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Original Article

Factors Affecting Gastric Perforation Patient Outcome with History of Arthritis and Long Term Use of NSAIDs in Dr. Kariadi Semarang Period 2020–2022

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Abstract

Background : The incidence of gastric perforation gives a high mortality outcome. The second most common cause of gastric perforation is long-term use of NSAIDs. In cases of arthritis during the COVID-19 pandemic, a conservative therapeutic approach and administration of NSAIDs are preferred. Due to this, researchers want to know the factors affecting gastric perforation cause by NSAIDs.
Methods : An analytic descriptive study with a retrospective cohort study design, using electronic medical records of patients at RSUP Dr. Kariadi Semarang from January 2020 – December 2022. Data collected was in the form of demographics, diagnoses, procedures, preoperative conditions, scoring system, and outcome.
Results : PULP score, one of prognostic factor, has a good level of significance compared to other scoring systems in determining the prognostic mortality of patients with gastric perforation. The combination of variables between the type of NSAIDs and the type of arthritis has a direct correlation with a positive inter-variable power of 86.7% and a significance of 0.049 on patient outcome.
Conclusion : NSAIDs pose a risk of gastric perforation in long-term use. tNSAIDs carry a higher risk inducing gastric perforation than selective NSAIDs.

Keywords : NSAIDs, Gastric Perforation, Arthritis, Scoring System

INTRODUCTION

The incidence of complications from peptic ulcers has not decreased. Bleeding and perforation are the most common complications. In a study conducted by Dadfar A *et al* in Norway, it was stated that the incidence of this complication is more common in women than men, and this risk increases with age > 65 years in the last 3 decades. NSAIDs can cause mucosal injury by inhibiting cyclo-oxygenase (COX)-1 by reducing cytoprotective mucosal prostaglandins and reducing secretion of the protective bicarbonate mucus barrier in the stomach and small intestine.[1]

NSAIDs are recommended as first-line therapy for arthritis to relieve inflammatory pain. In cases of arthritis during the COVID-19 pandemic, conservative therapeutic approaches and administration of painkillers have been widely used. The increase in the incidence of COVID-19 that occurred in 2020 has caused increasing health problems in the community such as postponement of elective surgery cases including in the musculoskeletal field.[3,4] As in a study conducted by Mikko uimonen *et al* it was said that the waiting time for surgery in the musculoskeletal field in Finland during the COVID-19 pandemic was a lengthening of the waiting time between 93 days to 100 days. Due to the limitations of the COVID-19 virus detection and screening system in the pandemic era resulted in limiting doctors' practice time and postponement of elective surgeries to reduce the risk of COVID-19 transmission in face-to-face outpatient sessions or in elective arthritis surgeries.[1,2,5,6]

According to the Indonesian Orthopedic Association in Orthi – Magz – May 2020, surgery is prioritized in orthopedic emergency cases and in patients who have complaints of severe pain in the musculoskeletal system that does not subside with medical administration.[7] Based on the problems above, the author wants to see which factors could affect the outcome of patients with gastric perforation due to NSAIDs and by finding these affecting factors, it is hoped that steps can be taken and consider to prevent gastric perforation.

METHODS

An analytic descriptive study with a retrospective cohort study design, using data sources obtained from patients electronic medical records at RSUP Dr. Kariadi Semarang from January 2020 – December 2022. Demographic data of patients with gastric perforation, the relationship between variables and outcomes, and the power between variables to affect outcomes are presented in the form of tables, graphs and diagrams which were processed using the SPSS ver 23 programming. Discussion of results research is presented using comparisons, literature review and data synthesis.

Patients who were included on this study which have diagnosed with gastric perforation due to long-term uses of NSAIDs and received definitive surgical therapy at Dr. Kariadi Semarang between January 2020 to December 2022. Patients who were excluded were patients who met the inclusion criteria but did not have data completed / insufficient of independent variables needed for data synthesis and patients whose outcome died with the main cause not from gastric perforation and its direct complications. Researchers have obtained research approval with ethical clearance from the Health Research Ethics Committee of RSUP Dr. Kariadi Semarang.

