

Radiation-induced nausea and vomiting

Is ABO blood group as important as radiation and patient-related factors? An observational study

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Abstract

Despite the improvements in cancer screening and treatment, it still remains as one of the leading causes of mortality worldwide. Nausea and vomiting as the side effects of different cancer treatment modalities, such as radiotherapy, are multifactorial and could affect the treatment continuation and patient quality of life. Therefore, the aim of this study was to assess the possible linkage between ABO blood groups and radiation-induced nausea and vomiting (RINV), also its incidence and affecting factors.

One hundred twenty-eight patients referring to Tohid hospital of Sanandaj, Iran, were selected and the patients and treatment-related factors were determined in a cross-sectional study. Patients' nausea and vomiting were recorded from the onset of treatment until 1 week after treatment accomplishment. Also, previous possible nausea and vomiting were recorded. The frequencies of nausea and vomiting and their peak time were examined during the treatment period.

The association between ABO blood group and the incidence of radiotherapy-induced nausea and vomiting (RINV) were significant and it seems that A blood group patients are the most vulnerable individuals to these symptoms. The association between Rhesus antigen and the time of maximum severity of RINV may indicate that Rhesus antigen affects the time of maximum severity of RINV. The incidence of RINV was not affected by Karnofsky performance status, but it was related to the severity of RINV. Furthermore, among the factors affecting the incidence of nausea and vomiting, nausea and vomiting during patient's previous chemotherapy, radiotherapy region, and background gastrointestinal disease were shown to be three important factors.

In addition to familiar RINV-affecting factors, ABO blood group may play an important role and these results address the needs for further studies with larger sample size.

Abbreviations: 5-HT = 5-hydroxytryptamine, CINV = chemotherapy-induced nausea and vomiting, GI = gastrointestinal, KPS = Karnofsky performance status, NCCN = National Comprehensive Cancer Network, Rh = Rhesus antigen, RINV = radiotherapy-induced nausea and vomiting, RT = radiotherapy.

Keywords: ABO blood group, radiotherapy, radiotherapy-induced nausea and vomiting

1. Introduction

Cancer is one of the leading causes of mortality worldwide, while radiotherapy (RT), surgery, chemotherapy, and hormone therapy

are its basic treatment options. About 40% of cancer patients undergo radiation therapy as the main or adjuvant treatment which destroys cancerous cells by ionizing radiation.^[1]

A conventional external RT regimen could be up to 40 fractions during 6 to 8 weeks and about 50% to 80% of cancer patients undergoing this type of treatment may show nausea and vomiting during and/or after their treatment process.^[2] Lower well-being and quality of life, physical and total energy, and more frequent anxiety and depressed mood have been reported among nauseated patients than the patients without nausea.^[3]

Nausea and vomiting could be induced by radiation (RINV) and by chemotherapy agents (CINV). These side effects are multifactorial and could disturb the treatment process and also patient quality of life.^[2,4] Radiotherapy-induced nausea and vomiting could induce dehydration, malnutrition, and electrolyte imbalance which all affect the patient quality of life and it is generally less severe and less frequent than CINV but could last longer and interrupt RT.^[5] Also, mild RINV is unpleasant and could affect the treatment process.^[2] Nausea itself has a higher frequency and greater effect on quality of life than vomiting and some studies have reported that nausea is the most distressing symptom of RT.^[6]

After patient irradiation during RT, free radicals will be released which induce inflammatory responses. Releasing histamines and other transmitters during the inflammatory reaction may be the cause of RINV.^[7] 5-hydroxytryptamine

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(5-HT) is released in response to the radiation and acts on the 5-HT receptor which could stimulate the vomiting center of medullary. This hypothesis needs more studies but, the use of 5-HT receptor antagonists, which prevent RINV could be an indirect proof for it.^[8]

