual confounding cannot be entirely excluded, despite our use of propensity score matching to balance the characteristics between the intervention and control groups. Future research could benefit from a multicenter design and pragmatic cluster-randomized controlled trials to validate and expand upon our findings.

Conclusion

This pre-post study evaluated the impact of a CFIR-ERIC-guided intervention on the rational use of PPIs for perioperative SUP. The results showed significant reductions in inappropriate PPI use, associated costs and DDD, although no significant change in PPI duration was observed.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author for reasonable requests.

Ethics Approval and Consent to Participate

The institutional review boards and ethics committee of Beijing Chaoyang Hospital, Capital Medical University reviewed and approved the study protocol (approval No 2023-ke-753). Participants gave informed consent to participate in the study before taking part.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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