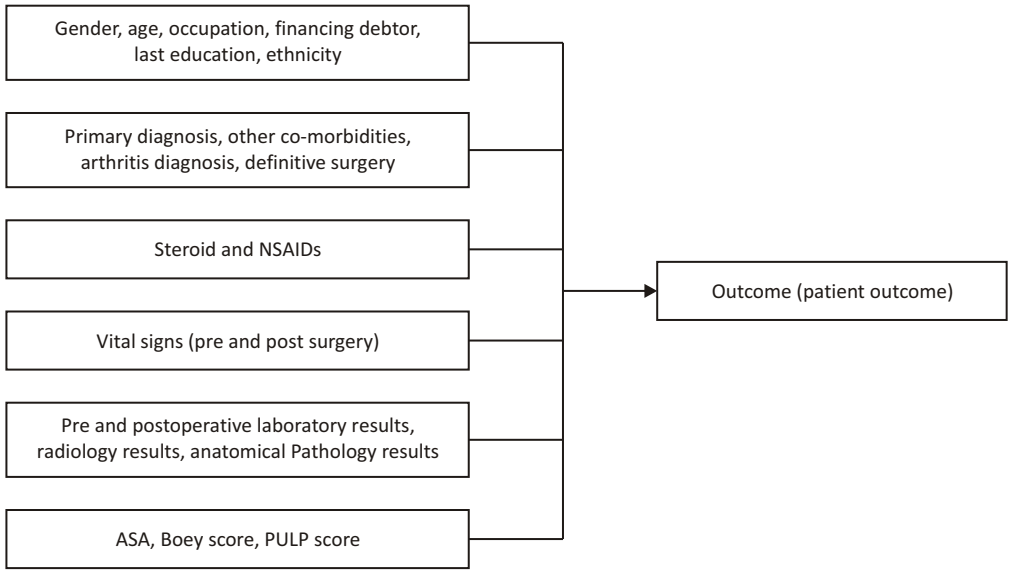


Figure 1. Variables that affects to outcome

RESULTS

Table 1 shows subject demographic caracteristics. Table 2 shows characteristics of independent variables. Table 3 shows characteristics of independent variables and outcome.

DISCUSSION

Gastric perforation is closely related to long-term use of anti-inflammatory drugs. NSAIDs are known to be the second causative factor in gastric perforation after Helicobacter pylori infection in initiating peptic ulceration in the upper GI tract. NSAIDs cause mucosal injury due to cyclo-oxygenase (COX)-1 inhibition along

TABLE 1
Subject Demographic Characteristics

No	Characteristics of Subjects	Type of Characteristics	Frequency	Percentage (%)
1	Gender	Male	4	66.7
		Female	2	33.3
2	Age	< 65 years	5	83.3
		More 65 years	1	16.6
3	Occupation	Housewaives	2	33.3
		Fisherman	1	16.7
		Private employees	2	33.3
		Farmer	1	16.7
4	Debtor	COVID funding	1	16.7
		Private	0	0
		JKN Non PBI	1	16.7
		JKN PBI	4	66.7
5	Last education	Elementary	3	50.0
		Junior High School	1	16.7
		Senior High School	1	16.7
		Non complete elementary	1	16.7
6	Ethnic Group	Java	6	100

TABLE 2
Characteristics of Independent Variables

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
Diagnosis					
1	Diagnosis	Peritonitis generalisata ec perforasi corpus gaster	2	3	1.000
		Peritonitis generalisata ec perforasi antrum gaster	1	0	
2	Other Comorbid	None	1	0	1.000
		Comorbid (heart disease, metabolic, kidney disease, liver disease, DM, HT)	2	3	

