The effectiveness of subcutaneously implanted epidural ports for relief of severe pain in patients with advanced-stage gynecological cancer: a prospective study

İleri evre jinekolojik kanserli hastalarda şiddetli ağrının giderilmesi için subkutanöz yerleştirilen epidural portların etkinliği: prospektif bir çalışma

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Summary

Objective: We aimed to evaluate the effectiveness of subcutaneously implanted epidural ports (SIEP) in the management of patients with advanced-stage gynecologic cancer-related severe chronic pain who do not respond to intravenous tramadol infusion, transdermal fentanyl, and oral morphine administration or who cannot tolerate the unacceptable and unmanageable side effects of these drugs.

Methods: In this prospectively designed study, SIEP to permit the administration of morphine were implanted for relief of severe chronic pain in 21 cases with stage IV gynecological cancer (ovarian [n=6], endometrium [n=3], cervix [n=10], vaginal [n=1], and vulvar [n=1]). In order to define the level of pain, visual analogue scale (VAS) and patient satisfaction score (PSS) were used before and on the 5th, 15th, and 30th days after epidural port application.

Results: The mean overall survival period of the cases undergoing epidural port application was 80 days (range: 31-560). In terms of pain parameters, values at the end of the 5th, 15th and 30th days (VAS2, VAS3 and VAS4) were significantly lower than the value before morphine application via SIEP (VAS1) ($p<0.01$). PSSs at the 5th, 15th and 30th days were significantly higher than the PSS before port implantation ($p<0.05$). Pain management was started with 2 mg morphine with a maximum of 4 mg morphine administered into the epidural space per day. No clinically detected infectious condition or morphine-related side effects that required treatment occurred during the follow-up.

Conclusion: Morphine administration via SIEP provided excellent pain relief without creating side effects, increased patient quality of life, and contributed to the patient's ability to enjoy life.

Key words: Advanced-stage gynecologic cancer; analgesia; chronic pain; subcutaneous epidural port.

Özet

Amaç: *İntravenöz tramadol infüzyonuna, transdermal fentanil ve oral morfin uygulamasına yanıt vermeyen ayrıca bu ilaçların kabul edilemeyen ve tedavi edilemeyen yan etkilerini tölere edemeyen; ileri evre jinekolojik kansere bağlı şiddetli kronik ağrısı olan hastaların yönetiminde subkutanöz yerleştirilen epidural portların etkinliğini değerlendirmektir.*

Gereç ve Yöntem: *İleriye dönük çalışma dizaynına göre, evre IV jinekolojik kanserli 21 hastada (over n=6, endometrium n=3, serviks n=10, vajina n=1 ve vulva n=1) şiddetli kronik ağrının giderilmesi için morfin uygulanmasına imkan veren epidural portlar subkutanöz olarak yerleştirildi. Epidural port uygulamasından önce ve 5., 15. ve 30. günlerden sonra ağrının seviyesini tanımlamak üzere görsel analog skalası (GAS) ve hasta memnuniyeti skorlaması (HMS) kullanıldı.*

Bulgular: *Epidural port uygulanan vakaların ortalama genel sağkalım süresi 80 gündü (dağılım 31-560). Ağrı parametreleri açısından, 5., 15. ve 30. günlerin sonundaki değerler (GAS2, GAS3 ve GAS4), epidural port yoluyla morfin uygulamasından önceki değerden (GAS1) anlamlı düşük idi ($p<0.01$). Beşinci, 15. ve 30. günlerdeki HMS, port yerleştirilmeden önceki HMS'den anlamlı yüksek idi, ($p<0.05$). Ağrı yönetimi 2 mg morfin ile başlatıldı ve en fazla 4 mg morfin epidural boşluğa günlük uygulandı. Takip sırasında, klinik olarak tespit edilen enfeksiyon durumu ve tedavi gerektirecek morfin ile ilişkili yan etki gelişmedi.*

Sonuç: *Subkutanöz yerleştirilen epidural port yoluyla morfin verilmesi yan etki yaratmadan mükemmel ağrı kontrolü sağlamakta, hayat kalitesini artırmakta ve ayrıca hayatdan zevk alma yeteneğine katkı yapmaktadır.*

Anahtar sözcükler: İleri evre jinekolojik kanser; analjezi; kronik ağrı; subkutanöz epidural port.

