

Overuse of Intravenous Proton Pump Inhibitors in General Medicine and Surgery Wards

Jay N Shah,¹ Jenifei Shah,² Pawan Sharma,³ Jesifei Shah,² Ashim Pandey,³ Chunauti Joshi,³ Devesh Adhikari,³ Grisha Gurung,³ Kalpashri Khatri,³ Lisa Basnet,³ Shailendra Shah,³ Romi Dahal,³ Deep Lamichane³

¹Department of Surgery, Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal, ²Rujin Hospital, Shanghai Jiao Tong University, Shanghai, China, ³Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal.

ABSTRACT

Background: Overuse of stress ulcer prophylaxis is prevalent globally despite guidelines leading to the added cost, especially the intravenous proton pump inhibitor (IVPPI). This study aims to analyze the prevalence of such overuse and be aware of rational use which may help develop local guidelines.

Methods: This study analyzed the prospectively collected data on IVPPI use in adult patients in general wards of medicine and surgery at Patan Hospital, Patan Academy of Health Sciences, Nepal, from April-Jun 2022. Ethical approval was obtained. Variables analyzed were the patient's age, gender, history of peptic ulcer disease, risk for stress ulcer and gastrointestinal bleeding, the status of nil per os (NPO \geq 12 hours), appropriate use of IVPPI, and cost.

Results: Prevalence of IVPPI use was 36.24% (274/756 admissions), surgery 39.45(189/479), medicine ward 30.68% (85/277). The mean age was 43.1 \pm 18.6 years, males 113(41.2%), surgery 189 (69%). Inappropriate overuse in 253(92.3%, significantly more in surgery-182 than medicine-7, $p=0.001$). Appropriate use was in 21 (7.7%, i.e., NPO-15, NPO + gastrointestinal bleed, and NPO + non steroid anti-inflammatory drugs each 3).

Conclusions: Prevalence of IVPPI use was 36.24%. Inappropriate overuse of IVPPI was high (92.2%, 253/274), more in surgery. The nil per os status was the main reason for appropriate use of IVPPI.

Keywords: Acid suppression therapy; cost; general medical surgical ward; intravenous proton pump inhibitor; stress ulcer prophylaxis guideline

INTRODUCTION

Proton-pump-inhibitors (PPIs) reduce gastric acid secretion by irreversibly blocking the H-K-ATPase, it also optimizes platelet function, inhibits fibrinolysis, stabilizes clots, and reduces the risk of ulcer re-bleeding.^{1,2} At equivalent doses, oral medication and intravenous PPI (IVPPI) have comparable acid suppression.³

The guidelines recommend stress ulcer prophylaxis (SUP) in critically ill patients with one out of two 'independent risk factors' (coagulopathy and mechanical ventilation) or two out of 12 'other risk factors'.⁴ The IVPPI is used for patients unable to tolerate orally or impaired gastrointestinal function, or risks of recurrent bleed.^{4,7} The widespread and unnecessary use of SUP, especially intravenous is prevalent in 60-96%.⁸⁻¹¹ Overuse of IVPPI

in general wards is unjustified, wastage of resources increases cost and adverse effects.^{5-10,12-15}

The findings will raise awareness and help in developing practice guidelines to minimize unnecessary use and help decrease the healthcare cost, more importantly in resource-limited low and middle-income countries.

METHODS

This was a cross-sectional study of prospectively collected data on the use of IVPPI in patients admitted to general wards from April-June 2022 at Patan Hospital (PH), Patan Academy of Health Sciences (PAHS), Nepal.

The adult patients aged \geq 14 years in this hospital are admitted to adult wards. Inclusion criteria were adult patients in general wards of medicine (general medicine,

Correspondence: Prof. Dr. Jay N Shah, Department of Surgery, Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal. Email: drjaywufe@gmail.com, Phone: +9779851040139.

psychiatry, cardiology, geriatric, rheumatology, renal, and dialysis) and surgery (general surgery-gastrointestinal, hepatopancreaticobiliary, breast, urology, oncosurgery; otorhinolaryngology, Orthopedic, Obstetrics, and gynecology) who received intravenous PPI (pantoprazole) during the hospital stay. Exclusion criteria were patients with an admission diagnosis of burn, sepsis, shock, in intensive care unit (ICU) or high dependency unit (HDU), flow chart Figure 1.

