



RESEARCH ARTICLE

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Incidence and risk factors for oxaliplatin-induced vascular pain during administration in Iraqi patients

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ARTICLE INFO ABSTRACT



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Introduction: The primary objective of this study was to identify the percentage of oxaliplatin-induced vascular pain during administration in Iraqi patients. The secondary objective was to identify the risk factors for vascular pain.

Methods: This is a cross-sectional observational study carried out at the Al-Andalus private hospital for cancer patients, Baghdad, Iraq. The study included 101 patients, diagnosed with one of the following cancers: colon, pancreatic, stomach, and rectal cancer, ranging from 18 to 80 years, and receiving oxaliplatin peripheral venous infusion. Data collected included: age, gender, diagnosis, history of chronic disease, treatment protocol, degree of pain severity, cancer stage, history of previous vascular pain, number of cycles, the incidence of vascular pain, oxaliplatin dose.

Results: Sixty-two patients out of 101 patients had experienced vascular pain during oxaliplatin peripheral venous infusion, representing about (61.4 %). History of diabetes mellitus was significantly associated with vascular pain induction (OR=1.59, [CI: 1.07 - 2.39]). The age group from 40-60 years old was significantly associated with 59 % higher odds of vascular pain (OR=1.59, CI: 1.07 - 2.39) than other age groups. Female patients were significantly associated with 59 % higher odds of vascular pain (OR=1.59, CI: 1.07 - 2.39) than males.

Conclusion: The results of this study indicate that history of diabetes mellitus, the age group from 40-60 years old, and female gender are risk factors for oxaliplatin-induced vascular pain in patients with GI malignancy. These findings could be useful to assess the risk of vascular pain in clinical settings.

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Introduction

Oxaliplatin is a third-generation platinum analog that is mainly used for the treatment of advanced colorectal cancer, gastric, pancreatic, esophageal, and ovarian cancers both in the adjuvant and metastatic settings (Devanabanda

& Kasi, 2021). Although peripheral neuropathy is a major adverse drug reaction in patients receiving oxaliplatin, mild to moderate vascular pain originating around the injection site during peripheral intravenous administration of oxaliplatin is also a significant problem and it develops in 41.2 % in patients who had no risk factor, 52.0 % in those



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who had one risk factor and 79.6% in those who had two or more risk factors (Suga et al., 2018). It lasts during the infusion and less than 1 hour after completion or interruption (Petrelli et al., 2015).

The development of vascular pain and phlebitis following intravenous infusion of antineoplastic agents subsequently increases the risk of discontinuation of chemotherapy (Nagao et al., 2017). Several methods for preventing or relieving oxaliplatin-induced vascular pain have been reported in clinical studies. Co-infusion of dexamethasone (Hata et al., 2015; Matsuyama et al., 2011; Yoshida et al., 2012), pre-warming the peripheral blood vessels (Miyajima et al., 2013), premedication with oxycodone, and changing the dose rate (Nagao et al., 2017) have all been investigated as ways of reducing oxaliplatin-induced vascular pain. Vascular pain has usually been evaluated by subjective methods, such as questionnaires and visual analog scale (VAS). The VAS is the most widely used tool for evaluating pain intensity. Patients were asked to indicate a point along a 100 mm scale bar depending on the strength of their pain, with 'no pain at all (0) at the left end of the scale and the worst pain (100) at the right end scale bar. The VAS score is considered to be a good indicator of subjective pain (Atisook et al., 2021). Patients having oxaliplatin-related vascular pain due to peripheral administration have a seriously impaired quality of life. Unfortunately, no drugs have yet been proven effective in alleviating peripheral neuropathy and vascular pain (Suwa et al., 2019).

Better information on the variability and frequency of adverse events and their impact on treatment will enable clinicians to establish strategies that preserve chemotherapy treatment without unduly incurring the development of vascular pain. The primary objective of this study was to identify the percentage of oxaliplatin-induced vascular pain during administration in Iraqi patients. The secondary objective was to identify the risk factors for vascular pain.