The number of studies regarding CINV is more than RINV. Among both of these studies, one perspective interested in the assessment of antiemetic drug's effectiveness and another perspective was the description of nausea and vomiting frequencies and their affecting factors. There are many factors affecting RINV, including patient specific and treatment factors, but it seems that we need more studies on individual risk factors in radiation therapy patients.^[2] The severity and time of clinical signs and symptoms could be affected by irradiated volume and physical properties of radiation and amount of the dose.^[8] The RINV could be reduced by better planning such as smaller irradiated volume, also RINV has to be managed for the patient which is inevitable.^[5]

The ABO blood group antigens and their association with a wide variety of conditions and pathologies such as cancers have been extensively investigated during the last 5 decades and a more consistent relationship is observed for pancreatic and gastric cancers.^[9] ABO blood group could be able to influence the individuals' predisposition to these disorders through their capacity of modulating the hemostatic system and the inflammatory response.^[10] Reports regarding the relation between ABO blood group and severity of various disorders, including cancers, were somewhat controversial.^[11] The incidence of RINV, its onset and peak, and their association with physical and patient-related factors and also its linkage with the ABO blood group were the aim of this study.

2. Material and methods

In this cross-sectional study, all of one hundred forty-four patients referring to Tohid hospital of Sanandaj, Iran, in 2015 which met inclusion criteria were selected. Fourteen people refused to cooperate and 2 others discontinued their treatment process. The patients with the ages under 18 years were excluded from the study and the other exclusion criteria were drug and alcohol addictions and previous radiotherapy. Also, critically ill patients, with a possible delay in their treatment process were not included at the study and the data of the patients which used anti-nausea and vomiting drugs for the situations other than radiotherapy during the study were not included too. Also, the x-ray was used for all of the included patients and the application of any other ionizing radiations was assumed as exclusion criteria except in mastectomy breast cancer patients in whom electron boost was used.

The age range of participants was 18 to 117 years. The simulations were done by a CT scanner (Light Speed RT 16, GE Healthcare) and the irradiation was performed by a linear accelerator (Synergy Elekta Platform, Elekta, Sweden).

The ABO blood groups were determined in the same laboratory and the patients were followed for 1 week before the onset of treatment until 1 week after treatment completion, as a short-interval follow-up. The data about the frequencies of nausea and vomiting and their peak time, their onset day, the number of nausea episode, the number of vomiting episode, mean of hours between treatment and RINV, frequent RINV episode time, and treatment interruption were collected during the study period.

Besides demographic information, the data about previous chemotherapy and surgery, the mean size and number of used fields, exposure regions, total dose and dose per fraction, treatment intent, the existence of distant metastasis, background gastrointestinal (GI) and pulmonary diseases, karnofsky performance status (KPS), and nausea and vomiting in any situation, such as pregnancy, motion sickness, and previous chemotherapy, were collected. The data about type of cancer and its stage, anti-nausea and vomiting and anti-steroid drug consumption also were collected and their associations with RINV were analyzed. The data of people who discontinued their treatment process were discarded to minimize the missing data.

The incidence of RINV was assessed based on patients' blood groups and other related factors. Among the patients who experienced RINV, for additional follow-up, the symptoms were assessed based on anti-nausea drug administration.

2.1. Statistical evaluation

The data were analyzed by SPSS software (SPSS Inc, Chicago, IL) using parametric and non-parametric tests. The age, total accumulated RT dose, fraction number and fraction doses, and other quantitative variables were compared between the groups by *t*-test, one-way ANOVA or Kruskal–Wallis tests based on its distribution. The associations between nominal variables such as RINV with other nominal or ordinal variables such as the stage of cancer were analyzed by χ^2 test. The *P*-value less than 0.05 was considered as significant.

2.2. Ethical review

The informed consent was taken from all of the participants and the study was approved by Kurdistan University of Medical Sciences ethical committee. The data and material are available with the first and corresponding authors.