The sample size was estimated at 270 ($N = z^2 \times p \times 1-p / e^2 = 246$ plus 10% extra for incomplete or missing data = $246+24 = 270$). The confidence level $z=95\%$, the margin of error $e=5\%$, and the prevalence of PPI $p=80\%$ inappropriate overuse use of IVPPI in general wards outside ICU).

Inappropriate overuse of SUP was defined as prescribing PPI without documented indication, 1) the first universally accepted guidelines for SUP by the American Society of Health Systems Pharmacists in 1999⁴ which require the presence of one of two 'independent risk factors' (coagulopathy and mechanical ventilation), or 2) other risk factors out of 12, Table 1a. Additional criteria for SUP included documented history of peptic ulcer disease (PUD), gastrointestinal bleeding (GIB), gastroesophageal reflux disease (GERD), Barret's esophagitis, Zollinger-Ellison syndrome (ZES), helicobacter pylori (HP) positive, and prolonged NPO (≥ 12 h) based on literature, Table 1b.^{6,7,9,11,16} Thus non-critically ill patients outside ICU who were not on prolonged NPO and could be prescribed oral SUP were considered inappropriate overuse, i.e. NPO, NPO with GIB risks, or NPO with NSAIDs.

Data were collected prospectively on a predesigned proforma. Study variables included baseline characteristics (age, gender, admitted ward); documentation or diagnosis of GERD, PUD, GIB; dose, and duration of IVPPI (pantoprazole), and prolonged nil

per os (NPO) status. One lecturer and intern doctors were briefed about the study and data collection from different wards. The lecturer was responsible to oversee the completeness of data. On the first day of data collection, relevant information from patients' charts was included, and on subsequent days the new admissions were based on census records by the nurses in each ward as per routine hospital practice.

For the ease of data collection, only five working days in a week (Sunday, Monday, Tuesday, Thursday, and Friday, because the hospital is off on Wednesday and Saturday) were chosen till the desired sample size was reached. Data were recorded in Microsoft Excel and migrated to SPSS for descriptive analysis (gender, admitted wards, appropriate use of IVPPI, and cost). A Chi-square test was used to find out the association between IVPPI use and admitted wards (medical or surgical services) and the use of IVPPI. A p-value ≤ 0.05 was considered statistically significant.

Ethical approval was obtained from the institutional review committee, IRC-PAHS.

RESULTS

Data of 274 patients receiving IVPPI in general wards were available for analysis (after excluding five for incomplete data). Out of 274, there were 189 (69%) in surgery and 85 (31%) in medicine wards. The overall prevalence of IVPPI use in general wards was 36.24% (274/756 admissions), surgery 39.45 (189/479), and medicine wards 30.68% (85/277).

The mean age was 43.1 y (SD 18.6), females 161 (58.8%), and inappropriate use of IVPPI 92.3% (253/274), Table 1. Among 7.7% (21/274) were an appropriate use of IVPPI, 15 for prolonged NPO of ≥ 12 h, and 3 each for NPO+GIB and NPO+NSAIDs, Table 1.

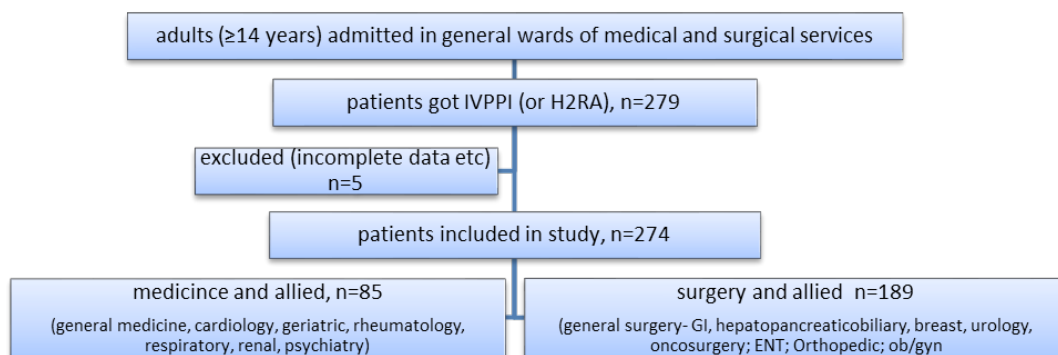


Figure 1. Flow chart of patients in general wards of medicine and surgery who received intravenous proton pump inhibitor (IVPPI) for acid suppression therapy or stress ulcer prophylaxis

