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RESEARCH ARTICLE

Impact of a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy in older hospitalized patients: a non-randomized controlled study

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Abstract

Background The potentially inappropriate use of the proton pump inhibitors is prevalent in older adults.

Aim To evaluate the impact of a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy in older hospitalized patients.

Method This parallel nonrandomized controlled study was conducted at an internal medicine service of a tertiary training and research hospital between September 2019 and August 2021. Older patients (≥ 65 years old and received proton pump inhibitors within 48 h of admission) were allocated to two groups according to their number of medical file records, whether odd or even, two groups: control and clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy (including medication reconciliation and medication review) during the hospital stay. Primary outcome measures were the rate of appropriate use of proton pump inhibitors during hospitalization and potentially inappropriate proton pump inhibitor use at discharge.

Results The rate of appropriate proton pump inhibitor use during hospitalization was significantly higher in the clinical pharmacist-led program (n = 100) than in the control group (n = 97) (46.4% vs. 79.0%; $P < 0.001$). The rate of potentially inappropriate proton pump inhibitor use at discharge was significantly lower (61.7% vs. 35.1%; $P < 0.05$) in the clinical pharmacist-led program among the older patients discharged with a proton pump inhibitor prescription.

Conclusion A clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy improved the rate of appropriate proton pump inhibitor use and reduced the potentially inappropriate proton pump inhibitor use during the hospital stay.

Trial Registration NCT05113667 (17 October 2021-*registered retrospectively*).

Keywords Geriatric · Medication review · Proton pump inhibitor · Potentially inappropriate medication

Impact statements

- A clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy optimized the use of proton pump inhibitors (PPIs) in older hospitalized patients.
- According to the secondary outcome findings of the study, the clinical pharmacist-led program reduced the cost of inappropriate use of PPIs without causing any harm.
- Further studies will be conducted to implement this clinical pharmacist-led service in Turkey.

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Introduction

More than half of the geriatric patients are discharged from the hospital with a prescription containing a proton pump inhibitor (PPI) [1]. PPIs have been reported to be the most potentially inappropriate medications used in older adults in the United States [2]. The inappropriate use of PPIs has been shown to be prevalent in older patients at admission to and/or discharge from an internal medicine or geriatric ward [3–6]. Older hospitalized patients who used a potentially inappropriate medication were more likely to have an increased risk of medication-related hospitalization and adverse drug reactions and/or drug events [7].

In addition to the use of potentially inappropriate medications, polypharmacy may increase adverse drug reactions in hospitalized older adults [8]. The long-term use of PPIs can cause several adverse effects, including nosocomial pneumonia, *Clostridioides difficile* infection, malabsorption of magnesium, vitamin B12, calcium, and iron, risk of fractures, and kidney disease [9].

There are effective interventions with limited evidence to reduce inappropriate use of PPIs in older adults [10]. A recent systematic review reported that mild- moderate improvements in the appropriate use of PPIs for the prophylaxis of stress ulcers could have been achieved with interventions (including education, structured clinical guidelines, and audit feedback) in hospitalized patients [11, 12]. A recent systematic analysis and meta-analysis reported an association between pharmacist intervention and a reduction in the inappropriate use of acid suppression therapy at discharge with significant heterogeneity [13]. These studies emphasized the need for high-quality studies. Pharmacist-led services, including medication reconciliation and medication review, have provided an opportunity to reduce the potential use of inappropriate medications used in older hospitalized patients [12, 14]. Although clinical pharmacy has a 30-year history in Turkey, clinical pharmacists are not regularly employed in hospitals, therefore studies evaluating the services provided by clinical pharmacists are needed. Beside post graduate programs in clinical pharmacy, Ministry of Health- Clinical Pharmacy Specialist Program has been run since 2018 at eight universities in Turkey. The first clinical pharmacy specialists were graduated from that program in 2021 and these clinical pharmacists will work in full time position at wards of hospitals. However, at the organisational level, the responsibilities of clinical pharmacists at healthcare system are still unclear.

Aim

This study aimed to evaluate the impact of a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy in older hospitalized patients.

Ethics approval

The study protocol was approved by the Clinical Trial Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital of University of Health Sciences (Date: 27.06.2019 Approval number: 2019/51). Informed consent was collected from all participants. The study was reported based on the recommendations of the Transparent Reporting of Evaluations with Non-randomized Designs (TREND) statement [15]. The study protocol was registered retrospectively at ClinicalTrial.gov (NCT05113667) after the study was completed.