3. Results

3.1. Patient-related factors

Of one hundred twenty-eight individuals, 46.9% were male and 53.1% were female and the mean age was 52.30 ± 17.03 years. Distant metastasis was diagnosed in 28.1% of cases and 57.0% had $KPS \geq 80$ and 43.0% had $KPS \leq 70$. Chemotherapy was not performed on the 56.3% of patients previously, but 11.7% had chemotherapy within 3 weeks before RT and the other 32.0% had previous chemotherapy more than 3 weeks ago.

Percentage of radiation therapies applied to different sites was as follows: 38.3% to the thorax and breast regions, 20.3% to abdomen and pelvic, 35.9% to head and neck, and 5.5% were applied to other sites. The breast cancers (25%), lymphomas, Hodgkin and non-Hodgkin (9.4%), brain cancers including astrocytoma, glioblastoma, meningioma, medulloblastoma, and ependymoma (9.4%), esophagus (3.9%), gastric (3.1%), endometrial (3.1%), larynx (3.1%), melanoma (2.3%) were involved most frequently. Of these patients, 30.5% were at end stage and 6.3% at stage 1.

The ABO blood group distribution of participants was 38.3%, 28.9%, 9.4%, and 23.4% for A, B, AB, and O blood groups, respectively. The other factors, including previous chemotherapy, surgery, background GI disease, pretreatment nausea, and vomiting (<7 days), are shown in Table 1.

Table 1
The investigated factors and their association with RINV.

Variables	RINV		P
	Yes	No	
Sex, number (%)			
Male	29 (48.33)	31 (51.67)	0.308
Female	39 (57.35)	29 (42.65)	
Treatment time, number (%)			
Morning	25 (55.55)	20 (45.45)	0.911
Mid-afternoon	7 (50)	7 (50)	
Late-afternoon	36 (52.17)	33 (47.83)	
Number of used fields, number (%)			
1	1 (100)	0 (0)	0.681
2	28 (50)	28 (50)	
3	11 (50)	11 (50)	
4	28 (57.14)	21 (42.86)	
Pervious chemotherapy, number (%)			
No chemotherapy	33 (45.83)	39 (54.17)	0.106
<3 wk ago	11 (73.33)	4 (26.67)	
>3 wk ago	24 (58.53)	17 (41.47)	
Mean field size, cm ² , number (%)			
<200	5 (41.66)	7 (58.34)	0.598
200–400	16 (50)	16 (50)	
>400	47 (55.95)	37 (44.05)	
Distance metastasis, number (%)			
Yes	22 (61.11)	14 (38.89)	0.257
No	46 (50)	46 (50)	
Surgery, number (%)			
Yes	44 (50)	44 (50)	0.195
No	24 (60)	16 (40)	
Background GI disease, number (%)			
Yes	34 (64.15)	19 (35.85)	0.027
No	34 (50)	34 (50)	
Pretreatment nausea and vomiting (<7 d), number (%)			
Yes	32 (69.56)	14 (30.44)	0.005
No	36 (44.44)	45 (55.56)	

GI=gastrointestinal, RINV= radiotherapy-induced nausea and vomiting.

3.2. Anti-nausea drug administration

If patients experienced RINV, they informed the physician and while the incidence of RINV was documented, the physician decided to administer the drugs or not. Anti-nausea drugs were administered in 36.7% of cases in which the incidence of RINV was observed earlier. In 16.4% of cases, while the incidence of RINV was observed, the physician decided not to administer anti-nausea drugs. The other 46.9% did not experience RINV and did not receive the drugs, subsequently.

The incidence of RINV was assessed based on their blood groups, before any anti-nausea drug administration, and is shown in Fig. 1A. Additional follow-up for the patients based on anti-nausea drug administration is shown in Tables 2 and 3.