TABLE 2. Continued

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
3	Sepsis	None	3	1	0.400
		Sepsis existance	0	2	
4	Arthritis	OA genu	1	2	0.189
		OA hip	0	1	
		RA genu	12	0	
		RA hip	0	0	
5	Definitive operation	Laparotomy omental plug	2	3	1.000
		Laparotomy omental patch	1	0	
Use of anti-inflammatory types					
6	Use of steroids	No usage history	2	3	1.000
		Has a long history of use	1	0	
7	NSAID type	Traditional NSAID	2	3	0.208
		COX-2 selective inhibitor	1	0	
Additional Examination					
8	Hb pre operation	Not diagnosed with anemia	1	1	0.800
		Diagnosed with anemia	2	2	
9	Leucosyt pre operation	Under 11.000	2	2	0.800
		Above 11.000	1	1	
10	Trombosit pre operation	150.000 – 400.000	3	3	1.000
		Under 150.000 or above 400.000	0	0	
11	Creatinine pre operation	Low (< 1.47)	2	2	1.000
		High (> 1.47)	1	1	
12	Natrium pre operation	Normal	3	0	0.05
		High	0	1	Linier 0.038
		Low	0	2	
13	Kalium pre operation	Normal	1	2	0.513
		High	1	0	
		Low	1	1	
14	Chlorida pre operation	Normal	2	1	0.317
		High	1	1	
		Low	0	1	
15	Hb post operation	Not diagnosed with anemia	0	1	0.317
		Diagnosed with anemia	3	2	

TABLE 2. Continued

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
16	Leucosyt post operation	Under 11.000	2	2	1.000
		Above 11.000	1	1	
17	Trombosit post operation	150.000–400.000	2	2	1.000
		Under 150.000 or above 400.000	1	1	
18	Patologic anatomy	Chronic gastritis	3	2	0.208
		Non chronic gastritis	0	1	
14	Chlorida pre operation	Normal	2	1	0.317
		High	1	1	
		Low	0	1	
15	Hb post operation	Not diagnosed with anemia	0	1	0.317
		Diagnosed with anemia	3	2	
16	Leucosyt post operation	Under 11.000	2	2	1.000
		Above 11.000	1	1	
17	Trombosit post operation	150.000–400.000	2	2	1.000
		Under 150.000 or above 400.000	1	1	
18	Patologic anatomy	Chronic gastritis	3	2	0.208
		Non chronic gastritis	0	1	
Physical Examination					
19	Pulse rate pre operation	60–100x/ minute	1	1	1.000
		Below 60 or above 100x/minute	2	2	
20	Systolic pre operation	more than equal to 100	3	1	0.400
		under 100	0	2	
21	RR pre operation	16–22x/ minute	0	0	1.000
		Above 22x/minute	3	3	
22	Temp pre operation	Normal (36–37.5°C)	0	0	1.000
		High (above 37.5°C)	3	3	
23	Pulse rate post operation	60–100x/ minute	3	1	0.400
		Below 60 or above 100x/minute	0	2	
24	Systolic post operation	more than equal to 100	3	1	0.400
		under 100	0	2	
25	RR post operation	16–22x/ minute	3	1	0.400
		Above 22x/minute	0	2	
26	Temp post operation	Normal (36–37.5°C)	3	3	1.000
		High (above 37.5°C)	0	0	

TABLE 2. Continued

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
Scoring system					
27	ASA pre operation	ASA 1	0	0	0.400
		ASA 2	0	0	
		ASA 3	2	0	1.000
		ASA 4	1	3	
28	BOEY Score	1 (mortality 10%)	1	0	0.189
		2 (mortality 55,5%)	2	1	
		3 (mortality 100%)	0	2	
29	PULP Score	Low risk (0–7)	3	0	0.05
		High risk (8–18)	0	3	Corelation Spearman 0.001 Linier 0.025

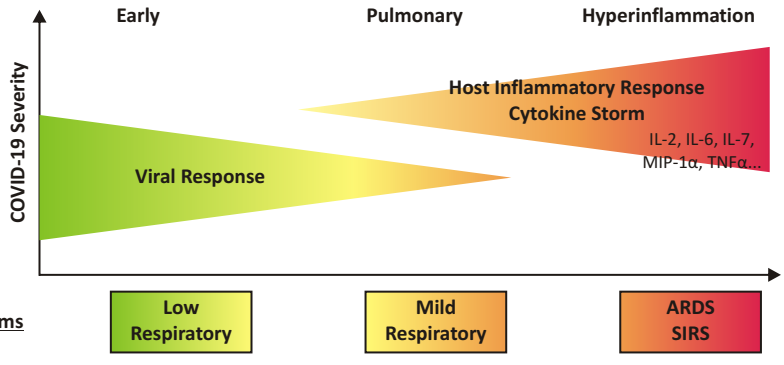
TABLE 3
Characteristics of Independent Variables and Outcome