Table 1a. American Society of Health-System Pharmacists guidelines on Stress Ulcer Prophylaxis^{4,17,18}

Type	Risk factor
Independent	1. Coagulopathy (including medication-induced coagulopathy): platelet count <50,000 [mm. SUP.3], INR >1.5, or PTT >2x control value
	2. Respiratory failure: mechanical ventilation [greater than or equal to]48 hours
Other	1. Spinal cord injuries
	2. Multiple trauma ([dagger]): trauma sustained to more than one body region
	3. Hepatic failure ([dagger]): total bilirubin level >5 mg/dL, AST >150 U/L (3x ULN), or ALT >150 U/L (3x ULN).
	4. Thermal injuries >35% of body surface area
	5. Partial hepatectomy
	6. Head injury with Glasgow coma score of [less than or equal to]10 or inability to obey simple commands
	7. Hepatic or renal transplantation
	8. History of gastric ulceration or bleeding during the year before admission
	9. Sepsis/septic shock ([dagger]): vasopressor support and/or positive microbiology cultures/ suspected infection
	10. Intensive care unit stay >1 week
	11. Occult or overt bleeding >6 days
	12. Corticosteroid therapy

Table 1b. Additional criteria^{6,7,9,11,16} to that of the above in table 1a

Additional	Risk factors*
	1. Gastrointestinal bleeding (GIB) melena or hematemesis
	2. Peptic ulcer disease (PUD) Gastric ulcer (GU) or Duodenal ulcer (DU)
	3. Barret’s esophagitis
	4. Gastroesophageal reflux disease (GERD)
	5. Zollinger-Ellison syndrome (ZES)
	6. Long-term (over a year) aspirin, continued during 1 month before admission
	7. Long-term (over a year) steroids, continued during 1 month before admission

*Evidence of endoscope, investigation, documented by treating physician

Table 2. Clinico-demographic data of IVPPI use among adult patients in general surgery and medicine wards of a university teaching hospital, N=274

Variables	N	%	
Gender	Male	113	41.2
	Female	161	58.8
Admitted ward	Surgery [#]	189	69
	Medicine [#]	85	31
Appropriate use of IVPPI*	Yes	21	7.7
	No	253	92.3
If yes indication	NPO	15	5.5
	NPO with GIB	3	1.1
	NPO with NSAID	3	5.5

[#]surgery = general surgery, gastrointestinal, hepatobiliary and pancreatic, breast, urology, oncosurgery;

#medicine and allied- general internal medicine, cardiology, respiratory, renal, rheumatology, psychiatry;

*appropriate use = documented indication as per guidelines in Table 1a, 1b, and NPO, NPO+GIB, or NPO+NSAID;

NPO= nil per os for ≥ 12 h, GIB= gastrointestinal bleed, NSAID= non-steroid anti-inflammatory drug

Table 3. Association appropriate use of IVPPI admitted wards, N=253

Admitted wards	Appropriate use of IVPPI (N)		Chi-square test	
	yes	No	χ^2 (1, N = 274)	p-value
Surgery	7	182	13.5	0.001
Medicine	14	71		

DISCUSSION

The overall overuse of SUP in the form of IVVPI among non-critical non-GIB patients in general wards of surgery and medicine outside ICU in this study was found in 92.2% (253/274). Among inappropriate overuse, it was more common in surgery (182 out of 189) than in medicine (71 out of 85), the difference was statistically significant (χ^2 13.5, p-value 0.001). Among 21 patients (7.7% of total 274 patients) who appropriately received intravenous, 15 (71.4%) were on prolonged NPO and 3 (14.3%) each for NPO plus GIB and NPO plus NSAIDs.

