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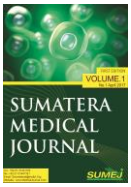

Factors Affecting Gastrointestinal Disorders in Patients Undergoing Regular Hemodialysis

R. Pasaribu, R. A. Muzasti

Sumatera Utara University College of Medicine, Division of Nephrology-Hypertension, Department of Internal Medicine

Abstract. Chronic Kidney Disease (CKD) is an immense health issue. The prevalence is increasing each year worldwide, including Indonesia. Consistent with this trend, the prevalence of hemodialysis (HD) as a therapy is also increasing. CKD as well as HD often result in some complications, one being gastrointestinal disorders. Many factors are correlated with the incidence of gastrointestinal disorders in CKD patients undergoing HD. This is an observational analytical research with cross-sectional study at RS Khusus Ginjal Rasyida Medan. The datas used in the research are primary datas, obtained from Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire to assess severity of gastrointestnal disorders in HD patients, and secondary datas, obtained from medical records of age, smoking history, use of aspirin, HD duration, BUN, and Kt/V (as a parameter of HD adequacy). Then the datas are analyzed univariately, bivariately, and mutivariately using biner logistic regression model. All patients (100%) suffer from gastrointestinal disorders, with the most common being mild ones (67,1%). Final multivariate analysis shows that the duration of HD, BUN level, and Kt/V are significantly correlated with worsening gastrointestinal disorders (OR:14,157 ,95%CI 2,851 ± 71,183, p=0,001; OR: 8,352, 95%CI 0,914 ± 76,344, p= 0,060; OR:8,219 ,95%CI 0,893 ± 75,674, p= 0,063).

Keyword: Factors affecting gastrointestinal disorders, hemodialysis

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1 Introduction

Each year, the prevalence of chronic kidney disease (CKD) is increasing[1]. According to Riset Kesehatan Dasar (Riskesdas) 2013, the prevalence of the citizens in Indonesia who suffered from CKD was 0.2%. Following the trend of increased prevalence of CKD, the number of people who go through hemodialysis (HD) was also increased. According to Riskesdas 2018, it was recorded that 19,3% of the population going through hemodialysis therapy.[2] CKD and HD can cause various complications, and gastrointestinal disorder is one of them. The complications in the gastrointestinal tract are fairly often found in kidney failure patients. [3] These gastrointestinal problems are constipation, abdominal pain, diarrhea, gastroesophageal reflux disease, indigestion, and

Corresponding author at: Sumatera Utara University College of Medicine , Medan, Indonesia

E-mail address: rosarina_pasaribu@yahoo.com

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eating disfunction.[4] The gastrointestinal disoders on CKD patients who undergo HD are caused by various factors, whether by uremia or the dialysis process, such as being elderly, use of aspirin, long-term dialysis, smoking, high blood urea nitrogen (BUN) ratio, and adequacy of HD (Kt/V). [5-9] Therefore, the authors are interested in conducting a study of the factors affecting gastrointestinal disorders in patients undergoing regular HD.

2. Methodology

This is an analytical observational research with a cross-sectional study design. This research was held in Rumah Sakit Khusus Ginjal Rasyida, Medan. Inclusion criteria in this research are patients over the age of 18 and agreed to be interviewed with the following exclusion criteria, patients who do not want to fill the questionnaire completely. Based on the calculation using the Lemeshow formula, there are 70 people who participated in this research. Datas were obtained from interview using Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire that has been translated to Indonesian and validated with 0,75 reliability score. This questionnaire is used to assess severity of gastrointestinal disorders and consists of 15 questions to which answers are never(0), sometimes(1), often(2), and always(3). The overall score is catagorized into mild (0-15) and severe (16-45).[10] In addition, the datas were also obtained from medical records to record the BUN ratio, Kt/v, age, use of aspirin, smoking history, and duration of HD. The statistical analysis is held using 24th SPSS version. Datas will be tested using Chi-Square, if the data are not qualified to use Chi-Square, Fisher Exact Test is used instead. Variables with p value<0.25 are included in multivariates test, it is considered significant if $p<0.05$.