No	Independent variable	R Square	Significancy
1	Type of NSAID used and type of arthritis	86.7%	0.049
2	Sepsis and other comorbid	55.6%	0.296
3	Operations (omental plug and patch) on the main diagnosis and perforation site	50%	0.354
4	Preoperative leukocytes and Hb	15%	1.000
5	Preoperative sodium, potassium, chloride	91.1%	0.130
6	Preoperative systolic and pulse	66.7%	0.192
7	Hb, leukocytes, and postoperative thrombocytes	33.3%	0.808
8	Preoperative ASA and PA results	55.6%	0.296

with reduced cytoprotective mucosal prostaglandins and reduced secretion of protective mucobicarbonate inhibitors in the stomach and duodenum.[8,9]

In a study conducted by Dadfar A *et al* who conducted a case study in Norway at the beginning of the 2000-2020 decade, it was stated that the incidence of complications due to NSAIDs was more common in women than men and this risk increased with age >65 years in 2 last decade.1 This is different from research at Dr. Kariadi General Hospital for the period 2020–2022 which found that males were more exposed to gastric perforations (66.7%) than females. Age under 65 years also has a higher percentage than those aged 65 years and over at 83.3%. The cut-off age of 65 years in this study was adjusted according to the PULP prognostic score, which said those over 65 years of age had a higher tendency of mortality. This can be confirmed logically because increasing age increases the decline in the function of vital organs which will assume a decrease in life expectancy.

Differences in the type of work, financing status (debtor), and the latest education in this study did not make a significant difference. The author also has not



OA Therapies	Early Pulmonary	Pulmonary / Hyperinflammation
NSAIDs	✓	~
Paracetamol	✓	✓
Corticosteroids	~	~
Opioids	Weak ✓ / ~ strong/IS	Weak ✓ / ~ strong/IS
mAbs	✓	✓

✓ Continue ~ Critical risk/benefit

Figure 2. Classification of COVID-19 disease states and overlaywith OA-associated treatments. The figure shows the escalatingphases of disease progression with COVID-19, with associated symptoms and the relevance of OA treatments with their possible continuation, disontinuation, or cos/benefit depending on available literature data. ARDs, cute respiratory distress syndrome:COVID-19, coronavirus disease 2019; IL, interleukin; IS, immunosuppressive; mAbs, monoclonal antibodies; MIP, macrophage inflammatory protein; NSAISs, nonsteroidal antiinflammatory drugs; OA, osteoarthritis; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor. [Colour figure can be viewed at wileyonlinelibrary.com]

found any literary sources confirming that demographic data on the variables of employment, debtors and education contribute significant significance. This is understandable because the differences in the variables above do not directly provide a potential difference in the pathophysiology of gastric perforation and its output. This also assumes that differences in financing status in the community do not make a significant difference to patient output.

In 70% of patients with a history of long-term use of NSAIDs had abnormalities on endoscopic examination (mucosal erosion, ulceration, and subepithelial bleeding) and only 10% complained of dyspeptic symptoms.[9] Serious complications of peptic ulcer (such as bleeding and perforation) can occur without any previous symptoms. Gastroduodenal peptic ulcer complications increase up to five times in patients who regularly consume NSAIDs. Peptic ulcer bleeding occurs when there is erosion into the subepithelial lining of blood vessels. It occurs more frequently in mucosal capillaries with a smaller caliber and if it occurs in a larger caliber the risk of bleeding is also more massive and rapid, thus giving the clinical presentation of patients with hematemesis melena. The clinical presentation of hypovolemic shock is also common in patients with ulcers and erosions of vessels of large caliber.[10–12]

Mucosal erosion and ulceration that causes bleeding can also cause iron deficiency anemia.[13] This is in accordance with the findings of the preoperative laboratory of patients at Dr. Kariadi General Hospital, Semarang, namely 66.7% had anemia in the iron deficiency category. Increased leukocytes are also present in the majority of patients with gastric perforation, this is in accordance with the theory of perforation development, namely sterile peritonitis becomes bacterial peritonitis in the advanced phase after 24 hours of perforation.

