Efficacy of gabapentin versus diclofenac in the treatment of chest pain and paresthesia in patients with sternotomy

Sternotomili hastalarda göğüs ağrısı ve parestezinin tedavisinde diklofenaka karşı gabapentinin etkinliği

İsmail Bıyık, Metin Gülcüler, Murat Karabiga*, Oktay Ergene[1], Nezih Tayyar[2]*

From Departments of Cardiology and *Cardiovascular Surgery, Uşak State Hospital, Uşak
[1]Department of Cardiology, Atatürk Education and Training Hospital, İzmir,
[2]Department of Management and Statistics, Uşak Universty , Uşak, Turkey

ABSTRACT

Objective: Chronic post-sternotomy chest pain and paresthesia (PCPP) are frequently seen and reduce the quality of life. We aimed to demonstrate the efficacy and safety of gabapentin compared with diclofenac in the treatment of PCPP and to elucidate the similarities of PCPP to neuropathic pain syndromes.

Methods: The prospective, randomized, open-label, blinded end-point design of study was used. One hundred and ten patients having PCPP lasting three months or more were randomized to receive 800 mg/daily gabapentin (n=55) and 75 mg/daily diclofenac (n=55) for thirty days. All patients have undergone cardiac surgery and median sternotomy. The perception of pain or paresthesia was evaluated as 0-Normal (no pain or paresthesia), 1-Mild, 2-Moderate, 3-Severe at baseline and after thirty days of treatment. Recurrences were questioned after three months. Statistical analyses were performed using independent samples t, Chi-square, continuity correction, Fisher's exact, Mann Whitney U and Kruskal Wallis tests.

Results: In gabapentin group, mean pain and paresthesia scores regressed from 2.12±0.76 to 0.54±0.83 ($p<0.001$) and from 1.72±0.74 to 0.49±0.62 ($p<0.001$), respectively. Mean pain and paresthesia scores regressed in diclofenac group from 1.93±0.8 to 1.0±1.13 ($p<0.001$) and from 1.76±0.74 to 1.24±0.96 ($p=0.002$), respectively. Although, both gabapentin and diclofenac were found to be effective without obvious side effects in the treatment of PCPP ($p<0.001$), gabapentin was found to be superior to diclofenac ($p=0.001$ and $p<0.001$, respectively). Adverse effects were seen in 7% of patients on gabapentin and 4% of patients on diclofenac. Results also showed that symptomatic relief with gabapentin lasts longer than diclofenac ($p<0.001$).

Conclusion: Both gabapentin and diclofenac are effective in the treatment of chronic PCPP, without obvious side effects. However, gabapentin is found to be superior to diclofenac and its effects sustain longer. The results show that there may be some evidence in PCPP as a kind of neuropathic pain. *(Anadolu Kardiyol Derg 2009; 9: 390-6)*

Key words: Sternotomy, pain, paresthesia, gabapentin, diclofenac

ÖZET

Amaç: Sternotomi sonrası kronik iskemik olmayan göğüs ağrısı ve parestezi (PCPP) sık görülmekte ve yaşam kalitesini azaltmaktadır. Bu çalışmada PCPP tedavisinde diklofenak ile karşılaştırıldığında gabapentinin etkinliği ve güvenilirliğini araştırmayı ve PCPP'nin nöropatik ağrı sendromlarıyla benzerliklerini aydınlatmayı amaçladık.

Yöntemler: Çalışmada prospektif, randomize, açık işaretli, körleştirilmiş son nokta tasarımı kullanıldı. Üç ay ya da daha uzun sure PCPP'si olan 110 hasta 30 gün 800 mg/gün gabapentin (n=55) ve 75 mg/gün diklofenak (n=55) tedavisine randomize edildi. Ağrı ve parestezi algılaması 0-Normal, 1-Hafif, 2-Orta, 3-Şiddetli olarak başlangıçta ve 30. günde değerlendirildi. Üç ay sonra nüks sorgulandı. İstatistiksel analizde bağımsız örneklem t, Ki- kare, süreklilik düzeltmesi yapılmış Ki-kare değeri, Fisher kesinlik, Mann Whitney U ve Kruskal Wallis testleri kullanıldı.

