Gazi Tıp Dergisi / Gazi Medical Journal

ARAŞTIRMA YAZISI - RESEARCH ARTICLE

2005: Cilt 16: Sayı 1: 15-18

COMBINATION OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION AND ONDANSETRON FOR PREVENTION OF CHEMOTHERAPY-INDUCED EMESIS IN GENITOURINARY TUMORS

Bülent BALTACI[1], Ayşegül CEYHAN[1], Ayşe ÖZCAN[1], Namık ÖZCAN[1], Zeki SANDIKÇI[2]

Purpose: We assessed the antiemetic effect of transcutaneous electrical nerve stimulation (TENS) and whether an ondansetron-TENS combination has a stronger antiemetic effect in patients receiving chemotherapy.

Methods: Two study groups were formed from 14 testis tumor patients scheduled for BEP (Bleomycin, Etoposide, Cisplatin) chemotherapy and 11 urinary bladder tumor patients scheduled for MVEC (Methotrexate, Vinblastine, Epirubicin, Cisplatin) chemotherapy. For three cycles of each chemotherapy regimen, TENS, ondansetron or ondansetron+TENS was applied randomly to each patient as an antiemetic therapy. Patients were asked to grade their nausea using a zero to ten scale during this therapy. In addition, the antiemetic attacks of each patient were registered.

Results: The ondansetron+TENS combination was significantly more effective than TENS and ondansetron alone for reducing nausea and preventing emetic attacks in both groups ($p<0.05$). Assessment of response to antiemetic therapy within groups with a chi-square test revealed that ondansetron alone was more effective than TENS alone; similarly, ondansetron+TENS was found to be more effective than ondansetron alone in both groups. This difference was statistically significant for both groups ($p<0.05$).

Conclusion: Ondansetron used alone has an acceptable antiemetic effect. TENS used alone has a minor antiemetic effect but TENS added to ondansetron is the most effective therapy preventing nausea and emetic attacks caused by chemotherapy.

Key Words: Emesis, chemotherapy, TENS, ondansetron.

Genitoüriner Sistem Tümörlerinde Kemoterapi Kaynaklı Emezisin Önlenmesinde Transkütanöz Elektriksel Sinir Stimülasyonu (Tens) İle Ondansetron Kombinasyonu

Amaç: Çalışmamızda kemoterapi alan hastalarda transkütanöz elektriksel sinir stimülasyonu (TENS)'nun antiemetik etkinliği ve TENS ile ondansetron kombinasyonunun daha güçlü antiemetik etki oluşturup oluşturmadığı araştırıldı.

Gereç ve Yöntem: Çalışma grupları BEP (Bleomisin, Etoposid, Sisplatin) kemoterapisi planlanan 14 testis tümörlü ve MVEC (Metotreksat, Vinblastin, Epirubisin, Sisplatin) kemoterapisi planlanan 11 mesane tümörlü hastadan oluşturuldu. Her olgunun üç siklusu randomize edilerek kemoterapi sırasında antiemetik tedavi olarak TENS, ondansetron, TENS+ondansetron uygulandı. Hastalardan antiemetik tedavi esnasındaki bulantılarını 0-10 arasında değişen bir skala ile değerlendirmeleri istendi. Ek olarak hastaların emetik atakları kaydedildi.

Bulgular: Her iki grupta ondansetron + TENS kombinasyonunun bulantıyı azaltmada ve emetik atakları önlemede tek başına TENS ve ondansetrona göre daha etkin olduğu bulundu ($p< 0.05$). Antiemetik tedaviye yanıt Ki kare testi ile her iki grup içi karşılaştırıldığında, tek başına ondansetronun tek başına TENS'ten ve ondansetron + TENS kombinasyonunun tek başına ondansetrondan her iki grupta da daha etkin olduğu saptandı.