The recommended use of IVVPI includes patients who require SUP but cannot tolerate it orally or have a pathological hypersecretory state (for example, ZES and risk of GIB). Inappropriate overuse of IVVPI is a waste, adds to the healthcare cost, and may also increase the risk of side effects like nosocomial pneumonia and spontaneous bacterial peritonitis in cirrhotic patients.^{6,7} Reason for overuse of SUP in surgery patients may be because of NSAIDs and NPO status. Prevalence of inappropriate SUP was inappropriately high among noncritical orthopedic trauma patients, 96.1% received AST, and IVVPIs accounted for 95.3%.¹⁹ In the present study, patients in both medicine and surgery wards received IVVPI as SUP without clear indication, more in surgery wards, (Table 2). The widespread overuse (misuse) of SUP has been reported globally in patients other than for established indications like GERD, PUD, GIB, or high-risk critically ill patients leading to wastage of resources and adding to the healthcare cost.^{5-9,14,16} The use of IVVPI for patients who can tolerate oral medicine is further unjustified because at an equivalent dose the oral intravenous preparation PPI has comparable acid suppression.³

Recent studies report a low frequency of clinically important bleeding and routine use of SUP does not significantly reduce bleeding. The inappropriate overuse of SUP has been questioned by the studies based on observations that superficial gastric erosion due to stress has a small risk of clinically significant bleeding and will require treating >900 low-risk patients to prevent one clinically significant GIB.²⁰ In non-ICU patients, the risk scores of 10 or more were found to be appropriate for SUP (to achieve number-needed-to-treat 95 to prevent one nosocomial GIB) with risk factors like age >60 years, liver disease, acute renal failure, sepsis, and use of anticoagulants.²¹ The studies concluded that there is no justification for routine AST and SUP in patients in general medical and surgical wards without known risk factors. In addition, when patients are not on prolonged NPO there is no justification to prescribe IVVPI.

The overuse of SUP is a global phenomenon, and continues in clinical practice in 60-95% of patients in general wards or after the patient is transferred out of ICU.²² Study reports that 71% (76 of 107) received IVVPIs without appropriate indication, 52% it was prescribed randomly, and 46% of patients were not NPO.⁸ The study further mentions some of the risk factors as 'admissions to a surgical ward, female patients, and junior doctors.'⁸ In the present study we did not specifically look into the prescribing physician's rank, because the hospital practice has a routine morning handover conference every day for new admissions, and daily morning ward rounds are done by the team, including faculties (lecturers to professors) to ensure the management is in agreement within the departments.

Non-steroidal anti-inflammatory drugs (NSAIDs) have complications of ulcers or bleeding in only 1-2%.²³ Historically, it took 100 years after the first NSAID (aspirin- acetylsalicylic acid in 1897) when the first PPI (omeprazole) became available in 1989, followed by other PPIs- lansoprazole in 1995, pantoprazole in 1997, rabeprazole in 1999, and esomeprazole in 2001.^{7,23} The term 'NSAID' appeared in literature only in the 1960s.²⁴ The NSAID effectively controls pain, inflammation, and pyrexia by inhibiting the cyclooxygenase (COX) enzyme and decreasing the biosynthesis of prostaglandins and thromboxane. The relative risk depends on the presence of risk factors (age >65 years, history of complicated PUD, two or more NSAIDs at the same time; concomitant therapy with antiplatelet agents, anticoagulants, corticosteroids; severe illness; and the type and dose of NSAID), HP infection. Different NSAIDs have RR of GI complications ranging from <2 (aceclofenac, ibuprofen, and celecoxib), 2 to 4 (rofecoxib, diclofenac and

ketoprofen, meloxicam, nimesulide, sulindac), 4 to 5 (tenoxicam, naproxen, diflunisal), and >5 (piroxicam, azapropazone and ketorolac and indomethacin).^{23,25}