Method

Study design

This prospective, open-label, parallel-arm, nonrandomized controlled study was conducted at an internal medicine service of a tertiary training and research hospital (300-bed) located in Istanbul, Turkey. The patients were recruited for this study between September 2019 and February 2020. The study analysis was finalized in August 2021.

Participants

Patients aged 65 years and older, admitted to the hospital for any reason and ordered to receive for at least one PPI dose within 48 h of admission were eligible for the present study. Patients who were transferred to another ward, such as an intensive care unit and/or had active gastrointestinal bleeding, or active malignancy, were excluded. Eligible patients were included when they were first admitted to the hospital, and they were excluded when they were admitted to the hospital during the study.

Assignment method

Patients were assigned to the study groups by their number of medical file records whether odd or even by a clinical pharmacist with an allocation ratio of 1:1. Patients with odd numbers were assigned to the control group, and patients with even numbers were assigned to the intervention group.

Interventions

The clinical pharmacist-led appropriate acid suppression therapy stewardship program was described according to the Template for Intervention Description and Replication (TIDieR) [16]. As a part of the clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy, a medication reconciliation service was provided within 48 h after patient admission by providing the best possible medication history. The clinical pharmacist reviewed the patients' medical chart and attended the daily visit with healthcare team. In this study, the clinical pharmacist was a hospital pharmacist who worked full time (responsible for traditional pharmaceutical services) at the study hospital. This study was designed as her PhD thesis on clinical pharmacy. There was no clinical pharmacist working at this hospital.

PPIs used during hospitalization and at discharge were assessed by the clinical pharmacist. Clinical pharmacist provided medication reconciliation service (at admission and discharge) and medication review service (during hospitalization and at discharge). At the beginning of the study, the recent guidelines for the appropriate use of PPIs were based on previous studies, developed in print [17–19] and distributed to all physicians in the internal medicine service where the study was conducted. During hospitalization, the American Society of Health System Pharmacist Guidelines for stress ulcer prophylaxis were used to evaluate the appropriate of PPI use during hospitalization. This guideline included pharmacokinetics, indications, risk factors, treatment duration, potential drug-drug interactions, adverse drug reactions, cautions, and deprescribing protocols [20]. During the hospital stay, and at discharge, the Medication Appropriateness Index (MAI) was calculated for PPIs by the clinical pharmacist [21]. In the case of inappropriate use of a PPI, the clinical pharmacist contacted the physician (face-to-face) and presented recommendations (such as switching the IV route to oral and/or cessation of the PPI). The control group received routine care in which the clinical pharmacist was not involved. During usual care, patients in control group did not receive any clinical pharmacist-led services (including medication reconciliation and medication review). Hospital pharmacists routinely dispensed the electronic order of physician without assessing appropriate use of a PPI based on recent guidelines. Outcome measures were assessed in both groups by the clinical pharmacist. However, no clinical pharmacist's recommendation presented to the physicians according to this analysis in control group, unless there was life-threaten problem.

Data collection

Older patients' age, sex, education level (based compulsory education year in Turkey: evaluated dichotomously: < 8 years and ≥ 8 years), history of hospitalization during the last 6 months, reason for hospital admission, PPI use before hospital admission, Charlson Comorbidity Index [22], the number of medications used before admission, receiving enteral nutrition, and length of hospital stays (days) were collected at the baseline. Laboratory data (INR [international normalized ratio], AST [aspartate aminotransferase], ALT [alanine aminotransferase], creatinine, platelet count, creatinine clearance) were assessed to identify appropriate PPI use during hospital stay based on the guidelines (data not shown).

Primary outcome measures

Primary outcome measures were the rate of appropriate use of PPIs based on the guidelines during hospitalization, and the rate of potentially inappropriate PPI use based on the AGS Beers Criteria©, 2019 at discharge. According to the AGS Beers Criteria©, PPIs usage for > 8 weeks is not recommended except for high-risk patients (such as patients using oral corticosteroids or chronic NSAIDs [nonsteroidal anti-inflammatory drugs]) due to the risk of *Clostridioides difficile* infection and bone loss and fractures [23]. If the patients newly commenced to PPI, the duration of their discharge prescription was assessed to identify potentially inappropriate PPI use according to AGS Beers Criteria©, 2019.