3.3. Radiotherapy-related factors

The mean accumulated RT dose was 46.46 ± 11.30 Gy (15–70 Gy range) while the mean number of fractions was 22.92 ± 7.34 and dose per fraction was 212.35 ± 49.07 cGy. The treatment intent for 45.71% was radical, 30.0% was palliative, 21.42% was adjuvant, and for 2.85% was neo-adjuvant. For 38.3% of the patients, 4 treatment fields were used and 17.2% had 3, 43.8% had 2, and 0.8% had 1 radiation field. The radiation (treatment) field size among 9.4% of patients was under 200 cm², in 25.0% was 200 to 400 cm², and in 65.6% of patients, field size was greater than 400 cm². For 35.2% of patients, the RT was performed in the morning, and 10.9% and 53.9% of the treatment procedures were performed in early and late afternoon, respectively. The treatment process was interrupted for less than 2 and more than 2 days in 13.3% and 18% of the patients, respectively.

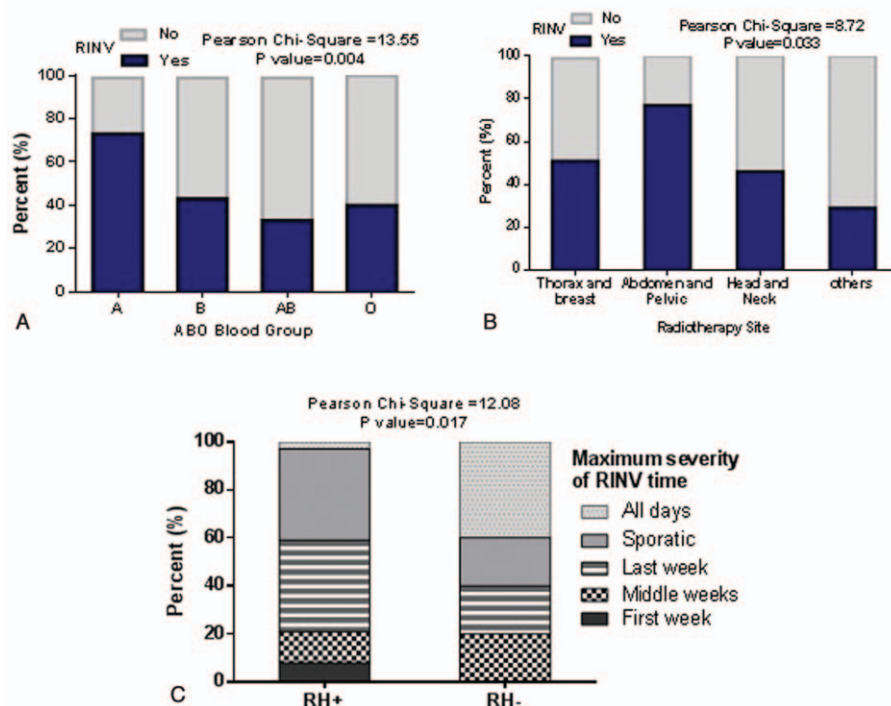


Figure 1. The association between ABO blood group (A) and radiotherapy site (B) with RINV induction. The association between the time of maximum severity of RINV and Rh of patients (C). Rh= Rhesus antigen, RINV=radiotherapy-induced nausea and vomiting.

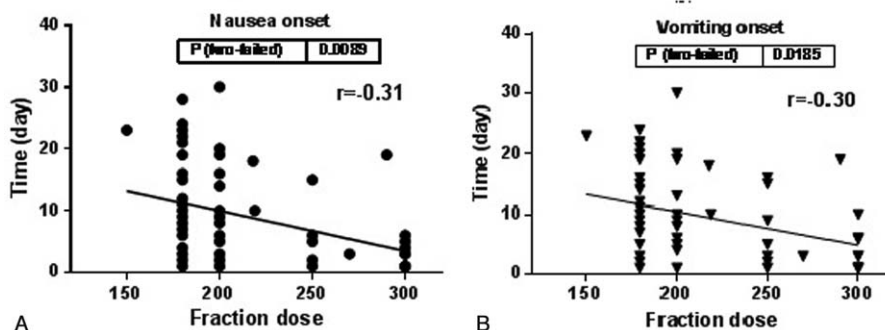


Figure 2. The correlation between nausea (A) and vomiting (B) onset with fraction dose.