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Introduction

Cancer pain is prevalent, extremely heterogeneous and most patients with cancer have pain.[1,2] Chronic severe pain occurs in approximately 33% of patients in active therapy and in 67% of patients with advanced disease.[3-5] It has been reported that 77% of pain was due to cancer, 19% resulted from treatment, and 4% was unrelated with cancer.[5-7] The majority of cancer patients with pain can be adequately managed with drug therapy along the lines of the World Health Organization analgesic ladder.[6,7]

Relief of severe cancer pain towards the end of life for many sufferers is a very important phenomenon worldwide.[7] Pain localization in patients with gynecologic cancer ranges from the upper abdomen to the lower extremities. Although using traditional non-opioid and opioid analgesics via the oral, transdermal, or parenteral route play a dominant role for controlling cancer pain and increasing opioid doses may provide analgesia in most patients, higher doses of opioids are often accompanied with undesirable side effects.[5-8] In this significant minority of patients, if pelvic and/or perineal pain relief is achieved only at the expense of severe side effects or there is resistance to traditional analgesics; selective interventional pain management procedures such as percutaneous tunneled epidural catheters, totally implantable systems for intrathecal administration, plexus hypogastricus block, the saddle or lower end block and chordotomy must be considered to reduce opioid side effects, gain better analgesic efficacy and enhance the quality of life.[7-12]

The development of minimally invasive techniques and completely implantable devices that permit the epidural administration of opioids quickly and safely offer higher quality analgesia with lesser side effects. Many cancer patients at advanced stage continue to be prescribed with subtherapeutic doses of pain medications resulting in undue suffering and diminished quality of life.[8-11]

The goal of this prospective study was to evaluate pain relief effectiveness of epidural morphine administration via subcutaneous implanted ports by visual analogue scale (VAS) and patient satisfaction score (PSS) in patients with advanced stage IV gynecologic cancer who do not respond to intravenous tramadol infusion, transdermal fentanyl and oral morphine also who do not tolerate their unacceptable and unmanageable side effects.

Materials and Methods

At a time of close to two years period, subcutaneous port implantation to epidural space was succeed in 21 of 22 patients with advanced stage IV gynecological cancer who do not benefit from intravenous tramadol infusion (3x100 mg/day), transdermal fentanyl (100 mcg/hour) and oral morphine (4x20 mg/day) and also not tolerate their unacceptable and unmanageable side effects. At Department of Gynecologic Oncology, Aegean Obstetrics and Gynecology Education and Research Hospital, the study was conducted on 21 patients that succeeded to respond the analgesic treatment. [ovarian cancer (n=6), endometrium cancer (n=3), cervix cancer (n=10), vaginal cancer (n=1) and vulvar cancer (n=1)]. Present prospective study was approved by the local ethics committee of our hospital and before the beginning of management written informed consent of all patients were taken.

All patients had different sites of body metastasis, and nociceptive pain was appeared at last. Localization of pain ranged from the upper abdomen to the lower extremities. They were hospitalized for the placement of epidural catheter, titration of medication and usually discharged after 1-3 days. Before the insertion of subcutaneous port, patients were evaluated by whole blood count, C-reactive protein (CRP) and coagulation screening, and a neurologic investigation was performed. Thirty minutes before the epidural port implantation, antibiotic prophylaxy was administered to all cases (Cefazolin sodium, 1 gr vial, IV). All ports were inserted in operating room under strict aseptic conditions. The skin that port wil be implanted was cleaned out with (10% Povidone iodine) four times in a manner of circular motion to the periphery. After waiting three minutes, epidural port Celsite® ST 304-19 or 20 polysulphone access port (B. Braun Medical, France) was implanted subcutaneously to all patients. L3-L4 or L4-L5 levels were used and the port was implanted to the anterior part of the trunk. In our practice, necessity that require the use of C-arm scopy has not occured in any case.

Morphine was administered via subcutaneous epidural port way. The preparation and calculation of the initial doses were as follows: 1 ml ampoules containing 10 mg of morphine were diluated with 9 ml saline. After this process, 1 ml of this diluated solution including 1 mg morphine was put into an enjectabl flakon and 9 ml saline was inserted. Consequently, 10 ml flakons were administered for the transition of morphine to all epidural space. As such, 10 ml enjectabl flacons including 1 mg morphine were primed by anesthesiologist, given a weekly basis and administered 12 hours apart to all patients. If analgesic effect is not sufficient, the epidural drug doses were escalated. 10 ml enjectabl flacons including 2 mg morphine were primed, given a weekly basis and administered 12 hours apart. Up to maximum, 4 mg morphine was given per day (2 mg morphine with 12 hours apart). The first test injection is made at the hospital and the patient is allowed to return home in 24-72 hours.

