

PLASMA BETA-ENDORPHIN LEVELS BEFORE AND AFTER RELIEF OF CANCER PAIN

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Background: Plasma β endorphin (BE) is an endogenous peptide opioid derived from pro-opiomelanocortin. Although the role of plasma BE in pain regulation is unclear, plasma BE levels have been reported to correlate inversely with pain levels in cancer pain.

Objectives: To measure BE levels in patients with cancer before and after pain relief with different analgesic modalities, to evaluate the relationship between cancer pain, pain control and plasma BE levels.

Methods: Prospective interventional study conducted in a university hospital setting. Patients with intractable pain due to upper abdominal visceral malignancies (pancreatic, liver and gastric cancers) agreed to participate in the study. Pain relief was provided with one of four primary

modalities: 1) oral continuous release morphine, 2) thoracic epidural morphine boluses, 3) alcohol celiac plexus blocks or 4) interpleural infusions of bupivacaine. Blood samples for plasma BE levels were taken before treatment and at the time of maximal pain relief obtained with the particular treatment modality. Pain levels were determined using a 10 cm visual analogue scale. BE levels were measured by competitive radioimmunoassay using ^{125}I β endorphin.

Results: Average pain scores decreased from 7.3 ± 1.27 (SD) before treatment to 1.2 ± 1.18 (SD) after treatment ($p < 0.0001$). Satisfactory pain relief was obtained with each of the four treatment modalities and was associated with a significant increase in plasma BE levels. The mean plasma BE level for all groups before treatment was 18.9 ± 5.4 pg/

ml (range 2.0 to 29.6 pg/ml) compared to 38.7 ± 17.6 pg/ml (range 13.2 to 67.9 pg/ml) after pain relief ($p < 0.0001$). Plasma BE levels increased with improved pain control with each of the four analgesic modalities, including oral and epidural morphine.

Conclusions: Plasma BE levels increased with improved pain control in patients with upper abdominal gastrointestinal malignancies. Although the role of plasma BE in pain pathophysiology is unclear, it appears that pain relief *per se*, and not the analgesic technique, modulates plasma BE levels. This suggests that plasma BE levels may serve as an objective measure of cancer pain severity and corroborate the patient's report of pain relief.

Keywords: Plasma endorphins, morphine, malignancy, celiac plexus, epidural analgesia.

Beta-endorphin (BE), an endogenous peptide opioid derived from pro-opiomelanocortin, is a neurohormone secreted by the anterior pituitary into the systemic circulation. Endorphins are found in regions of the brain involved in the perception of pain, including the nucleus accumbens and the arcuate nucleus.

Although the role of plasma BE in pain regulation is unclear, plasma BE levels have been reported to correlate inversely with pain levels in cancer pain (1,2) chronic daily headache (3) and post-operative pain (4). That is, plasma BE levels are lower in patients with poorly controlled pain, and increase with pain relief.

In this study, we measured plasma

BE levels in patients suffering from intractable pain due to upper abdominal malignancies, before and after pain relief, to evaluate the relationship between cancer pain, pain control and plasma BE levels. BE levels were determined by competitive radioimmunoassay using ^{125}I β endorphin.

METHODS

After institutional review board approval and informed consent, 20 patients with intractable upper abdominal cancer pain participated in the study. Tumor diagnoses included pancreatic, liver and gastric cancers.

Pain relief was achieved with oral controlled release morphine (MS Contin®), thoracic epidural morphine injections, alcohol celiac plexus blocks or interpleural bupivacaine infusions. For the oral morphine group, controlled release morphine tablets were administered every 12 hours. Additional doses of 10 mg of immediate release morphine were given every 4 hours as needed for breakthrough pain. Thoracic epidural catheters were in-

serted between T5 and T12, depending on the level of the most painful dermatome. Epidural morphine was administered in doses of 0.03 to 0.05 mg/kg in 10 ml of saline as intermittent injections, with a minimum dose interval of 4 to 6 hours. Celiac plexus blocks were done with CT guidance, using bilateral needle placement. After a test dose of 0.25% bupivacaine, 15 ml of 100% alcohol was injected bilaterally. Immediate release oral morphine was provided for breakthrough pain as needed to supplement pain relief provided by the celiac block. Unilateral interpleural catheters were inserted on the most painful side, between the seventh and eighth ribs, 8 to 10 cm lateral to midline, and 0.5% bupivacaine was infused for pain relief. Breakthrough pain was treated with immediate release morphine.