Interestingly, mortality due to ulcer bleeding has remained constant, even though the incidence of bleeding has decreased after advances in endoscopic and newer drugs. Studies reveal mortality is not a direct consequence of the bleeding ulcer but related to other conditions like cardio-pulmonary, multi-organ failure, or malignancy, and thus treatments directed for the bleeding ulcer have little impact on mortality.²³ The comparative study of oral vs. IVPPI shows that for bleeding peptic ulcers oral PPI is safe and can be used in place of IVPPI at a lower cost and can also be used for patients at high risk of re-bleeding.²⁶

The gap in the knowledge for the implementation of the international guidelines, and lack of national or institutional protocol combined with fear of gastric complications of NSAIDs, and the generally accepted perception that “it doesn’t harm to add” a PPI to the drug cocktail are some of the reasons for overuse of PPI.²⁷ Our findings suggest the need for the development of local guidelines for evidence-based practice of appropriate use of IVPPI in non-critical non-ICU patients in general wards. All the stakeholders, prescribing clinicians, hospital pharmacies, and management need to work together to decrease the overuse use of IVPPI, the cost, and side effects. Unexplained abdominal pain or vomiting should not be the indication for IVPPI unless there are other reasons and once the patient can tolerate oral medicine intravenous route should be discontinued.^{9,11,28} The education, multidisciplinary approach with appropriate intervention has shown improvements in rational use of stress ulcer prophylaxis in admitted patients for appropriate selection of drug, dose, route, and duration with a reduction in healthcare cost.²⁹

At an average cost of 80 NPR (125 Nepalese rupees = 1 USD) for one dose of 40 mg IV pantoprazole locally, it’s a considerable amount of saving not only for a low-income country but also a major chunk of increased health care costs globally.^{6,10} In the present study, 253 of 274 (92.3%) patients admitted in general medical and surgical wards had inappropriate overuse of 1582 dosages (average 6.3 injections) of IVPPI unnecessarily costing NPR 126562, which would translate to NRs 9,303,840/y in cost saving for approximately 20000 admissions in a year; which is substantial given the total charge of NPR 30,000 for a laparoscopic cholecystectomy including one-day bed charge of 300 NPR per day. This saving can pay 17

doctors for a whole year at a 48000/mo revised salary for entry-level doctors in Nepal.³⁰

Some of the limitations of this study could be that we were not able to analyze the ‘documented’ decision as to why intravenous PPI was used even when patients could tolerate it orally and could swallow the pill, were non-critical patients in the general ward outside of the intensive care unit. We did not specifically analyze the rank of prescribing doctors, and the side effects of proton pump inhibitors. We did not analyze whether oral stress ulcer prophylaxis was continued (another form of use of PPI) after stopping intravenous because in this study we concentrated on intravenous use only.

Our findings are consistent with the studies showing continued and widespread inappropriate overuse of intravenous proton pump inhibitor (IVPPI) among non-critical patients in general medical and surgical wards. Familiarity with evidence-based guidelines of stress ulcer prophylaxis, implementation of multidisciplinary intervention strategies is necessary for the development of hospital practice guidelines and monitoring for the rational use of stress ulcer prophylaxis (SUP), acid suppression therapy, especially the unnecessary intravenous use in patients in general wards.

The possible limitations of the present study may be that we did not specifically analyze the data from individual departments of surgery or medicine. This was mainly because we did not want to stigmatize the individual departments. Also, analyzing the overuse by individual departments will require an adequate sampling for each department. In the future, we plan to expand the study, possibly in multicenter to include more departments to analyze the overuse of IVPPI by a specific department.

CONCLUSIONS

This study found an overall prevalence of IVPPI use was more than 1/3rd (36.24%, 274 out of 756) among patients in general wards, more in surgery (39.45%, 189 out of 479) than in medicine (30.68%, 85 out of 277). Inappropriate overuse was high (92.3%, 253 out of 274), and significantly more in surgery (182 out of 189) wards. The NPO status was the most appropriate reason for IVPPI. Our findings reaffirm the reported overuse of IVPPI in non-critical non-ICU patients admitted to general wards.

ACKNOWLEDGEMENT

We thank the nurses in the surgery and medicine wards

for their support during the data collection.