Bulgular: Gabapentin grubunda ortalama ağrı ve parestezi değerleri sırasıyla 2.12±0.762'den 0.54±0.83'e ($p<0.001$) ve 1.72±0.74'den 0.49±0.62'e ($p<0.001$) geriledi. Diklofenak grubunda ortalama ağrı ve parestezi değerleri sırasıyla 1.93±0.8'den 1.0±1.13'e ($p<0.001$) ve 1.76±0.74'den 1.24±0.96'e ($p=0.002$) geriledi. Bu çalışmada, PCPP tedavisinde hem gabapentin, hem de diklofenak önemli yan etkiler olmaksızın etkili bulunmakla birlikte ($p<0.001$), gabapentinin diklofenaka üstün olduğu bulundu ($p=0.001$ ve $p<0.001$, sırasıyla). Gabapentin alan hastaların %7'sinde, diklo-

Address for Correspondence/Yazışma Adresi: Dr. İsmail Bıyık, Department of Cardiology, Uşak State Hospital, Uşak, Turkey
Phone: +90 276 223 45 19 Fax: +90 276 227 94 96 E-mail: ismailbiyikmd@yahoo.com

Presented at 24th National Cardiology Congress, October 24-27 , 2008, İstanbul, Turkey and American Heart Association (AHA) Scientific Sessions, November 08-12, 2008, New Orleans, Louisiana, USA

fenak alan hastaların %4 kadarında yan etkiler görüldü. Ayrıca sonuçlar gabapentin ile olan semptomatik iyileşmenin diklofenaktan daha uzun sürdüğünü gösterdi (p<0.001).

Sonuç: Sternotomi sonrası kronik iskemik olmayan göğüs ağrısı ve parestezi tedavisinde, hem gabapentin, hem de diklofenak önemli yan etkiler olmaksızın etkilidir. Bununla birlikte gabapentin diklofenaka üstündür ve etkileri daha uzun sürmektedir. Sonuçlar sternotomi sonrası görülen kronik iskemik olmayan göğüs ağrısı ve parestezide nöropatik ağrıya benzer bazı özelikler olabileceğini göstermektedir.

(Anadolu Kardiyol Derg 2009; 9: 390-6)

Anahtar kelimeler: Sternotomi, ağrı, parestezi, gabapentin, diklofenak

Introduction

The reported incidence of chronic post-sternotomy chest pain ranges from 17 to 56 % in several studies (1, 2). It may last for months and even years (3). Although, most of the patients have mild degree of pain, the incidence of moderate pain is about 13 % and severe incapacitating chronic post-sternotomy pain is seen in about 3-5 % of these patients (2, 4). Approximately, in one third of the patients, the chronic pain syndrome may disturb the quality of life, interfere with sleep, and reduce the work performance of the patients (4). These patients have been presenting to cardiologists and cardiovascular surgeons as well as pain clinics. Nerve injury may cause chronic, non-ischemic, long-lasting chest pain in patients undergoing heart surgery with sternotomy technique (5).

Gabapentin, a γ-amino butyric acid (GABA) analogue anti-convulsing agent, is reported that is also effective agent in chronic neuropathic pain from different etiologies (6). Diclofenac is a benzene-acetic acid derivative and is an effective single-dose treatment for moderate to severe postoperative pain (7).

In this study, we hypothesized that post-sternotomy chest pain and paresthesia (PCPP) may have neuropathic pain characteristics and may be effectively treated with an anti-convulsing agent such as gabapentin. Therefore, we aimed to demonstrate the efficacy of gabapentin and to compare with diclofenac in the treatment of chronic non-ischemic PCPP and to elucidate the similarities of PCPP to neuropathic pain syndromes.

Methods

The primary objective of this study was to evaluate the effect of different drugs on chest pain and paresthesia. Therefore, the prospective, randomized, open-label, blinded end-point design was chosen for this study (8). Cardiovascular surgeons selected and randomized the patients and an investigator blinded to treatment assignments evaluated the patients at second interview in thirty days and 3 months later. The study was approved by the local Ethics Committee and informed consent was obtained from each patient. The study was conducted in the outpatient clinics of the departments of cardiology and cardiovascular surgery. Eligibility criteria of this study were post-sternotomy chest pain or paresthesia lasting ≥3 months and time ≥3 months after sternotomy. Exclusion criteria of this study were accepted as osteoporosis, renal failure, hepatic dysfunction, peptic ulcer, chest pain with ischemic origin, pediatric cases, over production of scar tissue, thoracic surgery other than sternotomy, redo-bypass surgery, infection and sternal dehiscence. Patients with ischemic origin were clearly excluded from the study by means of using pain history, electrocardiography, exercise stress test and myocardial perfusion SPECT when it was required. To clearly analyze the effect of internal mammarian artery harvesting on PCPP, combined procedures were excluded from the study.