Before discharge, how to use these ready injectable flacons for self administration, signs of port site infection and careful port exit site care were taught in detail. Adequate training were given to the patients and relatives by the oncologists and anesthesiologist of our department. Most of the patients were followed-up weekly by physical examination, leukocyte count and CRP. Then weekly doses of ready enjectabl flakons were given. The control of the patients who can not come to hospital due to poor medical conditions were carried out as palliative home care by an investigator (S.S). Patients were questioned for analgesic effect and evaluated in terms of side effects of morphine administration, and also port site and other infection signs. Combination of epidural morphine with local anesthetics was not done due to adequate pain relief achievement with epidural morphine doses and likely to develop cardiovascular side effects of local anesthetics during palliative cancer pain at home. In some patients nonsteroidal antiinflammatory drugs (NSAIDs), tramadol and tricyclic antidepressant tablets are given as adjuvant analgesics when needed.

In order to define the level of pain, visual analogue scale (VAS) was used before and after 5th, 15th, and 30th days of the administration of morphine via epidural port way. VAS was evaluated between 0 and 10 scores. No pain means '0' and very strong pain means '10'. The other evaluation parameter is patient satisfaction score (PSS). PSS was ranked in between 0 and 3. Very unsatisfied means '0' and very satisfied means '3'.[13] Side effects were recorded on a daily basis. The statistical analysis of the datas were assessed by ANOVA and Pearson's chi-square test. These tests were performed by using SPSS 16.0 statistical package program (SPSS Inc, Chicago, IL, United States) and a p value less than 0.05 was considered as statistically significant.

Results

The demographic and clinical datas of patients with advanced stage gynecologic cancer are shown in Table 1. The mean time needed for the insertion of the epidural port was 19 minutes. One partial port occlusion (4.8%) was observed in 21 cases. Heparin

Table 1. Demographic characteristics of the cases

Type of cancer	Cases (n)	Mean ± SD
Endometrium cancer	3	57.2±6.4
Ovarian cancer	6	59.4±6.7
Cervix cancer	10	46.3±2.9
Primary vagina cancer	1	76
Vulva cancer	1	53

Table 2. The evaluation of pain relief according to visual analogue scale (VAS)

	Total	Mean
VAS1	193	9.19
VAS2	41	1.95
VAS3	31	1.47
VAS4	37	1.76

VAS1 vs. VAS2, VAS3 and VAS4; p<0.01.

Table 3. The evaluation of pain relief according to patient satisfaction score (PSS)

	Total	Mean
Before the management	8	0.38
5th day	57	2.71
15th day	57	2.71
30th day	54	2.57

Before the management vs. 5th day, 15th day and 30th day; p<0.05

and saline combination was used in order to open the port tip. No complication was occured during administration. However, in one case placement of the catheter was done to subarachnoid space. The maximum survival period was 560 days. Mean overall survival period of the epidural port applicated cases was 80 days (range 31 - 560 days). Up to maximum, 4 mg morphine was administered per day (2 mg morphine 12 hours apart).

In terms of pain parameters, values at the end of 5th, 15th and 30th days (VAS2, VAS3 and VAS4) were significantly lower than the value of prior to morphine application via epidural port way (VAS1), ($p<0.01$) (Figure 1) and (Table 2). Pain satisfaction score at the 5th, 15th and 30th days were significantly higher than the (PSS) prior to epidural port implantation ($p<0.05$), (Table 3). The comparison of VAS1, VAS2, VAS3, VAS4 scores and patient satisfaction scores seem to be parallel (Figure 2).

The number of injections applicated via epidural access ports to 21 patients permitted treatment for up to 1680 days and were more than 1884 injections without any complication. It has revealed 1.1 (min: 0.6-max: 1.6) injections/ days/ patients (Figure 3). During the achieved survival period, analgesia was achieved in 21 of 22 cases, whereas analgesic effect was not observed in one case due to placement of the catheter to subarachnoid space. Obtained analgesia level was very good (VAS2-4) in 21 patients. Resistance to injection and inadequate analgesia were recorded in only one patient with cervix cancer at the 90th day. During follow-up no infectious condition and no drug related side effects that require treatment were observed in our study group.