Material and methods

Study design and participants

This is a cross-sectional observational study carried out at the Al-Andalus private hospital for cancer patients, Baghdad, Iraq between the period of October 2020 and April 2021. The study included 101 patients, diagnosed with one of the following cancers: colon, pancreatic, stomach cancer, and rectal, between the ages of 18 and 80 years, and receiving oxaliplatin peripheral venous infusion.

Chemotherapy

The following chemotherapy protocols were administered to the patients:

(A) XELOX protocol (Oxaliplatin + Capecitabine). Day 1: oxaliplatin 130 mg/m² IV over 2 hours. Days 1–15: Capecitabine 1,000 mg/m² orally twice daily. Repeat cycle every 3 weeks.

(B) FLOT protocol (Fluorouracil + Leucovorin + Oxaliplatin + Docetaxel). Day 1: Docetaxel 50 mg/m² IV over 1 hour, oxaliplatin 85 mg/m² IV over 2 hours, with Leucovorin 200 mg/m² IV over 2 hours, followed by Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks for 4 cycles preoperatively and 4 cycles postoperatively for a total of 8 cycles.

(C) FOLFOX protocol (Fluorouracil + Oxaliplatin + Leucovorin). Day 1: oxaliplatin 85 mg/m² IV over 2 hours, with Leucovorin 200 mg/m² IV over 2 hours, followed by Fluorouracil 2,600 mg/m² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks for a total of 12 cycles.

(D) FOLFIRINOX protocol (Oxaliplatin + Irinotecan + Fluorouracil). Day 1: oxaliplatin 85 mg/m² IV over 2 hours, Irinotecan 180 mg/m² IV over 90 minutes, Leucovorin 400 mg/m² IV over 90 minutes, followed by Fluorouracil 400 mg/m² IV push, followed by Days 1–2, Fluorouracil 1,200 mg/m² IV continuous infusion over 24 hours (2,400 mg/m² IV over 46 hours). Repeat cycle every 2 weeks for a total of 12 cycles.

Data collection

Before data collection, oral consent was taken from patients. Clinical data were collected by a questionnaire and it included age, gender, diagnosis (colon, pancreas, rectum, stomach), history of chronic disease (diabetes mellitus, hypertension, neuropathy, none), treatment protocol (XELOX, FLOT, FOLFOX, FOLFIRINOX), degree of pain severity, cancer stage (TNM), history of previous vascular pain, number of cycles, the incidence of vascular pain, oxaliplatin dose. Pain assessment was done by visual analog scale (VAS). The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain" (Delgado et al., 2018).

Inclusion / exclusion criteria

Included in the study were patients between the age of 18 and 80 years, patients diagnosed with colon, pancreatic, rectal, and stomach cancer, and patients receiving oxaliplatin peripheral venous infusion. Excluded from the study were patients less than 18 years and more than 80 years, having a vascular disease other than malignancy (ex: severe atherosclerosis and deep venous thrombosis (DVT), and patients with central line port.

Ethical considerations

Ethical approval was obtained from the Ethics Committee of Al-Andalus Private Hospital for Cancer Patients, Baghdad, Iraq. All patients gave their informed consent before their inclusion in the study.

Statistical analysis

Data of all patients were entered and managed using the Statistical Package for Social Sciences (SPSS) software (version 25). Descriptive analysis for quantitative data included median and interquartile range instead of mean and standard deviation due to violation of normal distribution. For qualitative categorical variables, frequency and percentage were applied. A test of

significance for each baseline characteristic variable has been done to check for study sample randomization within each characteristic category. A multivariate logistic regression model has been done to adjust for that significant difference. The statistical analysis was based on a two-tailed test using a level of significance for analysis at $p \leq 0.05$.