Sometimes deep ulceration does not cause bleeding which is also at risk of perforation. The site of NSAID-induced peptic ulcer perforation is more common in the stomach than the duodenum and is associated with higher and longer-than-recommended doses of NSAIDs.[11,14] This is consistent with the presentation of surgical findings in research at Dr. Kariadi General Hospital Semarang for the period 2020–2022, namely the location of the findings in the

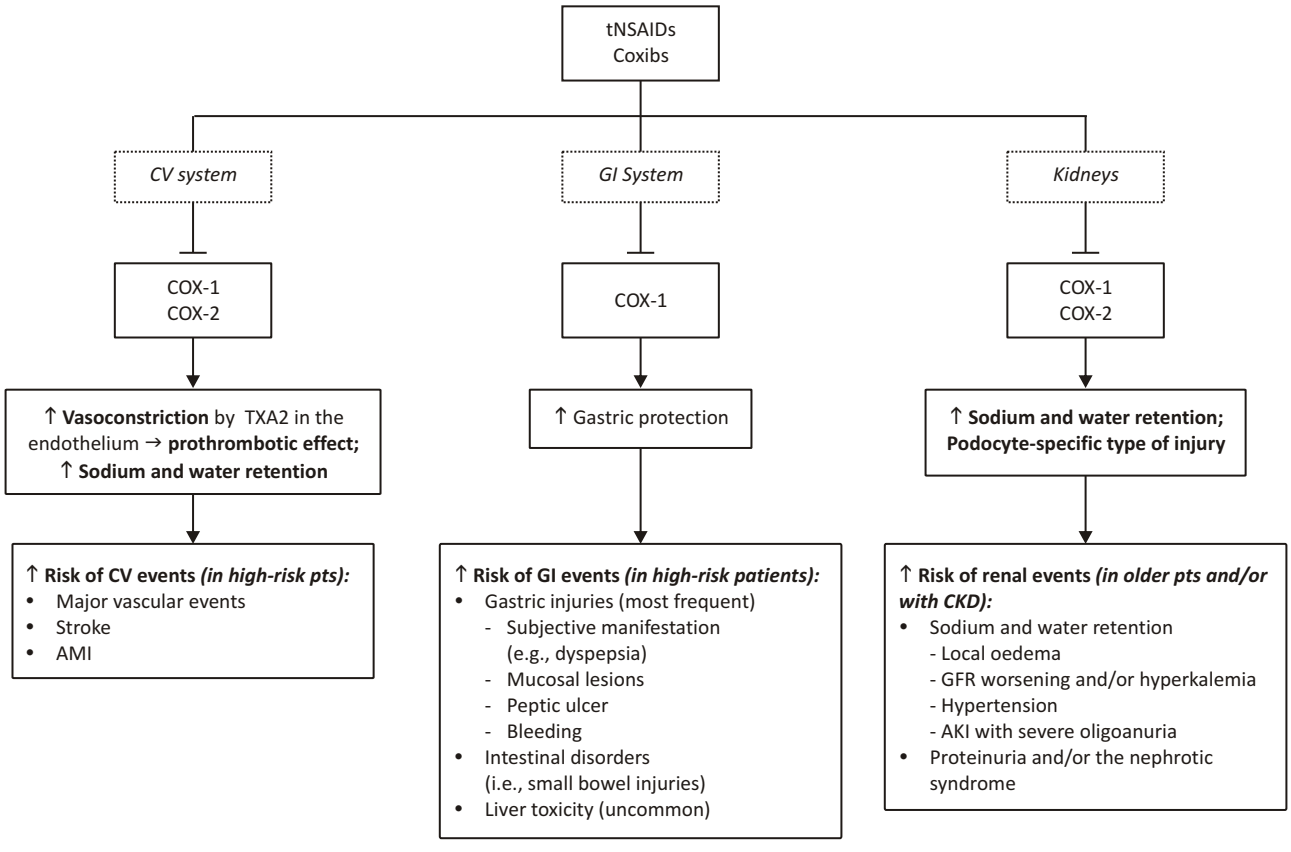


Figure 3.