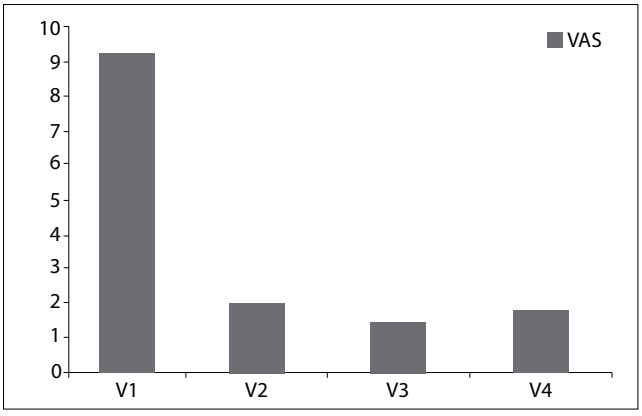

Figure 1. The evaluation of patients by visual analogue scale (VAS).

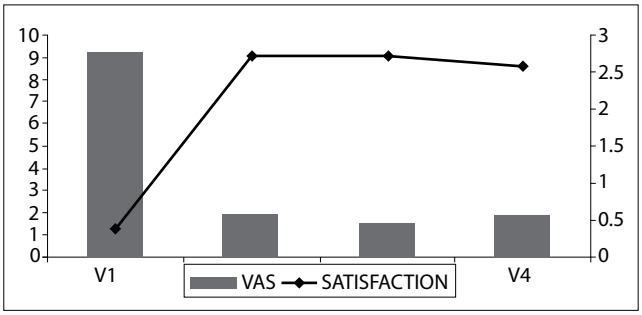

Figure 2. The analysis of VAS_1, VAS_2, VAS_3, VAS_4 and patient satisfaction scores.

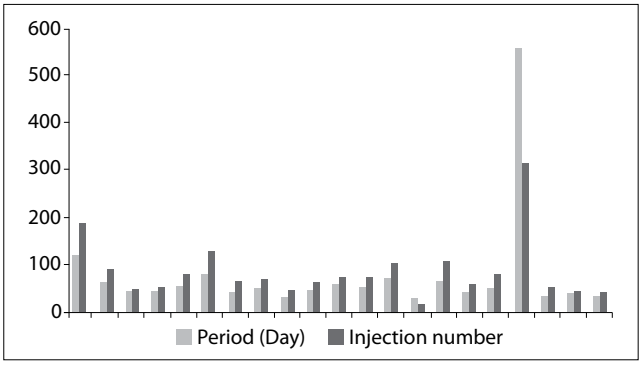

Figure 3. Mean overall survival of patients and number of daily injections.

Discussion

The incidence of pain among patients with gynaecological cancer was reported as 77% among fourteen types of cancer and is located on the tenth place.[14] The adequate analgesia was achieved by 45 to 100% of the patients with cancer pain who were using of the World Health Organization ladder.[15] Although traditional opioid use have been the cornerstone to relieve cancer pain, patients with advanced stage cancer require interventional pain techniques for effective pain management. It has been suggested that effective cancer pain management should be multidisciplinary and multimodal by using combination therapies and should be individualized with the aim to optimize pain relief by minimization of adverse effects.[1,2,7,8,10,15]

The application of epidural port, Celsite® ST 304-19 or 20 polysulphone access port, is a very effective method for cases who have undergone sequential strong opioid drug trials and unresponsive pain with unmanageable side effects. The most serious issue for epidural ports is infection. Introducing foreign material into the body implies a risk of infection, especially since there is a connection between the skin

and into the central nervous system (CNS). In most cases, the bacteria involved in foreign material infections are gram-positive cocci such as *Staphylococci*, specifically coagulase-negative *Staphylococci*. Rarely, gram-negative bacteria may also be involved. Moreover, this gives rise to a low virulent chronic infection with few general symptoms but a significant problem with local symptoms, difficulty in pain management or systemic dysfunction.[16]

The incidence of infection following catheter insertion is difficult to determine from previous studies since most authors do not report this complication and the catheters used in these studies were not the same catheters used in present study. During our study period, antibiotic prophylaxy was administered to all cases, but Holmfred et al. had not used prophylactic antibiotic for administration of epidural catheter.[16] One paper presented six cases of meningitis in relation to injection of morphine into a slow-release subcutaneous pump system.[17] In our series, no infection occured during the period of pain management. We consider that this was achieved by providing strict hygienic conditions while administrating ports at operating room and teaching home care rules to the patients and relatives in detail. Indeed, the follow up of home care conditions and the catheters are as important as the application of the catheters. Obstructive and /or infectious problems, if observed, should lead to serious medical conditions as well as removal of the catheter.