In the study period of six months, 110 patients were randomized to receive 800 mg once daily gabapentin (group 1) and 75 mg once daily diclofenac potassium (group 2) for thirty days to abstain from the peptic and renal adverse effects of long-lasting diclofenac therapy and to increase patients' coherence to the treatment. Dose titration was not made for gabapentin because 800 mg is the target dose of our study and the lowest effective dose of gabapentin therapy. Gabapentin therapy was stopped without dose titration after thirty days because of low dose and relatively short therapy duration.

All patients included in this study had undergone cardiac surgery with median sternotomy technique. The number of patients with bypass surgery or valve surgery was equally divided in both groups. The level of anticoagulation of patients taking warfarin was optimized to avoid from the potential adverse effects of both drugs on anticoagulation during study period. Upon registration, patients were questioned about subjectively grading of the severity of their chest pain and paresthesia on a ten point Visual Analogue Scale (VAS) (9), with 0 no discomfort (pain or paresthesia) and 10 being the worst discomfort imaginable (10, 11). Because of the difficulty and the subjectivity of patient's evaluation we used four points scoring scale in the evaluation of chest pain and paresthesia of the patients for simple, quick, and correct evaluation (10, 11). According to the method, perception of pain or paresthesia was evaluated as 0-Normal (no pain or paresthesia), 1-Mild (1-3 points), 2-Moderate (4-7 points), 3-Severe (8-10 points) based on patient's expression (10). At first, patients were questioned with 10-point VAS scale and then their points were rescored with four point scoring scale. Paresthesia has been accepted as any numbness or impaired sensation causing chest discomfort except distinguishable clear pain. The patients were followed up on out-patient basis during thirty days of the treatment and three months later. The superiority criterion was the significant reduction of the severity of pain or paresthesia between two drugs. The patients were questioned again about side effects of the drugs by another investigator blinded to the treatment assignments. Potential side effects of gabapentin such as weakness, somnolence, dizziness, headache, nausea, vomiting, ataxia, irritability, lack of appetite and potential side effects of

diclofenac such as allergic reactions, itching, urticaria, angioedema, diarrhea, nausea, stomachache, headache, hepatic dysfunction, renal impairment were clearly investigated. Hepatic transaminases and creatinine levels were measured at the beginning and two weeks intervals. Three months after the discontinuation of both drugs, an interview with the patients treated with the therapy was made to evaluate whether or not their symptoms exacerbated again. After recruitment to the study, two patients taking analgesia other than both study drugs as needed were excluded from the analysis. Low dose gabapentin therapy (800 mg once daily) was continued in patients whose symptoms exacerbated again.

Statistical analyses

All statistical analyses were performed with SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA).

Power analyses indicated that minimum 34 patients per group were required to detect the efficacy of each drug (α=0.05 and β=0.2). Non-parametric statistical tests were used since the variables used for pain or paresthesia perception were measured in ordinal scale. Wilcoxon Signed Rank tests were used to reveal the effectiveness of drugs. The amount of reduction in pain and paresthesia perception before and after the treatment was computed by subtracting perception scores after treatment from before treatment. Then more effective drug was found with Mann Whitney tests. Pearson Chi-Square was used to find out that the distributions of patients' sex, diabetics, surgery type and side effects were independent or dependent from the type of drug used. Independent samples t tests were used to figure out the distributions of patients' age and time after surgery were independent or dependent from the type of drug used. In order to reveal if there is any difference depending on patients' sex, diabetics, surgery type, side effects, age and time after surgery, initial degree of pain and paresthesia and reduction in the degree of pain and paresthesia were tested with either Mann-Whitney or Kruskal-Wallis tests. P values smaller than 0.05 were considered statistically significant.

Results

All patients completed the study. The characteristics of the patients and the main results of the study are summarized in Tables 1 and 2. The oldest patient was 80 years old and the youngest one was 24 years old. Twenty-three patients (21%) had diabetes mellitus. The months after surgery ranged 3 to 96 months. Seventy- four patients (69%) had bypass surgery and 34 patients (31%) had only valve surgery. The ratio of left internal mammarian artery (LIMA) use was 85% (63/74) in this study. There was no patient undergoing bypass surgery with double internal mammarian arteries in this study population.