3. Result

In this research, it is shown in table 1 that regular HD patients who has gastrointestinal disorders mostly are of elderly age, 40-60 years old (51,4%) The average duration of HD is (33,71 ± 35,293) months. According to smoking history, many of the HD patients do not smoke (72,9%). The prevalence of HD patients who use aspirin are (21,4%). The average BUN ratio in HD patients is (62,4157 ± 4,66997). HD patients who got adequate hemodialysis are 14,7%

The prevalence of regular HD patients who had gastrointestinal disorders based on Gastrointestinal Symptoms Rating Scale (GSRS) is (100%). According to GSRS, (67,1%) had mild gastrointestinal disorders and (32,9%) had severe gastrointestinal disorders.

Based on GSRS, there are 5 identifiable symptoms; abdominal pain (stomach pain, abdominal discomfort, nausea), reflux (reflux and heartburn), indigestion (rumbling, bloating, burping, passing gas or flatus), diarrhea (diarrhea, loose stools, urgent need for bowel movement), and constipation (constipation, hard stools, sensation of not completely emptying the bowel).[4] According to the questionnaire, 29,1% had abdominal pain, 28,6% had reflux, 71,8% had indigestion, 45,7% had constipation and 36,2% had diarrhea.

4. Discussion

In this research, it is obtained that the most prevalent proportion undergoing HD at Rumah Sakit Khusus Ginjal Rasyida Medan is the elderly group (40-60 years old) with a percentage of (51,4%), this result is consistent with data obtained from Indonesia Renal Registry where, the most prevalent group to undergo HD was the 45-64-year-old group with a percentage of (59,13%).[11] According to Hydarinia-Naieni *et al*, the most common group going through HD was patients of age 50 and above with percentage of (77,5%).[8] Whereas in a research by Dong *et al*, it was obtained that the average age of patients undergoing HD was (58.67 ± 14.39), which is older compared to the average age in this research (47,66 ± 13,069). [4]

Average duration of HD that patients go through is (33,71 ± 35,293) months, which is shorter compared to that of Shabka *et al*, (2,98 ± 3,42) years or (35,76 ± 41,04) months.[12] Patients with smoking history (27,1%) and using aspirin (smoking history and do not use aspirin 21,4%) are fewer than patients who do not. These findings are consistent with Hydarinia-Naieni *et al* in which the patients who have smoking history (8,75%) and use of aspirin (40%) are also fewer. [8]

The patients' average BUN level is (62,4157 ± 4,66997) mg/dL. Whereas in Kim *et al*, it was obtained that the average BUN level was (52,20 ± 30,21) mg/dL.[13] In this research, the average BUN level in patients with mild gastrointestinal is (62,354 ± 5,336) mg/dL while those with severe gastrointestinal disorders show (62,543 ± 2,973) mg/dL, these datas are slightly higher compared to those of Carrera-Jiménez *et al*, in which the average BUN level for mild gastrointestinal disorders was (60 ± 15) mg/dL and for severe gastrointestinal disorders was (61,6 ± 26) mg/dL.[5]

All patients in RSKG Rasyida Medan have Kt/V level more than 1,2, this finding is in parallel with the data obtained from Indonesia Renal Registry, where 74% patients

undergoing HD in Indonesia have already achieved Kt/V level target of more than 1,2. The adequate datas obtained in this research are only (14,3%) while the inadequate ones are (85,7%). The reason is because Kt/V is said to be adequate if the level is more than 1,2 for patients undergoing HD three times a week and more than 1,8 for patients undergoing HD two times a week.[11] Inadequate HD may cause non optimal therapy and will still cause sytemic problems that have been caused previously by CKD, and one of them is gastrointestinal disorders. Inadequate HD can still cause high urea level. Urea plays an important role in increased gastrin production that can cause irritation of mucosa, which then will lead to many gastrointestinal disorders.[8]

Based on GSRS (Gastrontestinal Symptoms Rating Scale) used in this research, all patients have at least one gastrointestinal disorder. This data is consistent with Daniel *et al* in which 90% of the CKD patients going through HD had gastointestinal symptoms.[14] In this research, it is obtained that indigestion is the most common symptom (71,8%) followed by constipation (45,7%), and the least common symptom is reflux (28,6%). But according to Zuvela *et al,* the most common ones were dyspepsia, abdominal pain, and constipation.[15]

Table 1 Baseline Characteristics of Regular Hemodialysis Patients at RS Khusus Ginjal Rasyida Medan