Secondary outcome measures

The MAI was used to evaluate the appropriate of prescribing PPIs to older people during hospitalization and at discharge. The original MAI has ten explicit criteria that are calculated for each prescribed medication. Higher scores represent the inappropriate use of each medication [21]. As a secondary outcome measure, in the follow-up assessment, the number of patients who were hospitalized for bleeding within 1 year after discharge was collected using their medical record.

Medication costs for the inappropriate use of PPIs during hospitalization and at discharge were evaluated in both groups from the institution's perspective. The potential cost of inappropriate PPI use after discharge was calculated each month. Indirect cost was not included in the analysis. All costs were adjusted to US dollars and the exchange rate for the conversion of Turkish Lira to US dollars was determined based on February 2020.

Sample size

The predicted rate of change in PPI use in the group that received the clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy was 40%, and this rate was 20% in the control group based on previous studies [24–28]. In the sample size calculation,

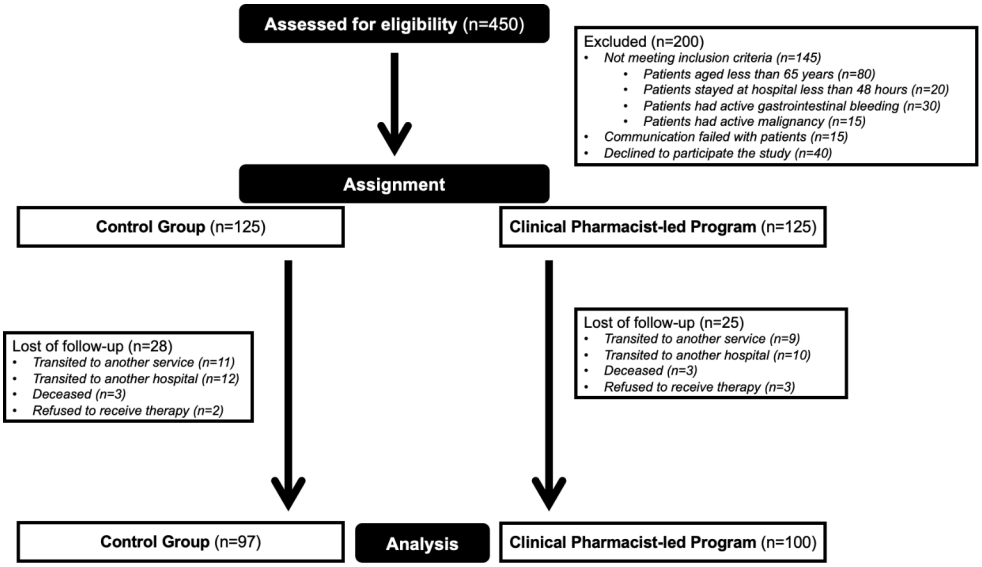

Fig. 1 The flow of participants through the study

Table 1 Characteristics of hospitalized older patients

	Control (n = 97)	Clinical Pharmacist-led Appropriate Acid Suppression Therapy Stewardship Program (n = 100)	*P*
Age (in years) Median (IQR)	79.0 (70.0–86.0)	78.5 (72.0-85.8)	0.95
Sex n (%)			
Female	53 (54.6)	61 (61.0)	0.37
Male	44 (45.4)	39 (39.0)	
Education (year) n (%)			
≤ 8	78 (80.4)	91(91.0)	0.05
> 8	19 (19.6)	9 (9.0)	
History of hospitalization during last 6 months n (%)			
Yes	18 (18.6)	17 (17.0)	0.92
Reason of admission to hospital			
Infection diseases	33 (34.0)	39 (39.0)	0.34
Nephrology	28 (28.9)	34 (34.0)	
Cardiovascular	14 (14.4)	10 (10.0)	
Gastroenterology	6 (6.2)	6 (6.0)	
Hematology	9 (9.3)	4 (4.0)	
Endocrinology	4 (4.1)	1 (1.0)	
Pulmonary diseases	3 (3.1)	6 (6.0)	
PPI use before hospital admission n (%)			
No	71(73.2)	80 (80.0)	0.34
Yes	26 (26.8)	20 (20.0)	
Charlson Comorbidity Index Median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–7.0)	0.34
The number of medications used before admission Median (IQR)	6.0 (3.0–8.0)	5.0 (2.0–8.0)	0.57
Enteral nutrition			
Yes	14 (14.4)	25 (25.0)	0.09
Length of hospital stay (day) Median (IQR)	8.0 (5.5–11.5)	8.0 (5.0–11.8)	0.94

IQR: Inter Quartile Range

with an alpha of 0.05, a power of 80% and a 15% dropout rate, 85 patients were required for each group.