Blood samples for BE levels were taken before treatment and at the time of maximal pain relief obtained with the particular treatment modality. Pain levels were determined using a 10 cm visual analogue scale ("no pain" - 0 cm and "the worst pain possible" -

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Table 1. Patient characteristics, type of pain treatment and pain scores before and after treatment.

Type of Analgesia	Number of Patients	Pain Scores* Before Treatment	Pain Scores* After Treatment
Epidural Morphine	6	6.7 ± 1.03	1.0 ± 1.26
MS Contin	3	7.3 ± 1.53	3.0 ± 0.00
Celiac Plexus	3	8.7 ± 1.15	1.7 ± 0.58
Interpleural	8	7.1 ± 1.46	0.4 ± 0.52
Average scores before and after treatment:		7.3 ± 1.27	1.2 ± 1.18

* Mean ± SD

Before and after treatment pain scores for each treatment group were significant ($P < 0.01$). With Bonferroni corrections, the differences in pain scores between treatment groups were not statistically significant.

10 cm). All endorphin samples were drawn at 9 AM to avoid diurnal variation. Plasma samples were purified on C-18 Sep Pak cartridges and stored frozen at -20° C until analyzed by competitive radioimmunoassay, using 125 I β endorphin.

Statistical significance was determined with a two-tailed Student's t-test with Bonferroni/Dunn corrections for multiple comparisons. Regression analysis of endorphin levels was done with a statistical computer package (StatView, Abacus Concepts, Berkeley, CA).

RESULTS

Average patient age was 58 years and mean weight was 70 kg. Patient treatment categories and average pain scores before and after treatment are shown in Table 1. Average pain scores decreased from $7.3 \pm$

1.27 (SD) before treatment to 1.2 ± 1.18 (SD) with pain relief ($p < 0.0001$). Satisfactory pain relief was obtained with each of the four treatment modalities. The pre-treatment pain scores for each treatment group were not significantly different from each other. Similarly, post-treatment pain scores were not statistically different between the four modalities. Therefore, the data for pre and post treatment endorphin levels, respectively, were pooled.

Satisfactory analgesia was associated with a significant increase in plasma BE levels. The mean plasma BE level before treatment was 18.9 ± 5.4 pg/ml (range 2.0 to 29.6 pg/ml) compared to 38.7 ± 17.6 pg/ml (range 13.2 to 67.9 pg/ml) after pain relief ($p < 0.0001$) (Fig. 1).

Although samples sizes were small, it does not appear that plasma BE levels were significantly different between spe-

Table 2. Daily morphin requirements for each analgesic modality

Analgesic Modality	Average Daily Opioid Requirement
Epidural morphine	11 mg (epidurally)
Oral morphine	76 mg
Celiac plexus block	6 mg
Interpleural infusion	8 mg

Satisfactory pain relief was obtained with each of the treatment modalities, despite the wide variation in total opioid doses required.

cific pain treatment modalities (Fig. 2). For comparison, the average oral morphine requirements for the individual treatment groups are shown in Table 2. Thus, morphine doses and route of administration (oral vs. epidural) did not appear to correlate with plasma BE levels. Rather, plasma BE levels correlated with the level of pain relief. Regression analysis of the data is depicted in Fig. 3.