Results

Table 1: Demographic data and baseline clinical characteristics

		Count (N=101)	Percent (%)	P-value
Age (years)	less than 40	19	18.8 %	< 0.0001
	40-60	55	54.5 %	
	more than 60	27	26.7 %	
Gender	Male	63	62.4 %	0.013
	Female	38	37.6 %	
Diagnosis	Colon	46	45.5 %	< 0.0001
	Pancreas	10	9.9 %	
	Rectum	34	33.7 %	
	Stomach	11	10.9 %	
History of chronic disease	Diabetes Mellitus	25	24.8 %	< 0.0001
	Hypertension	30	29.7 %	
	Neuropathy	2	2.0 %	
	No	44	43.6 %	
Treatment protocol	Xelox	64	63.4 %	< 0.0001
	Flot	9	8.9 %	
	Folfirinox	11	10.9 %	
	Folfox	17	16.8 %	
Degree of pain severity	Mild (grade 1)	16	15.8 %	< 0.0001
	Moderate (grade 2)	23	22.8 %	
	Moderate (grade 3)	18	17.8 %	
	Severe (grade 4)	3	3.0 %	
	Severe (grade 5)	2	2.0 %	
	No	39	38.6 %	
Stage T	NO	1	1.0 %	< 0.0001
	1	3	3.0 %	
	2	32	31.7 %	
	3	46	45.5 %	
	4	19	18.8 %	
Stage N	NO	2	2.0 %	< 0.0001
	0	3	3.0 %	
	1	40	39.6 %	
	2	54	53.5 %	
Stage M	3	2	2.0 %	< 0.0001
	0	84	83.2 %	
	1	17	16.8 %	
History of previous vascular pain	Yes	61	60.4 %	0.037
	No	40	39.6 %	
Cycles	2 cycles	28	27.7 %	< 0.0001
	3 cycles	25	24.8 %	
	4 cycles	19	18.8 %	
	5 cycles	6	5.9 %	
	6 cycles	11	10.9 %	
	7 cycles	4	4.0 %	

Incidence of vascular pain	8 cycles	6	5.9 %	0.022
	9 cycles	2	2.0 %	
	Yes	62	61.4 %	
	No	39	38.6 %	

Demographic data and baseline clinical characteristics are represented in **Table 1**. Included in the study were 101 patients. More than 50 % of study patients were between 40 and 60 years old. Male patients represented more than 60 %. About 45.5 % of patients were diagnosed with colon tumor, 33.7 % rectum, 10.9 % stomach, and 9.9 % by pancreas tumor. Patients with a history of hypertension represented about 29.7 %, while 24.8 % with a history of diabetes mellitus. More than 60 % of patients were on

Xelox treatment therapy while more than 16 % were receiving Folfox and the remaining were on Flot & Folfirinox therapies. More than 60 % of patients had a history of previous vascular pain. About 27.7 % of patients received 2 treatment cycles, 24.8 % received 3 cycles, and 18.8 % received 4 cycles. Sixty-two patients out of 101 patients had experienced vascular pain during oxaliplatin peripheral venous infusion, representing about (61.4 %).

Table 2: Comparative analysis between study protocols regarding vascular pain induction & severity degree

Protocols	Vascular pain			Severity degree					P-value	OR [95% CI]
	Yes N = 62	No N = 39	P-value	1 N=16	2 N=23	3 N=18	4 N=3	5 N=2		
Flot	7 (77.8 %)	2 (22.2 %)	0.45	3(33.3 %)	2(22.2%)	1(11.1%)	1(11.1%)	0(0.0%)		1.59 [1.07 - 2.39]
Folfirinox	5 (45.5 %)	6 (54.5 %)		1(9.1 %)	2(18.2%)	1(9.1%)	1(9.1%)	0(0.0%)		0.24 [0.03 - 1.54]
Folfox	12 (70.6 %)	5 (29.4 %)		3(17.6 %)	4(23.5%)	4(23.5%)	1(5.9%)	0(0.0%)	0.53	0.69 [0.08 - 4.21]
Xelox	38 (59.4 %)	26 (40.6 %)		9(14.1 %)	15(23.4%)	12(18.8%)	0(0.0%)	2(3.1%)		0.42 [0.06 - 1.89]