In general, it is assumed that percutaneous catheters are best suited for patients with very limited life expectancies because of the potential for dislodgement and the theoretically higher risk of infection.[11,18,19] Thus, we have decided to use epidural route and access port, which is easier and safer. In this respect; Samuelsson et al.[20] had found mean epidural morphine treatment time was 92 days, mean daily epidural start dose of morphine was 18 mg, subcutaneous catheter related problems and drug related complications with ratios of (9.4% and 5.2%), respectively in 146 patients. In this research performed in Sweden, the oral daily morphine-equivalent dose prior to inclusion was 164 mg.[20] In another study from the Netherlands by Driessen et al., a polyurethane epidural catheter was tunneled and connected to a subcutaneous port in 8 patients and they noted that all patients had significant or complete pain relief from 10 mg morphine/day, and only transient pruritis was the main drug related side effect.[21] Poletti et al. from United States (US) reported good pain relief by a regimen of long-term 2 mg epidural morphine administration twice daily with permanent indwelling systems for self-administration with a little drug tolerance reaction.[22] Denobile et al. from US demonstrated that the patients required 0.4-3.5 mg of morphine per hour with occasional boluses by using a totally implantable access system.[23] In a similar study from Israel performed in eighty cancer patients, treatment was started with a 2 mg test dose and up to maximum 18 mg of morphine administered through an indwelling epidural catheter and 76% of the patients experienced complete relief of pain.[24]

The most important issue could be the concentrations of opioids applied. Unfortunately, it was not possible to identify the optimal concentrations of opioids in the articles investigated. Nevertheless, a dose range of 2.3-18 mg morphine per day was detected.[20-25] An overview analysing intrathecal morphine therapy by Miele et al.[26] reported similar daily doses. The most obvious clinical superiority of epidural morphine application is to provide dose savings. The most serious complication is early and late occuring respiratory depression. In our series from Turkey, mean epidural morphine treatment period was 80 days, catheter related problems were (4.8%) and no drug related complications were observed during study period. In our practice, epidural morphine administration was started with a dose of 2 mg and excellent pain relief was achieved in 21 cases by administrating up to maximum 4 mg morphine per day (2 mg morphine 12 hours apart). In the light of previous studies and ours; it can be noted that the need for increased dosage seems to be related not only to changes in receptor sensitivity but also to changes in pain mechanisms and cancer type because recently European Pain in Cancer survey has been demonstrated that there are intercountry differences in terms of patient pain perception and treatment.[14]

Previously, the disadvantage of epidural port system is that they may become more expensive if survival is prolonged due to the cost of home care and main-

tenance so it has been said that only cancer patients with a short life expectancy (< or =3 months) should be treated with epidural analgesia.[11,18,23] However, nowadays the development and worldwide easy use of completely implantable, inexpensive, high quality and safe epidural ports lead to high satisfied analgesia via continous administration of low dose opioids. Moreover; the pain localization is a very important factor because lower abdominal severe pain due to advanced gynecologic cancer seem to be more easily reliefed with this technique.

Palliative care is becoming an emerging topic in Turkey within recent years. When this matter was considered for the purposes of Turkey, it was shown that there are few palliative care centers across the country. Also, it was noted that our country was lacking behind many countries with respect to morphine consumption per capita and the available morphine products within Turkish market were also lacking.[27] In the light of these realities, Turkish Cancer Control Department has launched a project so called Pallia-Turk to be implemented in 2011. In this context; we consider that the results of our study can burden the knowledge for the management of patients who are in need of acute-subacute and chronic palliation in terms of severe cancer pain and shed some light on Pallia-Turk Project which aimed to improve population-based palliative care system.

To the best of authors' knowledge; present study that was performed in patients with advanced stage IV gynecologic cancers is the most largest series study in the literature. In these patients who had resistance to and severe side effects of traditional narcotic administration methods; subcutaneous implanted epidural port use provided excellent pain-relief without side effects, increase quality of life and also contribute the ability to enjoy life. Moreover; morphine administration via subcutaneous implanted epidural port way for relief of advanced stage gynecologic cancer related intractable pain are not only effective, but also let these patients to spend rest of their lives at home free of pain.

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