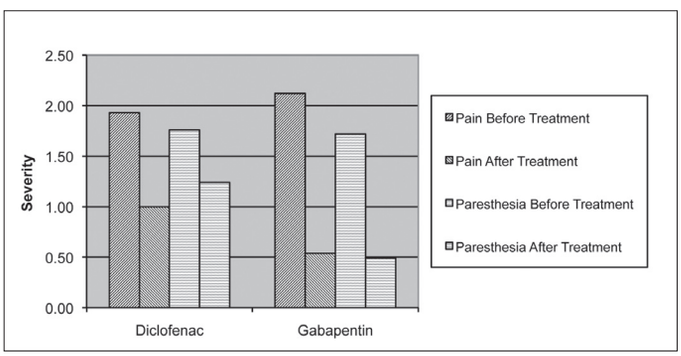

Figure 1. The effects of gabapentin and diclofenac on post-sternotomy pain and paresthesia

Of 108 patients included in the analyses, two did not have pain but had paresthesia, 32 had mild, 40 had moderate and 34 had severe pain; and 27 did not have paresthesia, 35 had mild, 32 had moderate and 14 had severe paresthesia. After the treatment, 61 were free of pain, 22 had mild, 15 had moderate and 10 had severe pain; and 62 were free of paresthesia, 31 had mild, 11 had moderate and 4 had severe paresthesia. Seven patients in group 1 and 24 patients in group 2 not responding to the therapy were treated by different agents and excluded from three months analysis.

In 54 patients taking gabapentin, mean pain and paresthesia scores significantly regressed (p<0.001) and (p<0.001), respectively. Among 54 patients taking diclofenac, mean pain and paresthesia scores also significantly reduced (p<0.001), (p=0.002), respectively (Table 2, Fig. 1). Adverse effects were observed in four patients with gabapentin (7%), all had nausea, and two patients with diclofenac (4%), both had mild stomachache. None of the patients discontinued the therapy. In 108 patients included in the analysis, both gabapentin and diclofenac were found to be effective without obvious side effects in the treatment of PCPP (p<0.001). Eighty seven percent of patients in gabapentin group and 56 % of patients in diclofenac group experienced benefit with the given treatment (Table 1). In the degree of PCPP relief , gabapentin was found to be superior compared with diclofenac (p=0.001), (p<0.001), respectively (Table 2).

Our results also revealed that the severity of chest pain was higher in patients less than 65 years (p<0.03), but there was no difference in the severity of paresthesia, and the effectiveness of both drugs on both pain and paresthesia was similar between two groups (Table 3). Although there was no significant gender difference in the severity of paresthesia between the patients, the female patients had significantly more severe pain scores than the male ones (p=0.003) (Table 3). The effectiveness of both drugs was similar in both sex groups.

At the presentation, there was no difference in the severity of both pain and paresthesia between patients undergoing bypass surgery with or without internal mammarian artery grafts and valve surgery. Both drugs had similar effectiveness in both surgery groups (Table 3).

We also evaluated the association between the severity of pain and paresthesia and the time after surgery. We subgrouped the patients as <1 year, 1 to 3 years and >3 years. Therefore, the analyzed data showed that there was no association between the severity of pain and paresthesia and the time after surgery, and both drugs had similar effectiveness in all subgroups (Table 4). In the view of the presence of diabetes mellitus, there was no difference in the severity of pain and paresthesia and the efficacy of both drugs in patients with or without diabetes

Table 1. The gender, history of diabetes mellitus, type of surgery, response to treatment, adverse effects of the drug in gabapentin and diclofenac groups

		Gabapentin		Diclofenac		
		N	%	N	%	p
Gender	Male	32	59	22	41	NS[1]
	Female	22	41	32	59	
Diabetes mellitus	Yes	15	28	8	15	NS2
	No	39	72	46	85	
Type of Surgery	Bypass	41	76	33	61	NS2
	Valve	13	24	21	39	
Benefit of medication	Yes	47	87	30	56	<.0012,*
	No	7	13	24	44	
Adverse Effects	Yes	4	7	2	4	NS3
	No	50	93	52	96	

1 - Chi square, 2 - Continuity correction, 3 - Fisher Exact tests
*The benefit of gabapentin therapy is significantly higher than of diclofenac one

Table 2. The severity of pain and paresthesia of the patients receiving gabapentin and diclofenac