gastric corpuscle as much as 83.3%. In addition to the clinical presentation of hypovolemic shock, sepsis/septic shock and complications due to gastric perforation are also common in patients who come to the emergency room or are hospitalized.[15,16]

In this study, sepsis was only found in 50% of definitive preoperative cases, possibly because patients who were consulted from the internal medicine department, or came directly to the emergency room, had good initial physical resistance to sepsis. This can be proven in the physical examination of vital signs and initial laboratory results which show that there is no deterioration in the condition to sepsis. In the initial management in a comprehensive and holistic way, tertiary hospitals also make a large contribution compared to hospitals that are not referral centers for the initial preoperative conditions.[17] However, according to the capacity of tertiary hospitals, cases with gastric perforation are often complicated cases. As many as 83.3% of cases of gastric perforation come with comorbid factors such as heart disease, metabolism, kidney disease, liver, DM and hypertension. These comorbid factors will contribute big points for increasing gastric perforation mortality scores such as the BOEY and PULP scores.[14,15,18]

Conservative therapeutic approaches for the treatment of patients affected by arthritis (OA, RA) need to be adjusted so as not to place the patient at further risk.[19] Osteoarthritis (OA) is the most common degenerative joint disease that affects quality of life and causes disability. OA is multifactorial. Common histopathological findings in OA are articular cartilage damage, subchondral bone sclerosis and osteophyte formation, joint cap hypertrophy, and periarticular muscle dysfunction, and synovial inflammation.[6,20,21] Synovitis is actually a hallmark of OA, characterized by increased vascularity, macrophage and lymphocyte infiltration, and villous hyperplasia. At present, there are no studies investigating the potential association between respiratory viral infections and the development of OA, as described for parainfluenza and coronavirus and the incidence of rheumatoid arthritis.[22] Similarly, looking the other way, there is no documentation of an increased risk of respiratory infections for OA patients compared with the general population.[23]

Osteoarthritis (OA) is a leading cause of disability among older adults worldwide. In Italy, the prevalence is 24.9% in women and 16% in men and is highest in people aged > 85 years (63.0% in women and 50.9% in men). The main risk factors for OA are age, sex, obesity and other mechanical factors. The most common lesions are the

joints of the knees, hips and hands. Patients often present with joint pain, joint stiffness, swelling and loss of normal joint function which negatively impact their quality of life. In this study it was found that the majority of arthritis diagnoses were genu OA, this is consistent with previous studies regarding the most common location of OA, namely genu predisposition.[23,24]

The goal of treatment is to relieve inflammatory pain and improve physical function through non-pharmacological and pharmacological interventions. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapy. The workings of a group of heterogeneous chemical agents that inhibit the production of prostaglandins (PG) and thromboboxane A through cyclooxygenase (COX) blockade. Traditional NSAIDs (tNSAIDs), which target COX-1 and COX-2 isozymes to varying degrees, have a consolidated role in the symptomatic treatment of pain in musculoskeletal disorders, but their long-term use is limited by toxicity, especially cardiovascular (CV), gastrointestinal (GI) and kidney toxicity.[15,23,25]

In a study at Dr. Kariadi Hospital in Semarang, it was found that the use of traditional NSAIDs had more presentations than selective COX-2 inhibitors of 83.3%. Although a COX-2 selective NSAID (coxib) was originally introduced as a safer alternative to tNSAIDs, their use is associated with a high risk of cardiovascular (CV) events.[22,26] According to a recent Italian long-term active pharmaceutical covigilance study, NSAIDs were responsible for 8.4% of emergency department visits and 24.4% of emergency department visits resulting in hospitalization.