3.4. Nausea and vomiting

Participants were categorized into two groups: RINV- (no vomiting and nausea episode) and RINV+ (minimum of 1 vomiting or retching episodes a day with nausea). Nausea with or without vomiting was seen among 53.1% of the patients.

The number of nausea episode (implying the magnitude of nausea) among RINV+ group was different between blood groups ($P=0.012$) but the number of vomiting is not associated with blood groups. The number of nausea episodes was higher in A (5.96 ± 6.21) compared with B (2.73 ± 4.66), and O (2.33 ± 4.82) blood groups. The onset time of RINV after each fraction and also the onset of both nausea and vomiting during treatment were not associated with blood group. The association between the ABO blood group and RINV and also the association between Rhesus (Rh) factor and time of maximum severity of RINV are shown in Fig. 1.

The one-way ANOVA tests showed that the age, total accumulated RT dose, fraction number, and fraction doses were not different between the RINV+ and RINV- groups. Nausea and vomiting also were not associated with the stage of cancer. Previous nausea in situations such as pregnancy or motion sickness was observed in 53.2% of cases, but their incidences were not associated with RINV ($P=0.396$).

The number of nausea and vomiting episodes were different in different KPSs ($P=0.004$ and $P=0.038$, respectively) and it was significantly associated with anti-nausea ($P<0.001$) and anti-steroid ($P=0.007$) drug consumption. Some important factors affecting RINV are shown in Figs. 1, 2, 3 and Table 1.

Nausea and vomiting were followed up for 7 days after treatment accomplishment. All of the investigated factors were not associated with nausea and vomiting after treatment completion.

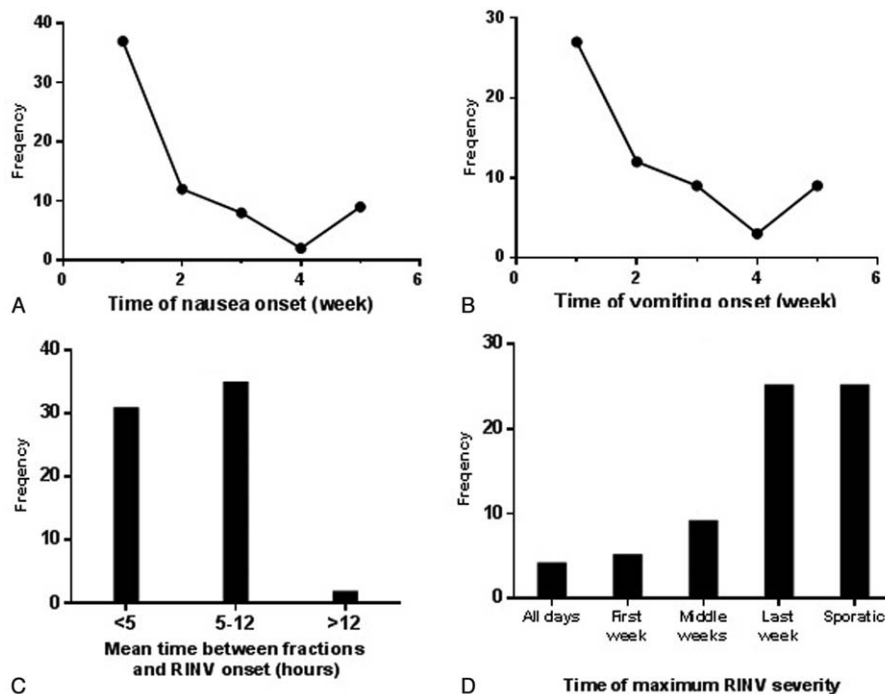


Figure 3. The frequency of nausea onset time (A), the frequency of vomiting onset time (B), the frequency of mean time between each fraction and RINV onset (C), and the frequency of maximum severity time of radiotherapy-induced nausea and vomiting (RINV) (D).