	Gabapentin				Diclofenac				p
	n	mean	SD	Min/Median/Max	n	mean	SD	Min/Median/Max	
Age, years	54	61.35	6.63	50/60/76	54	59.04	12.9	24/61/80	NS[1]
Months after surgery	54	29.20	21.18	3/24/96	54	27.33	35.45	3/24/96	NS[1]
Pain severity, points									
Before	52	2.12	0.76	1/2/3	54	1.93	0.82	1/2/3	NS[2]
After	52	0.54	0.83	0/0/3	54	1.00	1.13	0/1/3	<0.001[a]
Paresthesia severity, points									
Before	47	1.72	0.74	1/2/3	34	1.76	0.74	1/2/3	NS[2]
After	47	0.49	0.62	0/0/3	34	1.24	0.96	0/1/3	<0.001[b]
Pain severity Reduction, points (Before-After)	52	1.58	0.89	0/2/3	54	0.93	1.06	0/1/3	0.0012,[c]
Paresthesia severity reduction, points (Before-After)	47	1.23	0.76	0/1/3	34	0.53	0.86	0/0/3	<0.0012,[d]
	n	%			n	%			
Symptom exacerbation at 3rd month of follow-up,	12/47	25			21/30	70			<0.0013,[e]

1- Independent samples t, 2 - Mann Whitney U, 3 - Continuity correction tests
[a]Pain severity is lower in both groups after treatment
[b]Paresthesia severity is lower in both groups after treatment
[c]Pain severity reduction is higher in gabapentin group
[d]Paresthesia severity reduction is higher in gabapentin group
[e]Symptom exacerbation is lower in gabapentin group

mellitus (Table 4).

The symptoms exacerbated in 12 of 47 (25.5 %) patients treated with gabapentin and in 21 of 30 (70%) patients treated with diclofenac (p<0.001) three months after discontinuation of therapy. This result demonstrated that symptomatic relief with gabapentin lasts longer than diclofenac.

Discussion

This study reveals that in the treatment of chronic non-ischemic chest pain and paresthesia of patients with sternotomy,

Table 3. Effects of age, sex and surgery type on symptoms and treatment assignments[1]

			General					Diclofenac					Gabapentin				
			n	Mean	SD	M. Rank	p-s/ns	n	Mean	SD	M. Rank	p-s/ns	n	Mean	SD	M. Rank	p-s/ns
Age	Pain BT	< 65	66	2.15	0.77	58.33	0.027[a]	32	2.19	0.82	32.19	0.005[a]	34	2.12	0.73	26.47	0.984
		≥ 65	40	1.80	0.79	45.53	S	22	1.55	0.67	20.68	S	18	2.11	0.83	26.56	NS
	Paresthesia BT	< 65	49	1.78	0.80	41.62	0.750	20	2.00	0.79	20.30	0.051	29	1.62	0.78	21.98	0.165
		≥ 65	32	1.69	0.64	40.05	NS	14	1.43	0.51	13.50	NS	18	1.89	0.68	27.25	NS
	Pain BT-AT	< 65	66	1.30	1.04	55.24	0.435	32	1.00	1.14	28.13	0.706	34	1.59	0.86	26.65	0.919
		≥ 65	40	1.15	1.03	50.63	NS	22	0.82	0.96	26.59	NS	18	1.56	0.98	26.22	NS
	Paresthesia BT-AT	< 65	49	1.02	0.88	43.03	0.309	20	0.80	1.01	20.20	0.061	29	1.17	0.76	22.91	0.457
		≥ 65	32	0.81	0.86	37.89	NS	14	0.14	0.36	13.64	NS	18	1.33	0.77	25.75	NS
Sex	Pain BT	Male	52	1.79	0.70	45.04	0.003[b]	22	1.55	0.67	20.68	0.005[b]	30	1.97	0.67	23.53	0.077
		Female	54	2.24	0.82	61.65	S	32	2.19	0.82	32.19	S	22	2.32	0.84	30.55	NS
	Paresthesia BT	Male	41	1.66	0.79	38.01	0.210	14	1.57	0.76	14.93	0.173	27	1.70	0.82	23.28	0.649
		Female	40	1.83	0.68	44.06	NS	20	1.90	0.72	19.30	NS	20	1.75	0.64	24.98	NS
	Pain BT-AT	Male	52	1.21	0.89	52.94	0.849	22	0.82	0.96	26.59	0.706	30	1.50	0.73	25.17	0.431
		Female	54	1.28	1.16	54.04	NS	32	1.00	1.14	28.13	NS	22	1.68	1.09	28.32	NS
	Paresthesia BT-AT	Male	41	0.90	0.80	40.51	0.841	14	0.29	0.47	15.79	0.321	27	1.22	0.75	23.74	0.321
		Female	40	0.98	0.95	41.50	NS	20	0.70	1.03	18.70	NS	20	1.25	0.79	24.35	NS
Surgery Type	Pain BT	By-Pass	72	1.94	0.79	50.78	0.159	33	1.73	0.76	26.95	0.177	39	2.13	0.77	26.76	0.821
		Valve	34	2.18	0.80	59.26	NS	21	2.24	0.83	36.07	NS	13	2.08	0.76	25.73	NS
	Paresthesia BT	By-Pass	59	1.66	0.71	38.72	0.122	22	1.64	0.66	16.05	0.213	37	1.68	0.75	23.12	0.360
		Valve	22	1.95	0.79	47.11	NS	12	2.00	0.85	20.17	NS	10	1.90	0.74	27.25	NS
	Pain BT-AT	By-Pass	72	1.25	0.99	53.72	0.910	33	0.91	1.04	27.50	1.000	39	1.54	0.85	25.85	0.567
		Valve	34	1.24	1.13	53.03	NS	21	0.95	1.12	27.50	NS	13	1.69	1.03	28.46	NS
	Paresthesia BT-AT	By-Pass	59	0.93	0.89	40.71	0.848	22	0.45	0.91	16.23	0.233	37	1.22	0.75	23.65	0.716
		Valve	22	0.95	0.84	41.77	NS	12	0.67	0.78	19.83	NS	10	1.30	0.82	25.30	NS