In practice, drug and patient characteristics influence the choice of therapy. The efficacy profile of NSAIDs has been described by a meta-analysis of randomized controlled trials (RCTs). In 74 RCTs, totaling 58.556 OA patients, there was insufficient statistical evidence to support the superiority of diclofenac 70 mg/day, naproxen 750 mg/day and ibuprofen 1200 mg/day over placebo for pain and improvement of physical function. In contrast, for pain relief, diclofenac 150 mg/day and etoricoxib given at 30 mg/day, 60 mg/day and 90 mg/day had the probability of achieving a minimum clinically important difference compared with placebo C 95%, achieving 100% only. in the case of diclofenac 150 mg/day and etoricoxib 60 mg/day. Notably, a significant linear dose-effect response was found only for celecoxib (P=0.030), diclofenac (P=0.031) and naproxen (P=0.026).[26,27]

For improvement of physical function, minimal clinically significant treatment effect was observed for diclofenac 150 mg/day only. The authors concluded that diclofenac at a dose of 150 mg/day was the best NSAID in terms of improving pain and function in OA, exceeding the maximum doses of commonly used NSAIDs, including ibuprofen, naproxen, and celecoxib. Although etoricoxib at a maximum dose of 60 mg/day is as effective as diclofenac 150 mg/day for the treatment of pain, its estimated effect on physical disability is unclear. Finally, paracetamol has no clinical effect and is not recommended for the symptomatic treatment of OA.[26–28]

However, selection is constrained by patient age, co-morbidities and polypharmacy, and by the benefit/risk balance of the drug, which all together influence cardiovascular risk, gastrointestinal and renal function. While the efficacy profiles of various NSAIDs are described, the differences in safety profiles are not straightforward.[29]

The thing that attracted attention in this study was the finding that preoperative sodium had a significant difference with the occurrence of differences in the output of patients with gastric perforation. The authors have not found any literature studies that can directly prove that there is a relationship between sodium levels and gastric perforation output. Gastric perforation will give systemic effects, one of which will cause electrolyte imbalance, especially in patients with hypovolemic shock and septic shock. This should also be followed by an imbalance between potassium and chloride. However, in this study the levels of potassium and chloride did not make a significant difference to the patient's output. The authors also performed calculations on the gastric perforation prognosis scoring, and according to previous journal literature, PULP scoring has a better significance than other scoring systems.

The type of non-selective NSAID impacts the frequency of GI upset. This is in accordance with the results of multiple regression calculations which state that the combined variables between the type of NSAID and the type of arthritis have a direct correlation with a positive 86.7% inter-variable power and a significant difference in the relationship of 0.049. Results from two previous epidemiological studies confirmed the risk scale for various tNSAIDs (ie ibuprofen, diclofenac, naproxen, ketoprofen, indomethacin, piroxicam, and azapropazone); azapropazone and piroxicam were associated with the highest risk of gastroduodenal bleeding (odds ratios [OR] 23.4–31.5 and 13.7–18, respectively) and with diclofenac and ibuprofen with the lowest (OR 3.9–4.2 and 2). .0–2.9, respectively).[11,30]

CONCLUSION

NSAIDs cause mucosal injury due to cyclo-oxygenase (COX)-1 inhibition along with reduced cytoprotective mucosal prostaglandins and reduced secretion of protective mucobicarbonate inhibitors in the stomach and duodenum.[1,3,4] PULP score has a good level of significance statistical compared to other scoring systems in determining the prognostic mortality of patients with gastric perforation. The type of NSAID (traditional and selective) and the location of arthritis play a role in the

factors affecting of gastric perforation which could lead to increased mortality. The used of non-selective tNSAIDs with the location of genu has a higher effect on the occurrence of ulcers in the gastric mucosa which will lead to gastric perforation incidences. Appropriate considerations need to be declare in administering appropriate long-term anti-inflammatory drugs in patients with arthritis, this is adjusted to the patient's condition, history of other comorbidities and complications that are and may occur. Surgery is the modality therapy of choice for arthritis that cannot be treated with oral medication. Selective NSAIDs in this study are more recommended if patients suffer from arthritis who cannot undergo surgical therapy that requires long-term administration medicine.

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