Comparative analysis between study protocols regarding vascular pain induction and severity degree is presented in **Table 2**. There was no statistically significant difference

between the study protocols regarding neither vascular pain induction nor the degree of severity of induced pain (if there was)

Table 3: History of chronic diseases vs. vascular pain induction

Chronic disease	Vascular pain		P-value	OR [95% CI]
	Yes (n=62)	No (n= 39)		
Diabetes Mellitus	15 (60.0%)	10 (40.0%)	0.22	1.59 [1.07 - 2.39]
Hypertension	18 (60.0%)	12 (40.0%)		1.00 [0.33 - 2.97]
Neuropathy	2 (100.0%)	0 (0.0%)		-
No	27 (61.4%)	17 (38.6%)		-

The history of chronic diseases vs. vascular pain induction is presented in **Table 3**. There was no statistically significant association between overall chronic disease history and induction of vascular pain during oxaliplatin administration. The only history of diabetes mellitus was significantly associated with vascular pain induction (the

odds ratio of vascular pain in diabetes mellitus patients was 59 % higher than those without a history of diabetes mellitus (OR=1.59, [CI: 1.07 - 2.39]).

Table 4: Relation between administered doses of Oxaliplatin and vascular pain induction

	Vascular pain		P-value
	Yes	No	
Oxaliplatin dose(mg)			
Median	200.0	200.0	0.70
Inter Quartile Range (IQR)	(152.5 to 230.0)	(150.0 to 230.0)	

The relation between administered doses of oxaliplatin and vascular pain induction is presented in **Table 4**. The median dose administered for patients who developed vascular pain was equal to the median dose in patients who did not (p-

value =0.70); therefore, there was no statistically significant association between administered oxaliplatin dose and vascular pain induction.

Table 5: Relation between severity of pain, age, & gender

	Degree of Severity of Pain						P-value	OR [95% CI]
	No N=39	1 N=16	2 N=23	3 N=18	4 N=3	5 N=2		
Age								
less than 40	6 (31.6%)	2 (10.5%)	5 (26.3%)	6 (31.6%)	0 (0.0%)	0 (0.0%)	0.73	1.14 [0.38 - 3.69]
40-60	19 (34.5%)	11 (20.0%)	13 (23.6%)	8 (14.5%)	2 (3.6%)	2 (3.6%)		1.59 [1.07 - 2.39]
more than 60	14 (51.9%)	3 (11.1%)	5 (18.5%)	4 (14.8%)	1 (3.7%)	0 (0.0%)		0.49 [0.19 - 1.25]
Gender								
Male	26 (41.3%)	9 (14.3%)	12 (19.0%)	13 (20.6%)	2 (3.2%)	1 (1.6%)	0.75	0.74 [0.31 - 1.69]
Female	13 (34.2%)	7 (18.4%)	11 (28.9%)	5 (13.2%)	1 (2.6%)	1 (2.6%)		1.59 [1.07 - 2.39]

Relation between severity of pain, age, & gender is presented in **Table 5**. The age group from 40-60 years old was significantly associated with 59 % higher odds of vascular pain induction during oxaliplatin administration (OR=1.59, CI: 1.07 - 2.39) than other age groups. Female patients were significantly associated with 59 % higher odds of vascular pain induction during oxaliplatin administration (OR=1.59, CI: 1.07 - 2.39) than males.

Discussion

Mild to moderate vascular pain originating around the injection site during peripheral intravenous administration of oxaliplatin is a significant problem. We carried out this cross-sectional observational study at Al-Andalus Private Hospital for Cancer Patients, Baghdad, Iraq between the period of October 2020 and April 2021. The study included 101 patients, diagnosed with one of the following cancers: colon, pancreatic, stomach cancer, and rectal, between the

ages of 18 and 80, and receiving oxaliplatin peripheral venous infusion.