1. Mann Whitney U test
AT - after treatment, BT - before treatment, NS - non-significant, S - significant
[a]The severity of chest pain was higher in patients less than 65 years
[b]The female patients had significantly more severe pain scores than the male ones

although, gabapentin and diclofenac were effective without obvious side effects, gabapentin was found to be superior compared with diclofenac. This study also showed that the relief of symptoms with gabapentin persists longer than diclofenac.

In this study, younger patients (<65 years) had more severe pain but not paresthesia. Similar results are reported in literature previously (4). There are no clear reports on relations between PCPP and diabetes mellitus in which neuropathic pain are frequently seen. This study also revealed that there was no difference in the severity of pain and paresthesia in patients with or without diabetes mellitus. Present study demonstrated that there was no association between the severity of pain and paresthesia and the time after surgery. The syndrome of PCPP may last for months and even years (3, 12). This study also shows a sex difference in that the female patients had significantly more severe pain scores than the male ones. Kalso et al. (4) showed that there is no gender correlation with the presence of PCPP, but our study reveals a sex difference in the severity of chest pain. Women may have higher pain perception than men. There is no clear report comparing gender differences on post-sternotomy pain perception.

Surgical damage to nerves may take part in the etiology of PCPP. Sternal retraction stretching the nerves at the costo-vertebral junction, harvesting the internal thoracic artery with diathermy, misplacement of sternal wires, inter-costal drains and entrapment of nerves due to sternal sutures may damage to brachial plexus and inter-costal nerves (5). The mechanisms of chronic non-ischemic persistent chest pain in patients with sternotomy are not clearly understood. There are different hypotheses on the mechanisms of this late complication of sternotomy in the literature. Defalgue and Bromley (13) pointed out that the mechanism of this pain syndrome is neuralgia resulting from scar-entrapped neuromas associated with sternotomy. These neuromas may be associated with the damage of anterior ramie of inter-costal nerves by sternal wires, sternotomy and scar formation. Some authors also attribute this

Table 4. Effects of presence of diabetes mellitus and time after surgery on symptoms and treatment assignments