Sonuç: Tek başına ondansetron kullanımının hastalar tarafından kabul edilebilir antiemetik etkinliğe sahip olduğu, TENS'in tek başına kullanımının minör bir antiemetik etkinlik gösterdiği, ancak ondansetrona ek olarak TENS kullanımının kemoterapiye bağlı bulantı ve kusma ataklarının önlenmesinde en yüksek etkinliğe sahip olduğu sonucuna varıldı.

Anahtar Kelimeler: Emezis, Kemoterapi, TENS, Ondansetron.

[1] Ministry of Health, Ankara Research and Training Hospital, Department of Anesthesiology and Reanimation, Ankara, Turkey

[2] Ministry of Health, Ankara Research and Training Hospital, Department of Urology, Ankara, Turkey

Chemotherapy is commonly used for the treatment of genitourinary tumors. Chemotherapy regimens including cisplatin are usually preferred because of remission rates of 50-70%. However, cisplatin is the most emetogenic chemotherapeutic agent and most patients suffer from nausea and vomiting, which affect quality of life and maintenance of the treatment (1). Although the emetogenic mechanisms of cisplatin are not clearly understood, two mechanisms are thought to be responsible. The first involves cisplatin increasing the release of serotonin (5HT3) from intestinal mucosa, which triggers the vomiting reflex via afferent fibers of the vagus nerve (2-4). The second involves cisplatin increasing the levels of circulating serotonin, which stimulates the chemoreceptor trigger zone, resulting in nausea and vomiting (5-7). Cisplatin also exerts an emetogenic effect by decreasing the motility of the gastrointestinal system. In this respect, serotonin antagonists are the most effective and commonly used antiemetic agents for the prevention and treatment of cisplatin-induced nausea and vomiting. Ondansetron is a highly selective 5HT3 receptor antagonist that prevents the serotonin-induced depolarization of afferent vagal fibers (4,6). Ondansetron is also thought to affect the chemoreceptor trigger zone by blocking the emetogenic effect of substances formed by the metabolization of cisplatin (5,6,8). Nowadays, by the improvement of non-invasive and simple techniques, acupuncture is becoming more widely used. Acupressure (applying pressure to specific points) and transcutaneous electrical nerve stimulation (TENS) are noninvasive and simple variations of acupuncture devoid of side effects (9).

Recent studies showed that acustimulation is of limited benefit in treating anesthesia-, chemotherapy- and pregnancy-induced emesis (10-13).

We aimed to compare the effectiveness of ondansetron, TENS and ondansetron+TENS in the treatment of chemotherapy-induced emesis in patients with genitourinary tumors.

MATERIALS AND METHODS

After the approval of the ethics committee and written informed consent were obtained, 25 patients aged 17-74 were included in the study. Fourteen patients with testis tumor (Group I) and 11 patients with urinary bladder tumor (Group II) were scheduled for 4 treatments with bleomycin, etoposide, cisplatin (BEP) and methotrexate, vinblastine, epirubicin cisplatin (MVEC) regimens, respectively. Interval between the treatments was 28 days. The treatment protocols are presented in Table 1.

Table l. MVEC and BEP Protocols.

MVEC Protocol Used in Bladder Tumors
BEP Protocol Used in Testis Tumors

Day	Chemotherapeutic	Day	Chemotherapeutic
1	Methotrexate 30 mg/m²	1	Cisplatin 100 mg/m²
			Etoposide 120 mg/m²
2	Cisplatin 70 mg/m²	2	Bleomycin 30 mg/m²
	Vinblastine 3 mg/m²		Etoposide 120 mg/m²
	Epirubicin 40 mg/m²		
15	Methotrexate 30 mg/m²	3	Etoposide 120 mg/m²
22	Methotrexate 30 mg/m²	15	Bleomycin 30 mg/m²
		22	Bleomycin 30 mg/m²

Before each treatment, renal and liver function tests, complete blood counts and creatine clearance of each patient were studied. Patients with creatine clearance greater than 60 ml/min, with normal blood counts and biochemical tests and devoid of systemic disease that may cause emesis were included in the study.