Table 2**Additional follow-up among the patients who experienced RINV, based on anti-nausea drug administration.**

Variables	Anti-nausea drug administration, % (count)		P
	Yes	No	
Blood group			
A	44.1 (30)	8.8 (6)	0.024
B	14.7 (10)	8.8 (6)	
AB	1.5 (1)	4.4 (3)	
O	8.8 (6)	8.8 (6)	
Treatment interruption			
No	38.2 (26)	23.5 (16)	0.138
<2 d	8.8 (6)	4.4 (3)	
>2 d	22.1 (15)	2.9 (2)	
Time between treatment and RINV			
<5 h	25.0 (17)	20.6 (14)	0.055
5–12 h	41.2 (28)	10.3 (7)	
>12 h	2.9 (2)	0.0 (0)	
Max frequent RINV episode time			
<1 wk	4.5 (3)	3.0 (2)	0.001
Middle of the treatment	11.9 (8)	0.0 (0)	
Last wk	31.3 (21)	6.0 (4)	
Sporadic	14.9 (10)	22.4 (15)	
All days	6.0 (4)	0.0 (0)	
Following nausea and vomiting			
Yes	25.0 (17)	4.4 (3)	0.058
No	44.1 (30)	26.5 (18)	

RINV = radiotherapy-induced nausea and vomiting.

4. Discussion

One hundred twenty-eight individuals participated in this study. The RINV was seen among 53.1% of the patients. Feyer et al^[11,12] have reported a range of 50% to 80% RINV in RT depending on the RT site, 2 to 3 weeks after the onset of treatment, which is in agreement with our study. The Italian prospective observational trial on emesis in RT reported a 27.9% incidence of both vomiting and nausea, 27.1% vomiting, and 11% nausea among 1004 patients.^[13]

Our results showed that the association between the ABO blood group and the incidence of RINV was significant and the number of nausea episodes was higher in A in comparison with B and O blood groups and subsequently as shown in Table 2, the anti-nausea and vomiting drugs were administered significantly higher for A blood group than other patients. The Table 3 showed that among the patients who experienced RINV, anti-nausea drug administration is significantly associated with the number of nausea and vomiting episodes, as the index of the magnitude of RINV. These data suggest that both incidence and severity of RINV are associated with ABO blood group and it seems that individuals with A blood group are most vulnerable to RINV. These results are in agreement with Elahimaneh et al^[14] study, in which they concluded that A is the most radiosensitive

blood group. The relation between the ABO blood group and RINV was not studied yet, but it must be noted that there is a relation between the ABO blood group and cardiovascular disease, and cancers.^[15] Also, the prognostic values of the ABO blood group in some cancers are confirmed now.^[16–18] Stamatakos et al^[19] showed that the rate of ductal breast cancer is higher in patients with A blood group than other blood groups. The results obtained by Doll et al^[20] showed that the number of gastric ulcer and neoplasm in patients with A blood group was significantly higher than other blood groups.

The association of the ABO blood group and the onset time of nausea and vomiting episodes and also the time between each fraction and the onset of RINV were not statistically significant in our study. But, the association between Rh and time of maximum severity of RINV may indicate that Rh influences the time of maximum severity of RINV. More molecular and cellular studies are needed to determine the exact mechanism of this connection.

The incidence of RINV was not affected by KPS, but the number of nausea and vomiting episode was different in different KPSs which imply its relation to the severity of RINV. Chemotherapy-induced nausea and vomiting is another factor affecting RINV which is in agreement with Italian study and National Comprehensive Cancer Network (NCCN) clinical practice guidelines.^[13] Both groups suggested that concomitant

Table 3**The follow-up among the patients who experienced RINV, based on anti-nausea drug administration.**

Variables	Anti-nausea drug	N	Mean	SD	Minimum	Maximum	P
Number of nausea episode	Yes	47	9.60	6.05	1	30	0.001
	No	21	1.95	1.16	1	5	
Number of vomiting episode	Yes	47	10.91	10.2	0	50	0.001
	No	21	2.76	3.12	0	10	

RINV = radiotherapy-induced nausea and vomiting, SD = standard deviation.