			General					Diclofenac					Gabapentin				
			n	Mean	SD	M. Rank	p-s/ns	n	Mean	SD	M. Rank	p-s/ns	n	Mean	SD	M. Rank	p-s/ns
Diabetics[1]	Pain BT	Diabetics	23	2.17	0.83	59.20	0.286	8	1.75	0.89	24.25	0.501	15	2.40	0.74	31.90	0.080
		Non Diabetics	83	1.98	0.78	51.92	NS	46	1.96	0.82	28.07	NS	37	2.00	0.75	24.31	NS
	Paresthesia BT	Diabetics	20	1.50	0.83	35.65	0.198	8	1.50	0.93	13.50	0.160	12	1.50	0.80	19.67	0.169
		Non Diabetics	61	1.82	0.70	40.73	NS	26	1.85	0.67	18.73	NS	35	1.80	0.72	25.49	NS
	Pain BT-Pain AT	Diabetics	23	1.43	1.04	59.13	0.301	8	1.50	1.20	35.25	0.106	15	1.40	0.99	24.47	0.130
		Non Diabetics	83	1.19	1.03	51.94	NS	46	0.83	1.02	26.15	NS	37	1.65	0.86	27.32	NS
	Paresthesia BT-AT	Diabetics	20	0.95	1.05	40.08	0.830	8	1.00	1.31	20.75	0.212	12	0.92	0.90	19.21	0.130
		Non Diabetics	61	0.93	0.81	41.30	NS	26	0.38	0.64	16.50	NS	35	1.34	0.68	25.64	NS
Time After Surgery[2]	Pain BT	<1 year	41	2.00	0.84	52.84	0.634	24	2.00	0.83	28.83	0.646	17	2.00	0.87	24.56	0.774
		1-3 year	34	1.94	0.85	50.71	NS	18	1.78	0.81	24.83	NS	16	2.13	0.89	26.94	NS
		>3 year	31	2.13	0.67	57.44		12	2.00	0.85	28.83		19	2.21	0.54	27.87	
	Paresthesia BT	<1 year	33	1.73	0.67	41.09	0.572	14	1.71	0.47	17.50	0.093	19	1.74	0.81	24.00	0.927
		1-3 year	25	1.64	0.76	37.76	NS	12	1.50	0.80	13.83	NS	13	1.77	0.73	25.00	NS
		>3 year	23	1.87	0.81	44.39		8	2.25	0.89	23.00		15	1.67	0.72	23.13	
	Pain BT-Pain AT	<1 year	41	1.10	1.02	49.24	0.496	24	1.00	1.18	28.00	0.768	17	1.24	0.75	20.88	0.135
		1-3 year	34	1.35	1.01	56.56	NS	18	1.00	1.08	28.61	NS	16	1.75	0.77	28.50	NS
		>3 year	31	1.32	1.08	55.77		12	0.67	0.78	24.83		19	1.74	1.05	29.84	
	Paresthesia BT-AT	<1 year	33	0.97	0.81	42.27	0.611	14	0.57	0.76	18.64	0.660	19	1.26	0.73	24.37	0.622
		1-3 year	25	1.04	0.98	42.88	NS	12	0.67	1.15	17.67	NS	13	1.38	0.65	26.23	NS
		>3 year	23	0.78	0.85	37.13		8	0.25	0.46	15.25		15	1.07	0.88	21.60	

1 - Mann Whitney U, 2- Kruskall Wallis tests
AT - after treatment, BT - before treatment, NS - non-significant, S - significant

chronic pain syndrome to the damage of inter-costal nerves by dissection of internal mammarian artery (14). This hypothesis is supported by the higher pain incidence of 23% with LIMA harvested patients compared to lower pain incidence of 4.5% with saphenous grafts used patients (15). The reported similar incidence of this pain syndrome in patients undergoing bypass operation with or without LIMA grafts or valve surgery without bypass by Meyerson et al. (3) do not support this hypothesis. Kalso et al. (4), also, reported that the tymectomized patients with sternotomy had more severe pain than the bypass ones. In our study, the similar severity of the chronic PCPP in patients undergoing bypass surgery and valve surgery weakens this hypothesis and suggests that the damage of inter-costal nerves by dissection of internal mammarian artery may not be only cause responsible for the PCPP, so other etiologies may play a role in the etiology of this pain syndrome, also.

Neuropathic pain is defined by the International Association for the Study of Pain as the pain initiated or caused by a primary lesion or dysfunction of peripheral or central nervous system (16). The nature of the chronic non-ischemic persistent chest pain issued in this study may comply with peripheral neuropathic pain. In literature, there is no clear information in the treatment of the chronic neuropathic pain in patients undergoing heart surgery with sternotomy. Shioe et al. (10) showed that the use of gabapentin is effective in the treatment of persistent postoperative pain in patients undergoing thoracic surgery without sternotomy. Solak and colleagues (17) matched the effect of gabapentin and naproxen on the chronic post-thoracotomy pain in thoracic surgery patients without sternotomy. Their study showed that gabapentin is effective, and also superior to naproxen in the treatment of chronic post-thoracotomy pain. In these two studies (10, 17), the side effects of gabapentin were seen with high rates 40% and 35%, respectively. In our study, we observed less side effects of gabapentin with 7%. This was likely related to relatively lower dose of gabapentin and shorter duration of the gabapentin therapy. Shoe et al. (10) continued gabapentin therapy for a mean duration of 21.9 weeks at a dose of 900 mg daily. In Solak et al.'s study (17), gabapentin was titrated up to 2400 mg daily and was continued for 60 days. However, the effectiveness of gabapentin was quite high in our study. Therefore, we realized that the 800 mg daily moderate dose of gabapentin might be effective because most patients have low intensity of PCPP, so we may reduce high ratio of side effects of gabapentin. In this study, both drugs were found to be effective in the treatment of PCPP. These results suggest that PCPP may have both neuropathic and nociceptive pain characteristics. The anti-inflammatory effects of diclofenac on the chronic inflammation of nerve endings may

explain its effeccacy on paresthesia (7).