Patients in both chemotherapy groups were randomized into one of the ondansetron, TENS or ondansetron+TENS groups for 3 of 4 treatments with chemotherapy regimens. In the ondansetron groups, 4 mg of ondansetron was given as a slow intravenous injection before, in the middle and at the end of chemotherapeutic infusion, reaching a total amount of 12 mg. Similarly, in the TENS groups, TENS treatment was started 1 hour before chemotherapeutic infusion and continued throughout the infusion. TENS was applied using a Reliefband (Maven Labs Inc, CA, USA) generating burst stimulus with low current and frequency (4 Hz).

The Reliefband was placed to stimulate the P6 (Neiguon) point, 4-5 cm (2 tsun) proximal to the distal crease of the wrist between the palmaris longus and flexor carpi radialis tendons. Both ondansetron and TENS treatments were applied together in the ondansetron+TENS groups.

All patients were asked to assess their nausea during chemotherapeutic infusions for each antiemetic therapy using a nausea scale, previously used by Claybon (14), in which 0 represents no nausea and 10 the most severe nausea they can experience. For assessing vomiting attacks, a scale previously used by McMillan and colleagues (15) was used. They described vomiting as throwing up the contents of stomach, retching as trying to vomit without throwing up the contents of the stomach and emetic attack as vomiting once or retching 1 to 5 times in 5 minutes.

According to the description above, a complete antiemetic response is zero emetic attacks per day, a major response is 1-2 emetic attacks per day, and a minor response is 3-5 emetic attacks per day. Emetic attacks more than 5 per day indicated unresponsiveness to antiemetic therapy.

Nausea scores, emetic attacks and response to antiemetic therapy were recorded for ondansetron, TENS and ondansetron+TENS therapies applied in different treatment periods. Data were described as mean ± SD. For assessing response to antiemetic therapy a chi-square test was used. $p < 0.05$ indicated significance.

RESULTS

Mean ages of the patients were 28.64 ± 6.41 and 59.45 ± 9.71 in Groups I and II, respectively. No serious side effect was observed in any patient.

Mean nausea scores of the groups are shown in Table 2. Ondansetron alone was significantly more effective than TENS alone in preventing nausea in both groups ($p < 0.05$). Ondansetron+TENS was significantly more effective than TENS and ondansetron alone in reducing nausea in both groups ($p < 0.05$).

Table 2: Nausea Scales of Antiemetic Treatments (mean ± SD).

Antiemetic Treatment	Nausea Scale	
	Group I	Group II
Ondansetron	2.92±1.54	3.09±1.44
TENS	5.07±2.20	5.18±2.89
Ondansetron +TENS	0.50±0.65	1.18±1.16

Emetic attacks in the treatment groups are shown in Table 3. Ondansetron alone was more effective in preventing emetic attacks than TENS alone in both groups ($p < 0.05$). Ondansetron+TENS was significantly more effective than ondansetron alone and TENS alone in both groups ($p < 0.05$).

Table 3: Mean of Emetic Attacks Observed in Antiemetic Treatment Groups (mean ± SD).

Antiemetic Treatment	Emetic Attacks	
	Group I	Group II
Ondansetron	1.64±1.39	1.63±1.28
TENS	3.00±1.96	3.36±1.36
Ondansetron +TENS	0.35±0.49	0.81±0.98

Assessment of response to antiemetic therapy according to McMillan and colleagues is given in Table 4. A complete antiemetic response was achieved in 64% and 45.5% in the ondansetron+TENS groups in Groups I and II, respectively. In the ondansetron group in Group I, a complete response and a major response were observed in 7.1% and 71.4% of patients, respectively. In the ondansetron group in Group II, a complete response and a major response were observed in 18.2% and 54.5% of patients, respectively. In the TENS groups a minor response was observed in most of the patients in Groups I and II.