Variable	Mean ± SD, n (%)
Age (years old)	47,66 ± 13,069
Young Adult(18-40)	21(30)
Adult(40-60)	36(51,4)
Elderly(>60)	13(18,6)
Age (years old)	47,66± 13,069
Adult (18-60)	57 (81,4)
Elderly (>60)	13(18,6)
Aspirin	
Yes	15(21,4)
No	55(78,6)
Duration of Hemodialysis	33,71 ± 35,293
Short-term Hemodialisis (≤12 months)	22(31,4)
Long-term Hemodialysis (>12 months)	48(68,6)
Blood Urea Nitrogen (BUN)	62,4157 ± 4,66997
High Risk (>56 mg/dl)	59(84,3)
Low Risk (<56 mg/dl)	11(15,7)
Smoking History	
Yes	19(27,1)
No	51(72,9)
Kt/V (2 times a week)	1,4916 ± 0,07095
Adequate	1(1,6)
Inadequate	60(98,4)
Kt/V (3 times a week)	1,5044 ± 0,03283
Adequate	9(100)
Inadequate	0(0)
Kt/V	1,4933 ± 0,06724
Adequate	10(14,3)
Inadequate	60(85,7)

Gastrointestinal Problem rate(GSRS)	
Mild(1-15)	47(67,1)
Severe(16-45)	23(32,9)

Table 2 Baseline Characteristic of Hemodialysis Patients with Gastrointestinal Problem

	Total n=70	**Severe Gastrointestinal Problem Mean ± SD, n (%)**	**Mild Gastrointestinal Problem Mean ± SD, n (%)**	**p**	**OR(95%CI)**
Age (tahun)		47,217 ±11,786	47,872 ± 13,771	0,859	0,889
Adult (18-60)	57	19(33,3)	38(66,7)		(0,242 ± 3,262)
Elderly (>60)	13	4(30,8)	9(69,2)		
Aspirin				0,057	3,048
Yes	15	8(53,3)	7(46,7)		(0,941 ± 9,871)
No	55	15(27,3)	40(72,7)		
Duration of Hemodialysis		49,391 ±43,626	26,043 ±27,842	0,004[a]	7,778
Short-term (≤12 months)	22	2(9,1)	20(90,9)		(1,632 ± 37,065)
Long-term (>12 months)	48	21(43,8)	27(56,3)		
Blood Urea Nitrogen (BUN)		62,543 ±2,973	62,354 ± 5,336	0,063	5,946
High (>56 mg/dl)	59	22(37,3)	37(62,7)		(0,712 ± 49,649)
Low (<56 mg/dl)	11	1(9,1)	10(90,9)		
Smoking History				0,315	1,745
Yes	19	8(42,1)	11(57,9)		(0,586 ± 5,201)
No	51	15(29,4)	36(70,6)		
Kt/V		1,490 ±0,074	1,495 ±0,065	0,092	5,211
Adequate	10	1(10,0)	9(90,0)		(0,618 ± 43,919)
Inadequate	60	22(36,7)	38(63,3)		

[a]Significant(p-value ≤0.05)

Based on this research, the duration of hemodialysis is related significantly (p = 0,004) to the occurrence of worsening gastrointestinal disorders. This is consistent with the findings of Santoso *et al* which found that severe decreased appetite happened mostly in patients going through HD for more than a year, compared to those with duration of less than a year with the (p=<0,001), the decreased appetite is caused by gastrointestinal disorder. [16] This happened because long-term hemodialysis induce decrease in appetite.

Long-term hemodialysis cause gastric problem that eventually will increase gastric acid and render patients to lose appetite and body weight significantly.[17]

In this research, patients who use aspirin tend to have severe gastrointestinal disorders compared to ones who do not, with prevalence of (53,3% VS 27,3%). The reason behind this is aspirin can damage the mucosa of gastrointestinal wall. Ulcer formation by aspirin is caused by topical injury and systemic effect of prostaglandin mucosa layer depletion by COX inhibitor. Prostaglandin plays an important role in protecting the integrity of gastric mucosa by increasing local blood flow, synthesis and secretion of mucus and bicarbonate. Without the normal production of prostaglandin, gastric environment will be susceptible to exogenous (i.e. smoking) or endogenous factors (H. pylori, acid, pepsin, bile acid) and as the result, is more susceptible to developing gastric ulcer and bleeding as complications. Acid environment cause aspirin to stay unionized and accumulate in gastric mucosa cell, which change cell permeability and promp ulceration.[18,19,20] However, statistically the use of aspirin does not have significant correlation with gastrointestinal problem (p=0,057). This finding is consistent with Hydarinia-Naieni *et al* (p=0,360).[8]