CONFLICT OF INTEREST

None

REFERENCES

1. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care.* 2005 Mar;20(1):35–45. [DOI, PubMed, Google Scholar, Full Text]
2. Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. *BMJ.* 2005 Mar 12;330(7491):568. [DOI, PubMed, Google Scholar, Full Text]
3. Olsen KM, Devlin JW. Comparison of the enteral and intravenous lansoprazole pharmacodynamic responses in critically ill patients. *Aliment Pharmacol Ther.* 2008 Aug 1;28(3):326–33. [DOI, PubMed, Google Scholar, Full Text]
4. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and Approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm.* 1999;56(4):347–79. [DOI, PubMed, Google Scholar]
5. Grube RRA, May DB. Stress ulcer prophylaxis in hospitalized patients not in intensive care units. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm.* 2007 Jul 1;64(13):1396–400. [DOI, PubMed, Google Scholar]
6. Nasser SC, Nassif JG, Dimassi HI. Clinical and cost impact of intravenous proton pump inhibitor use in non-ICU patients. *World J Gastroenterol WJG* [Internet]. 2010 Feb 28 [cited 2020 Jan 3];16(8):982–6. [DOI, PubMed, Google Scholar, Full Text]
7. Pang SH, Graham DY. A clinical guide to using intravenous proton-pump inhibitors in reflux and peptic ulcers. *Ther Adv Gastroenterol.* 2010 Jan;3(1):11–22. [DOI, PubMed, Google Scholar, Full Text]
8. Slattery E, Theyventhiran R, Cullen G, Kennedy F, Ridge C, Nolan K, et al. Intravenous proton pump inhibitor use in hospital practice. *Eur J Gastroenterol Hepatol.* 2007 Jun;19(6):461–4. [DOI, PubMed, Google Scholar]
9. Craig DGN, Thimappa R, Anand V, Sebastian S. Inappropriate utilization of intravenous proton pump inhibitors in hospital practice--a prospective study of the extent of the problem and predictive factors. *QJM Mon J Assoc Physicians.* 2010 May;103(5):327–35. [DOI, PubMed, Google Scholar, Full text]
10. Bischoff LM, Faraco LS, Machado LV, Bialecki AV, de ALMEIDA GM, Becker SC. Inappropriate usage of intravenous proton pump inhibitors and associated factors in a high complexity hospital in Brazil. *Arq Gastroenterol.* 2021;58:32–8. [DOI, PubMed, Google Scholar, Full text]
11. Elmubarak AA, Badi S, Yousef BA. Adherence to Stress Ulcer Prophylaxis Guideline in Medicine Unit at Soba University Hospital: A Descriptive Retrospective Study. *Dr Sulaiman Al Habib Med J.* 2021 Jun 29;3(3):125–30. [DOI, Google Scholar, Full text]
12. Laheij RJF, Sturkenboom MCJM, Hassing RJ, Dieleman J, Stricker BHC, Jansen JBMJ. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA.* 2004 Oct 27;292(16):1955–60. [DOI, PubMed, Google Scholar, Full text]
13. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA.* 2006 Dec 27;296(24):2947–53. [DOI, PubMed, Google Scholar, Full text]
14. Nasser SC, Nassif JG, Dimassi HI. Clinical and cost impact of intravenous proton pump inhibitor use in non-ICU patients. *World J Gastroenterol WJG.* 2010;16(8):982–6. [DOI, PubMed, Google Scholar, Full text]
15. Mohzari YA, Alsaegh A, Basheeruddin Asdaq SM, Al Shanawani SN, Albraiki AA, Bagalb A. The Pattern of Intravenous Proton-Pump Inhibitor Utilization at an Academic Medical Center in Riyadh, Saudi Arabia. *J Res Pharm Pract.* 2020 Sep;9(3):151–4. [DOI, PubMed, Google Scholar, Full text]
16. Guillaumondegui OD, Gunter OL, Bonadies JA, Coates JE, Kurek SJ, De Moya MA, Sing RF, Sori AJ. Practice management guidelines for stress ulcer prophylaxis. Chicago: Eastern Association for the Surgery of Trauma. 2008:1-24. [Google Scholar, Full Text, Weblink]
17. Foroughinia F, Madhooshi M. Attachment to stress ulcer prophylaxis guideline in the neurology wards of two teaching and non-teaching hospitals: A retrospective survey in Iran. *J Res Pharm Pract.* 2016;5(2):138–41.