Assessing response to antiemetic therapy within the groups with the chi-square test revealed that ondansetron alone was more effective than TENS alone; similarly, ondansetron+TENS

Table 4: Response to Antiemetic Treatment (number of cases (X %)).

	Complete Response		Major Response		Minor Response		No Response	
Antiemetic Treatment	Group I (n=14)	Group II (n=11)	Group I (n=14)	Group II (n=11)	Group I (n=14)	Group II (n=11)	Group I (n=14)	Group II (n=11)
Ondansetron	1(7.14)	2(18.18)	10(71.4)	6(54.54)	3(21.4)	3(27.27)	0	0
TENS	1(7.14)	0	4(28.57)	4(36.36)	7(50)	6(54.54)	2(14.28)	1(9.09)
Ondansetron + TENS	9(64.28)	5(45.45)	5(37.71)	5(45.45)	0	1(9.09)	0	0

was more effective than ondansetron alone in both groups. This difference was statistically significant for both groups ($p < 0.05$).

DISCUSSION

Nausea and vomiting can be induced by the activation of visceral afferents of the vagus nerve or by the stimulation of the nausea-vomiting center in the area postrema on the brain stalk directly or by sympathetic fibers (6). After intestinal mucosal cell damage caused by cisplatin, released serotonin stimulates vagal afferents, resulting in nausea and vomiting (2-4). The chemoreceptor trigger zone is rich in 5HT3 receptors and can be stimulated by both circulating serotonin and serotonin in cerebrospinal fluid (5-7). Hence, cisplatin can indirectly stimulate the chemoreceptor trigger zone by elevating circulating levels of serotonin (5,6).

Cisplatin differs from other antineoplastic agents by way of its two phases of elimination half-life. This difference is of more importance in cases of nausea and vomiting comparing other chemotherapeutic regimens. Cisplatin's first elimination half-life is 30 minutes. Nausea and vomiting that start with the infusion of cisplatin and go on for the first 24 hours are described as cisplatin-related acute emesis. The second elimination half-life is 60 hours, which is responsible for nausea and vomiting attacks seen a few days after cisplatin infusion and described as cisplatin-related late emesis (16). Continuation of comfortable and acceptable chemotherapies can be managed by different antiemetic therapies. Today, the most effective antiemetic therapy is managed by serotonin (5HT3) antagonists (ondansetron, tropisetron, granisetron). These drugs are relatively expensive and there is no significant difference between their effectiveness, but ondansetron is the most frequently used (17).

Ondansetron is a highly selective 5HT3 antagonist that displays its action by preventing the depolarization of afferent vagal fibers stimulated by serotonin. In addition, ondansetron is thought to exert its action directly on the nausea-vomiting center by blocking the actions of emetogenic substances like serotonin, released by the action of cytotoxic agents (5,6). The optimum dose of ondansetron for preventing emesis caused by chemotherapeutics is 0.18 mg/kg/day (18). Ondansetron has minimal side effects. A commonly reported side effect is headache, which responds to simple painkillers. Rarely chest pain, arrythmias, and anaphlactoid reactions are reported (6). In our study, 2 patients (8%) had headaches, which we thought were related to ondansetron.

The combination of P6 (Neiguon) point stimulation by TENS with ondansetron can result in effective antiemesis without increasing the ondansetron dose (15). In our study, we divided the optimum dose of ondansetron into 3 and applied it at the beginning, in the middle and at the end of the chemotherapeutic infusions.

In a study by Cubeddu and colleagues (17), when ondansetron was given to cisplatin infused patients, the mean number of emetic attacks was 1.5 while it was 5.5 in the placebo group.

Saller and colleagues (19) investigated the effectiveness of TENS in 24 patients with head and neck tumors and reported that TENS enhanced the antiemetic effect of metoclopramide. In another study, Dundee and colleagues reported that TENS applied during chemotherapy significantly reduced nausea and vomiting (20).