In our study, sixty-two patients out of 101 patients had experienced vascular pain during oxaliplatin peripheral venous infusion, representing about (61.4 %). In a study carried out by Yoshida et al., vascular pain developed in 34 patients (72.3 %) out of 47 patients who received XELOX + bevacizumab therapy for metastatic colorectal cancer (Yoshida et al., 2012). In comparison to oxaliplatin-induced peripheral neuropathy, a study carried out by Ali et al. reported that the acute and chronic incidence of oxaliplatin-induced peripheral neuropathy among 121 patients at Khartoum Oncology Hospital was found to be 49.6 % and 41.3 % respectively (Ali et al., 2020).

In our study, there was no statistically significant difference between the study protocols regarding neither vascular pain induction nor the degree of severity of induced pain. On the

other hand, in a multicenter study of the Yokohama Clinical Oncology Group (YCOG) in Japan, it was reported that the rate of grade ≥ 2 vascular pain was 55.3 % in the group receiving Capeox (capecitabine and oxaliplatin) therapy only and 53.8 % in the group receiving Capeox therapy (capecitabine and oxaliplatin) with 400 mg/day of celecoxib ($p = 1.000$) (Suwa et al., 2019).

In our study, only a history of diabetes mellitus was significantly associated with vascular pain induction (OR=1.59, [CI: 1.07 - 2.39]). In addition, there was no statistically significant association between administered oxaliplatin dose and vascular pain induction. Comparatively, in a study carried out by Suga et al., it was reported that BMI (BMI < 22), clinical-stage (I-III), and oxaliplatin dosage (130 mg/m² versus dose reduction) were identified as independent risk factors for the development of vascular pain (Suga et al., 2018). Moreover, Takagi et al. have reported that oxaliplatin dosages of more than 175 mg/body are significantly related to the development of vascular pain, suggesting that vascular pain is more likely to occur at higher oxaliplatin dosages (Takagi A, 2015).

In our study, the age group from 40-60 years old was significantly associated with 59 % higher odds of vascular pain induction during oxaliplatin administration (OR=1.59, CI: 1.07 - 2.39) than other age groups. Moreover, female patients were significantly associated with 59 % higher odds of vascular pain induction during oxaliplatin administration (OR=1.59, CI: 1.07 - 2.39) than males. In a study carried out by Kawazoe et al., multivariate logistic regression analysis revealed that the female gender was significantly associated with an increased risk of venous pain during all courses of oxaliplatin treatment (Kawazoe, 2017). On the other hand, when compared to oxaliplatin-induced peripheral neuropathy, Mizrahi et al. reported that also older age ($\beta = 0.08$; 95% CI, 0.06 to 0.11; $P < .001$), and female gender ($\beta = -1.08$; 95% CI, -1.76 to -0.16; $P = .01$) were associated with worse peripheral neuropathy pain (Mizrahi et al., 2021).

This study can be evaluated in terms of its strengths and limitations. To our knowledge, this study was the first to focus on vascular pain caused by oxaliplatin in Iraq. A limitation of this study was that pain prevalence was underestimated because it was mild pain so we need prospective trials with close monitoring of the patients during infusion. Another limitation is that in this study we used oxaliplatin from one manufacturer due to its sole availability; therefore, we need to do comparative observational studies between different manufacturing pharmaceutical companies.

Conclusion

The results of this study indicate that history of diabetes mellitus, the age group from 40-60 years old, and female gender are risk factors for oxaliplatin-induced vascular pain in patients with GI malignancy. These findings could be

useful to assess the risk of vascular pain in clinical settings. Based on the results of this study together with previous findings, we suggest that the best option for the management of oxaliplatin-induced vascular pain may be carefully timed.

Conflict of Interest Statement:

The authors declare that they have no conflict of interest.

Ethics Statement:

Ethical approval was obtained from the Ethics Committee of Al-Andalus private hospital for cancer patients, Baghdad, Iraq. All patients gave their informed consent before their inclusion in the study.

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