

Efficacy of Epidural Analgesia in Patients with Cancer Pain: A Retrospective Observational Study

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Purpose: Pain in terminal cancer patients may be refractory to systemic analgesics or associated with adverse drug reactions to analgesics. Epidural analgesia has been effectively used in such patients for pain control. However, this method does not provide pain relief to all patients. The efficacy and complications of continuous epidural analgesia were evaluated for expanding efficacy in terminal cancer patients. **Materials and Methods:** The charts of patients who received epidural analgesia for over 5 years for the control of terminal cancer pain were reviewed retrospectively. **Results:** Ninety-six patients received 127 epidural catheters. The mean duration for epidural catheterization was 31.5±55.6 (5-509) days. The dose of epidural morphine increased by 3.5% per day. The efficacy of epidural analgesia at 2 weeks follow up revealed improved pain control (n=56), as the morphine equivalent drug dose dropped from 213.4 mg/day to 94.1 mg/day ($p<0.05$) at 2 weeks follow up. Accordingly, after 2 weeks institution of epidural analgesia, there was a significant reduction in the proportion of patients with severe pain, from 78.1% to 19.6% ($p<0.05$). **Conclusion:** Epidural analgesia was an effective pain control method in patients with terminal cancer pain, however, a systematized algorithm for the control of cancer-related pain in needed.

Key Words: Bupivacaine, cancer pain, epidural analgesia, morphine

INTRODUCTION

Cancer has been the most common cause of death in Korea since 1983. The number of cancer patients was 153237 in 2006 and 161920 in 2007, with an increased frequency of 5.1% and 11.0%, respectively, in comparison to 2005. Alarmingly, the incidence and prevalence of cancer continues to increase. Assuming a lifespan of 76 years in men and 83 years in women, one out of three men and one out of four women are predicted to develop cancer during their lifetime in Korea.¹

Seventy-five to 80% of terminal cancer patients complain of cancer-related pain.² The World Health Organization and National Cancer Care Network presented algorithms for cancer pain control.^{3,4} These guidelines have been validated in clinical practice and were shown to provide effective analgesia in 70-90% of patients.^{3,5}

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However, it is very difficult to control cancer-related pain refractory to medical management.³ For these patients, continuous epidural analgesia (EA), intrathecal analgesia (ITA), and intracerebroventricular analgesia (ICVA) have been very effective.⁶⁻¹⁰ Therefore, EA or ITA is considered the fourth ladder of treatment.³

ITA and ICVA have many advantages. However, they necessitate more aggressive surgical procedures and are very expensive. And the risk of spinal infection, confusion, and sedation are also high.¹⁰

EA is easy to perform and is effective for patients with a predicted survival less than three months.¹¹ The cost is also covered for 95% of cancer patients by national health insurance in Korea. For these reasons, the EA is preferred and is used for control of cancer-related pain in Korea. Nonetheless, the efficacy of EA varies among patients.

The purpose of this study was to evaluate the efficacy and complications of continuous epidural analgesia in order to improve its efficacy for control of cancer-related pain.

MATERIALS AND METHODS

Ninety-six terminal cancer patients were referred to the pain clinic for pain control and were administered EA from 2005 to 2009. A retrospective review of their medical records was performed.

A coiled 18G epidural catheter (Arrow, Arrow International Inc., Reading, PA, USA) was used for catheterization, which tunneled into the nearby trunk. Morphine, bupivacaine, and ketamine were used for most patients as the initial epidural drugs. After the daily total opioid dose was converted into an intravenous morphine equivalent dose, epidural morphine was injected at 1/4-1/6 of the intravenous morphine dose.

Bupivacaine 12.5-25 mg/day and ketamine 10-20 mg/day were injected at 2 mL/h according to the patient's pain severity, cancer progress, pain location, and type of pain. Adjuvant analgesics were used including antiepileptic drugs, antidepressants, anti-inflammatory drugs, and, in some cases, steroids.

Patient characteristics including age, gender, primary cancer, pain location, pain type, and causes of pre-epidural failure were evaluated. In addition, the mean duration of epidural catheterization, the level of the EA, the position of the tip of the epidural catheter, the number of reinsertions, and the catheter course were also evaluated.

The mean daily doses of epidural morphine at the start and termination were also evaluated. The dose escalations of the epidural morphine, the ratio of the maximum dose to the minimum start dose, were evaluated for the daily increase percentage of epidural morphine.

As the survival period of more than 2 weeks had the highest number of patients (n=56), the efficacy of pain control was indirectly evaluated according to changes in intravenous morphine equivalent drug dose (MEDD) and the degree of pain at pre-epidural and 2 weeks follow up. The degree of pain was defined as none to mild, moderate, and severe. Complications were also evaluated.