Study limitations

Some important limitations of the present study are the subjectivity of pain and paresthesia evaluation as in other pain studies, that a control group of patients was not constituted due to pain syndrome, patients did not have clear information on their post operative analgesia, and that there was no clear information about the method of LIMA harvesting and the technique of sternal closure. In the evaluation of both pain and paresthesia, we used a four- point rating score for simple and correct evaluation. This method may reveal some insufficiency in paresthesia evaluation. However, it is difficult to assess or rate patient's pain or paresthesia because the level of perceived discomfort may be greater than observed and is completely subjective. Although it was reported that prospective, randomized, open-label, blinded end-point design yields the similar results as double-blind and placebo-controlled studies, our data should be confirmed in double-blind, placebo-controlled studies with a larger size (8). We also consider that exacerbation incidence of PCPP in this study is high. This result may be related to short treatment duration in our study. Thus, we recommend that these patients should be treated at least three months with low dose gabapentin.

Conclusion

Both gabapentin and diclofenac are effective in the treatment of chronic PCPP, without obvious side effects. However, gabapentin is superior to diclofenac in the treatment of chronic PCPP of patients with sternotomy and its effects last longer. The results show that there may be some evidence in PCPP as a kind of neuropathic pain. Although, better response to gabapentin therapy in PCPP may suggest neuropathic etiology, large-randomized and placebo-controlled trials with longer duration are required.

References

1. Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. Anesthesiology 2006; 105: 794-800.
2. Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery-a prospective study. Acta Anaesthesiol Scand 2001; 45: 940-4.
3. Rowe MA, King KB. Long-term chest wall discomfort in women after coronary artery bypass grafting. Heart Lung 2003; 27: 184-8.
4. Kalso E, Mennander S, Tasmuth T, Nilsson E. Chronic post-sternotomy pain. Acta Anaesthesiol Scand 2001; 45: 935-9.
5. Alston RP, Pechon P. Dysesthesia associated with sternotomy for heart surgery. Br J Anaesth 2005; 95: 153-8.
6. Cheng JK, Chiou LC. Mechanisms of the antinociceptive action of gabapentin. J Pharmacol Sci 2006; 100: 471-86.
7. Barden J, Edwards J, Moore RA, McQuay HJ. Single dose oral diclofenac for postoperative pain. Cochrane Database Syst Rev 2004; 2: CD004768.
8. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992; 1: 113-9.
9. Chapman JR, Syrjala KL. Measurement of pain. In: Loeser JD, editor. Bonica's management of pain. Third edition. Philadelphia: Lippincott Williams Wilkins; 2001. p. 310-28.
10. Sihoe AD, Lee TW, Wan IY, Thung KH, Yim AP. The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients. Eur J Cardiothorac Surg 2006; 29: 795-9.
11. King KM, Tsuyuki R, Faris P, Currie G, Maitland A, Collins-Nakai R. The Women's Recovery from Sternotomy (WREST) study: design of a randomized trial of a novel undergarment for early use after sternotomy. Am Heart J 2005; 149: 761-7.
12. King KM, Parry M, Southern D, Faris P, Tsuyuki RT. Women's Recovery from Sternotomy-Extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. Heart 2008; 94: 493-7.
13. Defalgue RJ, Bromley JJ. Poststernotomy neuralgia: A new pain syndrome. Anesth Analg 1989; 69: 81-2.
14. Conacher ID, Doig JC, Rivas L, Pridie AK. Intercostal neuralgia associated with internal mammary artery grafting. Anesthesia 1993; 48: 1070-1.
15. Eng J, Wells FC. Morbidity following coronary artery revascularization with the internal mammarian artery. Int J Cardiol 1991; 30: 55-9.
16. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132: 237-51.
17. Solak O, Metin M, Esme H, Solak O, Yaman M, Pekçolaklar A, et al. Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain. Eur J Cardiothorac Surg 2007; 32: 9-12.