Data analysis

The variables are presented as median (interquartile range) or number (%). The Kolmogorov-Simonov test was conducted to determine the use of either parametric or non-parametric test. The Mann-Whitney U test for continuous data (including MAI score of PPI use during hospitalization and MAI score of PPI use at hospital discharge) and Chi Squared test for nominal data were used to compare the control group and the group who participated in the clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy (including the rate of appropriate use of PPIs based on the guidelines during hospitalization, the rate of potentially inappropriate use of PPIs according to the AGS Beers Criteria©, 2019 at discharge). Fischer's exact test was used to compare the groups (including the number of patients who were hospitalized for bleeding within 1 year after discharge). $P < 0.05$ were considered statistically significant.

Results

A total of 450 patients were assessed for eligibility, and 200 patients were excluded because they did not meet the inclusion criteria (Fig. 1). Among them, 197 older hospitalized patients (n = 97 in the control group, n = 100 in the intervention group) were included in the study. At baseline, there was no significant difference between the characteristics of older hospitalized patients in either group ($P > 0.05$). Older hospitalized patients' characteristics are shown in Table 1.

There was no statistically significant difference between the two groups in the rate of PPI use before hospital admission (20.0% for the clinical pharmacist-led program vs. 26.8% for the control group; $P > 0.05$).

The rate of appropriate PPI use during hospitalization was significantly higher in the clinical pharmacist-led program than in the control group (79.0% for the clinical pharmacist-led program vs. 46.4% for the control group; $P < 0.001$). The rate of potentially inappropriate PPI use at discharge was significantly lower in the clinical pharmacist-led program among older patients discharged with a PPI prescription (35.1% for the clinical pharmacist-led program vs. 61.7% for the control group; $P < 0.05$). The frequency of PPI use in older patients is shown in Table 2.

The median MAI scores for PPIs used during the hospital stay were significantly reduced in the clinical pharmacist-led program compared with the control group (13.0 [12.0–14.0] for the clinical pharmacist-led program vs. 15.0 [13.0–18.0] for the control group; $P < 0.001$). The median MAI scores for PPIs used at hospital discharge were significantly diminished in the clinical pharmacist-led program compared with the control group (11.0 [11.0–13.0] for the

Table 2 The frequency of PPI usage in hospitalized older patients

	Control (n = 97)	Clinical Pharmacist-led Appropriate Acid Suppression Therapy Stewardship Program (n = 100)	*P*
Appropriate use of PPIs based on the guidelines at hospital stay n (%)			
No	52 (53.6)	21 (21.0)	< 0.001*
Yes	45 (46.4)	79 (79.0)	
PPI used at hospital discharge n (%)			
No	50 (51.6)	63 (63.0)	0.10
Yes	47 (48.4)	37 (37.0)	
Potentially inappropriate PPIs by using AGS Beers Criteria©, 2019 at discharge n (%)	n = 47*	n = 37*	
No	18 (38.3)	24 (64.9)	0.07*
Yes	29 (61.7)	13 (35.1)	

* the number of the patients discharged with a PPI prescription; PPI: Proton Pump Inhibitor; *$P < 0.05$

Table 3 MAI scores of PPI in hospitalized older patients

	Control (n = 97)	Clinical Pharmacist-led Appropriate Acid Suppression Therapy Stewardship Program (n = 100)	*P*
MAI score of PPI during hospitalization Median (IQR)	15.0 (13.0–18.0)	13.0 (12.0–14.0)	< 0.001*
MAI score of PPI at hospital discharge Median (IQR)	n = 47*	n = 37*	
	13.0 (11.0–13.0)	11.0 (11.0–13.0)	0.04*

* the number of the patients discharged with a PPI prescription; MAI: Medication Appropriateness Index; PPI: Proton Pump Inhibitor; IQR: Inter Quartile Range; *$P < 0.05$

clinical pharmacist-led program vs. 13.0 [11.0–13.0] for the control group; $P < 0.05$). MAI scores of PPIs used in older patients are presented in Table 3.