Statistical analysis

The results are presented as the mean±SD or incidence (percentage). Paired samples t-test was used to examine the change in MEDD, at pre-epidural and 2 weeks follow up. Statistical analyses were performed using SPSS software version 13.0. *p*-value<0.05 was considered significantly significant.

This study was approved by the Institutional Review Board of - St. Vincent's Hospital, College of Medicine, The Catholic University of Korea (IRB approval number: VC 10RIS10061).

RESULTS

Two hundred and twenty-eight hospitalized cancer patients with pain were referred to the pain clinic due to severe adverse drug reactions or ineffective pain control in spite of opioid administration. One hundred and thirty-two (58%) patients had at least one EA performed. Ninety-six (42%) patients underwent continuous EA.

Patient characteristics including age, gender, primary cancer, pain location, type of pain, and pre-epidural failure are shown in Table 1. Ninety-six patients were treated using 127 catheters. The catheter characteristics are shown in Table 2. Positions of the catheter tips of 73 catheters were confirmed by plain radiographs. Forty-eight (65.7%) catheters were located at the target site level or within 3 cm of the target site, while 25 (34.2%) catheters were inappropriately placed outside the target site.

The mean epidural doses of morphine at the start and termination were 21.24±20.6 mg and 56.7±61.4 mg, respectively. The mean dose escalation of epidural morphine over time was 2.8±2.3. Mean duration of epidural catheterization

Table 1. Patient Characteristics

| | Total (n=96) |
|---|--------------|
| Age (yrs) | |
| 40< | 9 (9.4%) |
| 41-59 | 35 (36.5%) |
| 60≤ | 52 (54.2%) |
| Sex | |
| Male | 54 (56.2%) |
| Female | 42 (43.8%) |
| Primary cancer | |
| Lung cancer | 18 (18.8%) |
| UGI cancer | 23 (24.0%) |
| Hepatobiliary cancer | 10 (10.4%) |
| Pancreatic cancer | 15 (15.6%) |
| Rectosigmoidal cancer | 13 (13.5%) |
| Urogenital cancer | 7 (7.3%) |
| Etc. | 10 (10.4%) |
| Pain location | |
| Head, neck and upper extremity | 8 (8.3%) |
| Chest, abdomen and back, sacral and lower extremity | 88 (91.6%) |
| Pain type | |
| Somatic | 10 (10.4%) |
| Visceral | 57 (59.4%) |
| Neuropathic | 2 (2.1%) |
| Mixed | 27 (28.1%) |
| Pre-epidural failure | |
| Inappropriate pain control | 75 (78.1%) |
| Intolerable side effect | 21 (21.9%) |

UGI, upper gastrointestinal.

Values are expressed as the incidence (percentages).

was 31.5±55.6 days, and the dose of epidural morphine increased by 5.3% per day.

The efficacy of EA at 2 weeks follow up revealed improved pain control (n=56), as MEDD dropped from 213.4±221.7 (10-1480) mg/day to 94.1±145.0 (30-680) mg/day at 2 weeks follow up ($p<0.05$). After 2 weeks institution of EA, there was a significant reduction in the proportion of patients with severe pain, from 78.1% to 19.6% ($p<0.05$).

Catheter related complications were as follows: mild, such as spontaneous removal or removal by mistake in 15 patients (15.6%). And moderate complications, including infection, occlusion, oozing, and formation of fibrous sheath occurred in 14 patients (14.6%). Infection occurred at the entrance and tunnel sites, but all infections were controlled by antibiotics and/or catheter removal. Bloody discharge occurred in 2 patients with a long-term catheter. Severe complications such as epidural abscess or hematoma did not occur. Oozing occurred in three patients, perhaps

Table 2. Catheter Characteristics

| | Total (n=96) |
|---|-------------------|
| Mean duration of epidural catheterization (days/person) | 31.5±55.6 (5-509) |
| Epidural level | |
| Cervical | 6 (6.3%) |
| Thoracic | 61 (63.5%) |
| Lumbosacral | 29 (30.2%) |
| Number of catheterizations | |
| 1 | 73 (76.1%) |
| 2 | 15 (15.6%) |
| 3 | 8 (8.3%) |
| Catheter maintenance | |
| Catheter in place until the time of death | 73 (76.0%) |
| Change to intravenous morphine | 23 (24.0%) |

Values are expressed as the incidence (percentages).

due to the draining of interstitial fluid through the puncture site caused by generalized edema. Presenting drug related complications included respiratory depression to a rate of 8 breath/min in 1 patient, motor block in 1 patient, hypotension in 1 patient, and sensory deficits in 2 patients. All of these problems were resolved with dose reduction. Constipation occurred in most patients, and urinary retention was resolved by symptomatic treatment.