- [DOI, PubMed, Google Scholar, Full text]
18. Vazin A, Mousavinasab SR, Sabetian G. Evaluation of Stress Ulcer Prophylaxis Guideline in the Intensive Care Units of a Teaching Hospital: A Cross Sectional Study. *J Pharm Care*. 2020 Jun 26;65–9. [DOI, Google Scholar]
 19. Li H, Li N, Jia X, Zhai Y, Xue X, Qiao Y. Appropriateness and Associated Factors of Stress Ulcer Prophylaxis for Surgical Inpatients of Orthopedics Department in a Tertiary Hospital: A Cross-Sectional Study. *Front Pharmacol*. 2022;13:881063. [DOI, PubMed, Google Scholar, Full text]
 20. Stevens AM, Thomas Z. The Case against Stress Ulcer Prophylaxis in 2007. *Hosp Pharm* [Internet]. 2007 Nov 1 [cited 2020 Jan 3];42(11):995–9. Available from: <https://doi.org/10.1310/hpj4211-995> [DOI, Google Scholar]
 21. Herzig SJ, Rothberg MB, Feinbloom DB, Howell MD, Ho KKL, Ngo LH, et al. Risk factors for nosocomial gastrointestinal bleeding and use of acid-suppressive medication in non-critically ill patients. *J Gen Intern Med*. 2013 May;28(5):683–90. [DOI, PubMed, Google Scholar]
 22. Ghosh A, Dey S. Inappropriate use of proton pump inhibitors in non-critical indoor patients in a tertiary care teaching hospital in Eastern India. *Int J Res Med Sci*. 2019 Dec 25;8(1):230–3. [DOI, Google Scholar, Full Text, Weblink]
 23. Lai PSM, Wong YY, Low YC, Lau HL, Chin KF, Mahadeva S. Unexplained abdominal pain as a driver for inappropriate therapeutics: an audit on the use of intravenous proton pump inhibitors. *PeerJ*. 2014;2:e451. [DOI, PubMed, Google Scholar, Full text]
 24. Sostres C, Gargallo CJ, Lanás A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther*. 2013;15(Suppl 3):S3. [DOI, PubMed, Google Scholar, Full text]
 25. Buer JK. Origins and impact of the term “NSAID.” *Inflammopharmacology*. 2014 Oct;22(5):263–7. [DOI, Pubmed, Google Scholar]
 26. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf*. 2012 Dec 1;35(12):1127–46. [DOI, PubMed, Google Scholar, Full text]
 27. Toosi SMV, Vahed ARE, Maleki I, Bari Z. Comparison of oral versus intravenous proton pump inhibitors in preventing re-bleeding from peptic ulcer after successful endoscopic therapy. *Middle East J Dig Dis*. 2018;10(4):236. [DOI, PubMed, Google Scholar]
 28. van den Bemt PMLA, Chaaouit N, van Lieshout EMM, Verhofstad MHJ. Noncompliance with guidelines on proton pump inhibitor prescription as gastroprotection in hospitalized surgical patients who are prescribed NSAIDs. *Eur J Gastroenterol Hepatol*. 2016 Aug;28(8):857–62. [DOI, PubMed, Google Scholar]
 29. Hong Y, Ye Z, Gao Z, Rao Y. Continuous improvement on the rationality of prophylactic injectable PPIs usage by a clinical pharmacist-led guidance team at a Chinese tertiary teaching hospital. *J Int Med Res*. 2020 Oct;48(10):300060520954729. [DOI, PubMed, Google Scholar, Full text]
 30. admin. New Salary Scale of Health Workers in Nepal with Position 2078 - LokSewa Job Nepal [Internet]. 2021 [cited 2022 Jun 29]. [Weblink]