In our study, the mean emetic attacks in the ondansetron groups numbered 1.64 ± 1.39 and 1.63 ± 1.28 in Groups I and II, respectively. Major response rates to antiemetic therapy were 71.4% and 54.5% in the ondansetron groups in Groups I and II, respectively. In the light of these data, ondansetron was thought to be effective in preventing chemotherapy-related emesis.

According to traditional Chinese medicine, life energy in humans (chi) circulates in channels called meridians. Interruption of the circulation of chi causes diseases. Reestablishment of circulation can be afforded by the stimulation of special points on these meridians (acustimulation) (21). One of the methods of acustimulation is acupressure, the other is transcutaneous electrical stimulation (9). These methods are cheap and free of side effects (20). They are especially useful for subjects who are allergic to antiemetics and in which the antiemetic dose must be decreased to reduce the side effects. Reducing the dose will also reduce the cost of therapy, another point to keep in mind.

It is reported that TENS is less effective than acupuncture but more effective than acupressure (20). In previous studies, non-pharmacological methods like acupuncture and

acupressure were reported to be comparably effective as antiemetics, but new generation antiemetics like ondansetron were not included in these studies (22-25).

Pearl and colleagues (26) investigated the effectiveness of TENS in preventing cisplatin-related emesis in patients with gynecologic tumors. All patients received a standard antiemetic protocol including dexamethasone, ondansetron and lorazepam 30 minutes before chemotherapy. They applied TENS or placebo-TENS to all patients. Antiemetic therapy succeeded in all patients. Although there was no difference between the groups, patients in the active TENS group stated that the device definitely reduced their nausea and vomiting, that she or he must go on using the device, that they were willing to buy the device, and that using the device was more comfortable and they recommended it to others.

In our study we achieved 50% minor response in Group I and 42.9% minor response in Group II in the TENS groups. Hence, TENS alone is insufficient for preventing chemotherapy-related emesis.

In conclusion, we found that ondansetron was an effective agent in preventing chemotherapy-related emesis. Furthermore, we observed that the ondansetron+TENS combination was more effective. Since TENS alone has little antiemetic effect, we do not recommend the use of TENS alone. In addition to previous studies, we also found that TENS is devoid of side effects and can be safely used. One thing to be stressed is that P6 stimulation must be started before emetic stimulation to be effective.

We know that ondansetron is an expensive choice for preventing chemotherapy-related emesis. Despite ondansetron therapy, we were unable to achieve the complete prevention of nausea and vomiting. Therefore, we conclude that to reduce the cost and side effects and to augment the comfort of antiemetic therapy during chemotherapies, the TENS combination is an effective choice that must be kept in mind.

Correspandance Address
Ayşe ÖZCAN, MD
380. Sok. İdareciler Sitesi B-Blok No:32 Karakusunlar Ankara 06530
Tel: 0 312 595 31 75
e-mail: namikayse@yahoo.com