DISCUSSION

The results of this study showed that continuous epidural analgesia significantly decreased the MEDD of morphine in terminal cancer patients and reduced the proportion of patients with severe pain.

Prior studies previously reported that the continuous EA was effective in 50-90% of patients.^{7,9,12} Ballantyne and Carwood¹⁰ reported EA showed excellent pain relief in 72% of patients with terminal cancer-related pain by performing a meta-analysis of 31 studies. Burton, et al.¹³ reported there was a significant reduction in the proportion of patients with severe pain from 86% to 17% after neuroaxial analgesia. In our study, EA was deemed effective in 80.4% of patients.

In our study, EA was effective immediately after institution in the majority of patients however, approximately 30% of patients showed decreased efficacy over time. Mercadante¹⁴ suggested that tumor progression, psychological factors, development of pseudotolerance caused by dural thickening, impedance of transdural diffusion, epidural metastasis with the invasion of nerve roots, and reactive fibrosis were some of the potential causes of reduced effectiveness

over time. In addition, inappropriate evaluation, the lack of knowledge and time of physicians, and the fear of opioid use were the causes of inappropriate control of cancer-related pain in EA.¹⁵ Subsequently, despite disease progression, continuous dose adjustments were not administered. In control of cancer-related pain using systemic analgesics, similar practice is demonstrated.¹⁶

Some adjuvants can be commonly used for improving efficacy of epidural morphine. Bupivacaine-morphine combination presents more effective analgesic effect than morphine alone, more effective relief of the neuropathic component of pain, and there is no neurotoxicity in long-term infusion.¹⁷ However, ketamine, a N-methyl-D-aspartic acid antagonist, is questionable because of preservative (chlorbutanol) related neurotoxic effects. Spinal myelopathy has also been reported with intrathecal injection of ketamine in large doses. However, the combination of small amounts of ketamine is helpful in pain relief in patients.¹⁸

Infection is a major problem associated with catheter use. Ruppen, et al.¹⁹ reported that catheter related infection were superficial 4.6% and deep 1.2% in a systemic review of 24 studies. Infection may more readily occur with long term of catheter insertion, without subcutaneous tunneling, and catheter type. In our study, infections occurred in 10% of the patients. Fortunately, there were no deep infections and all were controlled by the administration of antibiotics or by removing the catheter. Accordingly, patients and caregivers should be instructed on wound care as well as signs and symptoms indicative of infection.

There were 11 spontaneous catheter removals, which were reduced by fixing the entrance site and the catheter with DuoDERM® (Unomedical, Mona Vale, NSW, Australia) and sterile strips. Infections in 4 patients and spontaneous removal of the catheter in 4 of 11 patients occurred in those who did not undergo subcutaneous tunneling, demonstrating the importance of subcutaneous tunneling.²⁰ The formation of a fibrous sheath at the catheter tip can occur after long-term administration of drugs.²¹ In such cases, patients may complain of pain during epidural bolus injection. In our study, a fibrous sheath appeared along with bloody discharge after long term catheterization in 2 patients, and catheters were removed.

Constipation is the most common side effect of opioids, occurring in most of the patients in our study. Although drugs were used to relieve the constipation, most of the patients were not well controlled. Recently methylnaltrexone has been introduced to treat opioid induced constipation.²² How-

ever, it is not available in Korea. Urinary retention was also severe if the catheter tip was located in the lower lumbar epidural space. This was treated by symptomatic therapy.

The optimal time for commencing EA remains unclear. Often, spinal opioid treatment was initiated before optimal systemic opioid administration was achieved.¹⁴ However, indiscriminate use of spinal opioids should be discouraged.²³ In our study, seven patients could have been adequately controlled pain by appropriate systemic analgesics alone. Currently, we consider EA in patients with intolerable side effects despite systemic analgesics or in patients with refractory pain despite receiving morphine 100 mg/day intravenously.

The limitations of this study were as follows: first, this was a retrospective study. Second, we did not use an objective pain score. This trend was shown in most papers concerning neuroaxial therapy for terminal cancer pain.¹⁰ Although it is possible to measure pain scores during the early period of disease, it becomes difficult to measure as the disease progresses. Additionally, other limitations include the absence of a comparison group, bias with patient reporting of symptoms and analgesic intake, as well as inaccurate data in the medical records.

In conclusion, in terminal cancer patients with severe drug side effects or refractory pain, epidural analgesia was an effective pain control method, however, a systematized algorithm for improving the efficacy of epidural analgesia is needed.

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