In this research, patients who have smoking history tend to have severe gastrointestinal disorders compared to the ones who do not have smoking history, with prevalence of (42,1% VS 29,4%). This is because cigarette smoke and its active substances can cause mucosal cell death, inhibition of cell renewal, decrease in blood flow to gastrointestinal mucosa, and disturbance of mucosal immunity system.[21] However, statistically in this research there is no significant correlation between smoking history and gastrointestinal problem (p=0,315). This is consistent with the findings in Fidekiewicz which stated that smoking did not have significant correlation with irritable bowel syndrome, which was a gastrointestinal disorder (p=0,144).[22]

In this research, patients who have BUN level >56 mg/dL tend to have severe gastrointestinal disorder compared to the ones with BUN level less than 56 mg/dL, with the prevalence of (37,3% VS 9,1%). The reason behind is the high urea level in blood could cause uremic syndrome in advanced chronic kidney disease patients, which can lead to various systemic organ disorders, and gastrointestinal disorder is one of them. Urea can increase the diffusion of ion hydrogen back through mucosa wall and increase gastrin level due to decreased gastrin clearance through kidney. The increase in gastrin synthesis eventually acts as an important stimulus to acid secretion,one of

several factors related to gastric mucosa injury in kidney failure patients. Gastrin decreases pyloric sphincter tone, a high level of gastrin can cause biliary reflux, which will worsen mucosa injury. Even though statistically there is no significant correlation between BUN and degree of gastrointestinal problem (p=0,063), this is consistent with the findings in Hydarinia-Naieni et al (p=0,514). [3,8.23]

Patients with inadequate hemodialysis tend to have severe gastrointestinal disorder compared to patients with adequate hemodialysis (36,7% VS 10%). This is because the poor adequacy of hemodialysis may cause a non optimal therapy and will still cause sytemic problems that have been promoted previously by CKD, and one of them is gastrointestinal disorders. Inadequate hemodialysis can also causes urea to remain high. Urea plays a great role in increasing gastrin, which cause mucosa injury, eventually resulting in various digestive symptoms. However statistically, in this findings there is no significant correlation between Kt/V and degree of gastrointestinal problems (p=0,092). This is consistent with Gök et al with (p=0,18). [3,8,24]

In this research, statistically there is no significant correlation between age and gastrointestinal disorders (p=0,889). This finding is consistent with Hydarinia-Naieni et al (p=0.549), this can happen when the elder group patients, in answering the questionnaire, are affected by chronic symptoms they have had for a long time, which made them feel used to it, that the patients feel it is difficult to differentiate the degree of the symptoms. In other study, it is also stated that elder group patients are more conservative to pain and reluctant to tell others when the pain take place. [5,8,25]

According to the final result of multivariate analysis, hemodialysis duration is a dominant risk factor that cause worsening of gastrointestinal symptoms in regular hemodialysis patients with (p= 0,001). Patients that have been through hemodialysis for a long time (more than 1 year), are 14 times more likely to have severe gastrointestinal disorders. Followed by BUN (Blood Urea Nitrogen) and adequacy with (p= 0,063, OR= 8,219 and p=0,060, OR= 8,352).

Table 3 Final model of biner logistic regression

Variabel	OR	95% CI	*p value*
Hemodiaylisis duration	14,157	2,815 –71,183	0,001
BUN	8,352	0,914 –76,344	0,060
Adequacy HD(Kt/V)	8,219	0,893 – 75,674	0,063

5. CONCLUSION

1. The prevalence of hemodialysis patients having gastrointestinal disorders is 100% with the most common being mild gastrointestinal disorders. (67,1%).
2. There is significant correlation between hemodialysis duration and worsening of hemodialysis duration (p=0,004).
3. Based on multivariate analysis, worsening gastrointestinal symptoms is affected by duration of hemodialysis as the dominant factor, followed by BUN level and adequate hemodialysis Kt/V, where long-term hemodialysis (≥12 months), high BUN level (≥ 56 mg/dL), adequate hemodialysis (≥1,2 for three times a week and ≥1,8 for twice a week) patients are 14,157; 8,352; and 8,219 times more at risk respectively in worsening of gastrointestinal disorders compared to patients with short-term hemodyalisis (<12 months), low BUN level (<56 mg/dL), and inadequate hemodialysis (<1,2 for three times a week and <1,8 for twice a week).

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