RT and chemotherapy increases the chance of nausea and vomiting. In our study, by excluding patients with concomitant chemoradiation, RINV episodes in patients with radiation therapy alone showed that the management of RINV induced by radiation therapy alone is as important as RINV in patients with concomitant chemoradiation. This may be a result of the same pathophysiology of both RINV and CINV.^[12]

We showed that the other important factor on RINV was RT region, which is consistent with other studies.^[3,12] These studies have reported the abdomen or pelvic region to be the most critical organs responsible for radiation-induced emesis. Similarly, Enblom et al^[3] study reported that nausea was more frequent in those receiving RT to the lower abdomen or pelvis compared to the head and neck area radiated patients. The mechanism might be related to a toxin released by the degradation of tumor proteins. The production of a second messenger resulting from radiation-associated cellular damage would be considered.^[21,22]

In our study, the number of used fields, the time of previous chemotherapy, mean field size, distance metastasis, and surgery were not related to the incidence of RINV. Gagnon et al^[23] have demonstrated that the GI tract is more sensitive to radiation-induced damage in the late morning than in the afternoon but the association of morning, mid-afternoon, and late afternoon RT with RINV was not statistically significant in our study. Albeit Gagnon et al study was limited to prostate cancer patients in contrast to our study, in which a wider variety of cancer patients was examined.

The age, sex, total dose, fraction number, and fraction doses were not different between the RINV+ and the RINV- groups. However, the higher fraction dose significantly induced nausea and vomiting earlier in the treatment course. Among these factors, the RT regimen and radiation dose were reported as the important factors in RINV in previous studies. Feyer et al^[12] reported that RT-related factors, such as the site of irradiation, dosage, fractionation, irradiated volume, and RT techniques, are related to RINV which is somewhat different compared with our study. These differences could be due to the fact that the standard regimen is vastly employing in our clinic that it may enhance the accuracy of our results because of the limitation in RT techniques and patient related factors. Notwithstanding these outcomes, nausea, and vomiting until 7 days after treatment completion were not associated with the investigated factors.

The RINV began in the first week for 54.4% of cases, then these were reduced to 2.9% until the fourth week, but at the fifth week, the onsets of RINV were increased to 13.2%. This increase of RINV could be as the result of the higher dose threshold in some individuals, emetogenic potential of the therapy, or may be as a result of the difference in the induction mechanism. To compare the mechanisms of RINV in patients which begun in the early and late period of RT, prescription of 5-hydroxy tryptamine receptor antagonists and the comparison of its outcome could be helpful in future studies.

Also in our study, the mean time between each fraction and the RINV symptom initiation was <5 hours for 45.6% of the patients and it was between 5 and 12 hours for 51.1% of the patients. For 2.9% of cases, this was >12 hours. Our study results also suggest that maximum frequent episodes of RINV occur predominantly in the early phase of treatment and should be considered by health-care professionals for prophylactic measures such as prescription of anti-nausea and vomiting drugs for the early weeks and to motivate the patients to continue their treatment courses without distress.^[24]

5. Conclusion

We have demonstrated that patients with A blood group, perhaps, are at higher risk of RINV compared with other blood groups. This is a novel concept since no other studies have specifically examined the link between ABO blood groups and RINV, while it might be an important individual risk factor of RT and may be chemotherapy patients. This addresses the need for further studies with more statistical power to develop a risk-adjusted treatment for RINV.

In addition, in order to increase our understanding of its etiology as well as increasing our knowledge of radiation therapy and related health care, molecular and cell-based approaches will need to be considered.

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