One year after discharge, 6 patients in the control group were hospitalized for gastrointestinal bleeding, compared with only 1 patient in the clinical pharmacist-led program; however, this difference was not statistically significant. ($P > 0.05$). When compared to the control group, the clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy was cost saving for older hospitalized patients who used PPIs inappropriately during hospitalization and after discharge (per month). The clinical outcomes and health costs in older hospitalized patients are shown in Table 4.

Discussion

Statement of key findings

To the best of our knowledge, this is the first nonrandomized controlled study investigating the impact of a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy on older hospitalized Turkish patients. Older hospitalized patients who participated in a clinical pharmacist-led program had lower MAI scores for PPI use and a higher rate of appropriate PPI use than the control group during the hospital stay. The clinical pharmacist-led program decreased potentially inappropriate PPI use at discharge. A decline in inappropriate PPI use with a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy resulted in decreased health costs for older hospitalized patients during hospitalization, and after discharge (per month).

Table 4 Comparison of clinical outcome and health costs in hospitalized older patients

	Control (n = 97)	Clinical Pharmacist-led Appropriate Acid Suppression Therapy Stewardship Program (n = 100)	*P*
The number of patients who hospitalized for bleeding within 1 year after discharge n (%)	6 (6.2)	1(1.0)	0.062
			Cost saving
	(n = 52)*	(n = 21)*	
Total cost of inappropriate PPI used during hospitalization (USD)	704.37	245.32	459.05
	(n = 29)**	(n = 13)**	
Total cost of potentially inappropriate PPI usage at hospital discharge (USD) (per month)	79.17	35.49	43.68

* the number of patients used inappropriate PPI during hospitalization; ** the number of the patients used potentially inappropriate PPI at hospital discharge

Strengths and weaknesses

Type of the study (a controlled study) was one of the strengths of this study. The findings of this study promoted involvement of clinical pharmacists into multidisciplinary team to improve medication safety, which are essential for development and implementation of clinical pharmacist-led services in Turkey. The present study has some limitations. The outcome assessment was performed by the clinical pharmacist that provided the intervention using an implicit assessment of appropriate use. This study was conducted in a single hospital within a short period of time by a single clinical pharmacist. This could result in lack of generalizability. According to the components of philosophy of practice for comprehensive medication management [33], the clinical pharmacist-led program in the present study has some limitations (such as lack of patient engagement in care and patient education and counselling and follow-up during transition of care). In the follow-up assessment, only bleeding within 1 year after discharge was assessed without evaluating PPI-related adverse effects (including *C. difficile* or nosocomial pneumonia).

Interpretation

In line with the findings obtained from the control group in the present study, more than half of the older hospitalized patients inappropriately used PPIs for the management of peptic ulcers and gastrooesophageal reflux disease after discharge from internal medicine services in Italy [24].

In pre- and post-intervention (without a control group) studies, a pharmacist-driven guideline reduced PPI use in hospitalized patients in a non-intensive care unit [25] and infection disease service [26].

Prospective interventions targeting appropriate PPI prescription (clinical pharmacist-led audit, feedback, and guideline implementation) significantly reduced inappropriate acid suppression therapy in hospitalized patients, even in follow-up visits at the outpatient clinic [27]. The education program increased the interventions of the medical team, which targeted a decline in the inappropriate PPI use in older hospitalized patients [28]. After establishing a pharmacy, therapeutics committee and education program,

Atkins et al. showed an increase in the appropriate use of PPIs for stress ulcer prophylaxis, especially in older hospitalized patients [29].

In quasi-experimental studies [30, 31], pharmacist-led programs showed cost saving in optimizing the rational use of acid suppressive agents without any difference or reduction in adverse events.

Clinical pharmacist-led medication review services increased the appropriate of prophylactic acid suppression therapy in patients by reducing the cost of elective surgery [32].

Further research

The impact of a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy on patient-related outcomes could be evaluated in future studies. Our intervention targeted the overprescription of PPIs during hospitalization and at discharge. The underprescription of PPIs could be evaluated in future studies.

Conclusion

In this study, a clinical pharmacist-led stewardship program for the appropriate use of acid suppression therapy was optimized for the usage of PPIs in older hospitalized patients. This program improved the appropriate use of PPIs for stress ulcer prophylaxis during the hospital stay and reduced the rate of potentially inappropriate use of PPIs at discharge. According to the secondary outcome findings of the study, the clinical pharmacist-led program reduced the cost of inappropriate PPIs without causing any harm. The further studies will be conducted to implement this clinical pharmacist-led service in Turkey.

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Conflicts of interest The authors declare no conflict of interest.

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