REFERENCES

1. Wyngaarden JB, Smith LH, Bennett JC. Cecil Textbook of medicine. Philadelphia: W.B. Saunders Company; 1992.
2. Costall B, Domeney AM, Naylor RJ, Tattersal FD. 5-Hydoxytryptamine M-receptor antagonism to prevent cisplatin-induced emesis. Neuropharmacology 1986; 25:959-961.
3. Andrews PL, Rapeport WG, Sanger GJ. Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol Sci 1988; 9: 334-341.
4. Hawthorn J, Ostler KJ, Andrews PL. The role of abdominal visceral innervation and 5-Hydroxytriptamine M-receptors in vomiting induced by the cytotoxic drugs cyclophosphamide and cisplatin in the ferret. Q J Exp Physiol 1988; 73: 7-21.
5. Higgins GA, Kilpatrick GJ, Bunce KT, Jones BJ, Tyers MB. 5-HT3 receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Br J Pharmacol 1989; 97: 247-255.
6. Milne RJ, Heel RC. Ondansetron. Therapeutic use as an antiemetic. Drugs 1991; 41:574-595.
7. Lichter I. Nausea and vomiting in patients with cancer. Hematol Oncol Clin North Am 1996; 10: 207-220.
8. Naylor RJ, Inall FC. The physiology and pharmacology of postoperative nausea and vomiting. Anaesthesia 1994; 49 (supp): 2-5.
9. Beal MW. Acupuncture and acupressure. Applications to women's reproductive health care. J Nurse Midwifery 1999; 44(3): 217-230.
10. Dundee JW, Chestnutt WN, Ghaly RG, Lynas AG. Traditional Chinese acupuncture: a potentially useful antiemetic? Br Med J 1986; 293: 583-584.
11. Ho CM, Hseu SS, Tsai SK, Lee TY. Effect of P-6 acupressure on prevention of nausea and vomiting after epidural morphine for postcaesarean section pain relief. Acta Anaesthesiol Scand 1996; 40: 372-375.
12. Dundee JW, Ghaly RG, Fitzpatrick KT, Lynch GA, Abram WP. Acupuncture to prevent cisplatin-associated vomiting. Lancet 1987; 1: 1083.
13. De Aloysio D, Penacchioni P. Morning sickness control in early pregnancy by Neiguan point acupressure. Obstet Gynecol 1992; 80(5): 852-854.
14. Claybon L. Single dose intravenous ondansetron for the 24-hour treatment of postoperative nausea and vomiting. Anaesthesia 1994; 49 (suppl): 24-29.
15. McMillan C, Dundee JW, Abram WP. Enhancement of antiemetic action of ondansetron by transcutaneous electrical stimulation of the P6 antiemetic point, in patients having highly emetic cytotoxic drugs. Br J Cancer 1991; 64(5): 971- 972.
16. Perez EA, Hesketh PJ, Gandara DR. Serotonin antagonists in the management of cisplatin-induced emesis. Semin Oncol 1991; 18: 73-80.
17. Cubeddu LX, Hoffman IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 1990; 322: 810-816.
18. Grunberg SM, Stevenson LL, Russell CA, McDermed JE. Dose ranging phase I study of the serotonin antagonist GR38032F for prevention of cisplatin induced nausea and vomiting. J Clin Oncol 1989; 7(8): 1137-1141.
19. Saller R, Hellenbrecht D, Buhring M, Hess H. Enhancement of the antiemetic action of metoclopramide against cisplatin induced emesis by transdermal electrical nerve stimulation. J Clin Pharmacol 1986; 26: 115-119.
20. Dundee JW, Yang J, McMillan C. Non-invasive stimulation of the P6 (Neiguan) antiemetic acupuncture point in cancer chemotherapy. J R Soc Med 1991; 84(4): 210-212.
21. Helms JM. The basic, clinical and speculative science of acupuncture. In. Helms JM (ed): Acupuncture energetics. A clinical approach for physicians. Berkeley, Medical Acupuncture Publishers, 1995. p. 20-39.
22. Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: A meta analysis. Anesth Analg 1999; 88(6): 1362-1369.
23. Yang LC, Jawan B, Chen CN, Ho RT, Chang KA, Lee JH. Comparison of P6 acupoint injection with 50% glucose in water and intravenous droperidol for prevention of vomiting after gynecological laparascopy. Acta Anaesthesiol Scand 1993; 37: 192-194.
24. Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KT, Lynas AG. Effect of stimulation of the P6 antiemetic point on postoperative nausea and vomiting. Br J Anaesth 1989; 63(5): 612-618.
25. Stein DJ, Birnbach DJ, Danzer BI, Kuroda MM, Grunebaum A, Thys DM. Acupressure versus intravenous metoclopramide to prevent nausea and vomiting during spinal anaesthesia for cesarean section. Anesth Analg 1997; 84(2): 342-345.
26. Pearl ML, Fischer M, McCauley DL, Valea FA, Chalas E. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induced nausea and vomiting in gynecologic oncology patients. Cancer Nurs 1999; 22(4): 307-311