DISCUSSION

Plasma BE levels were increased following relief of cancer pain compared to baseline pain scores prior to pain relief. This study is in agreement with the reports by Lopez and colleagues (1) and Mystakidou et al (2), who found lower plasma BE levels in patients with poorly controlled pain due to breast, lung and visceral malignancies, and increased plasma BE levels after pain reduction. Both

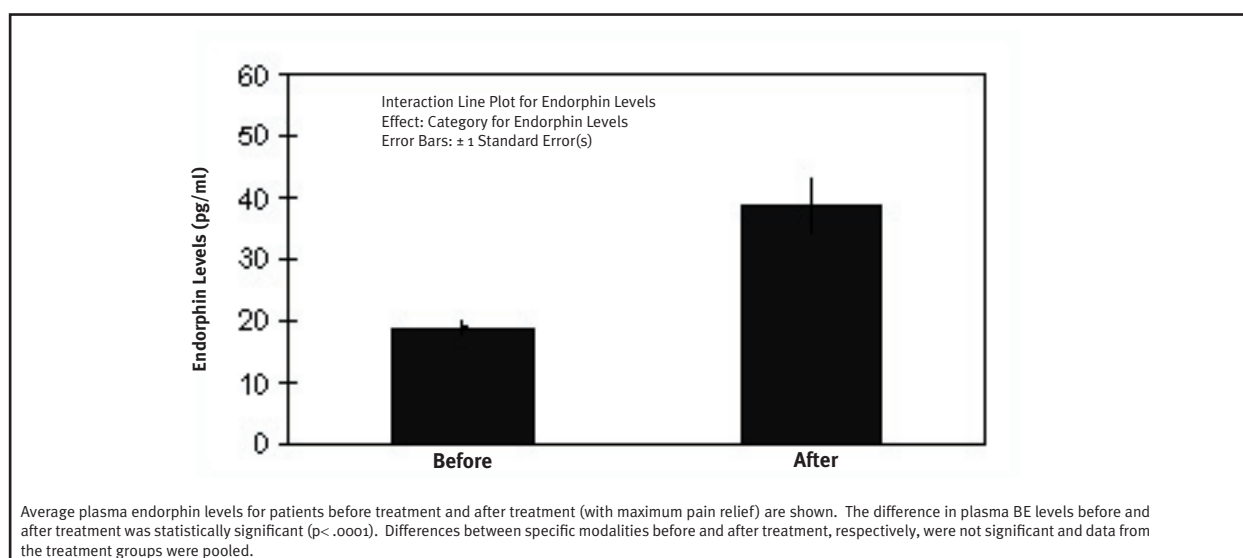


Fig 1. Endorphin levels before and after pain relief.

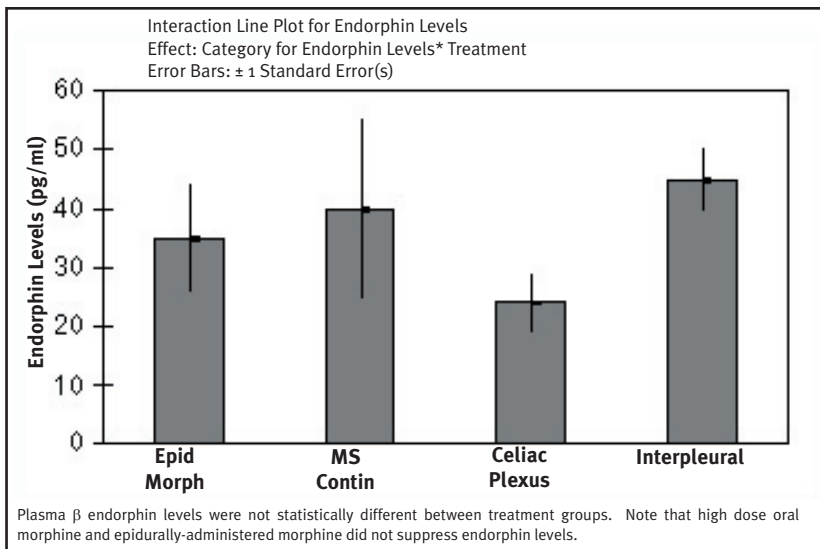


Fig 2. Endorphin levels and treatment modalities.

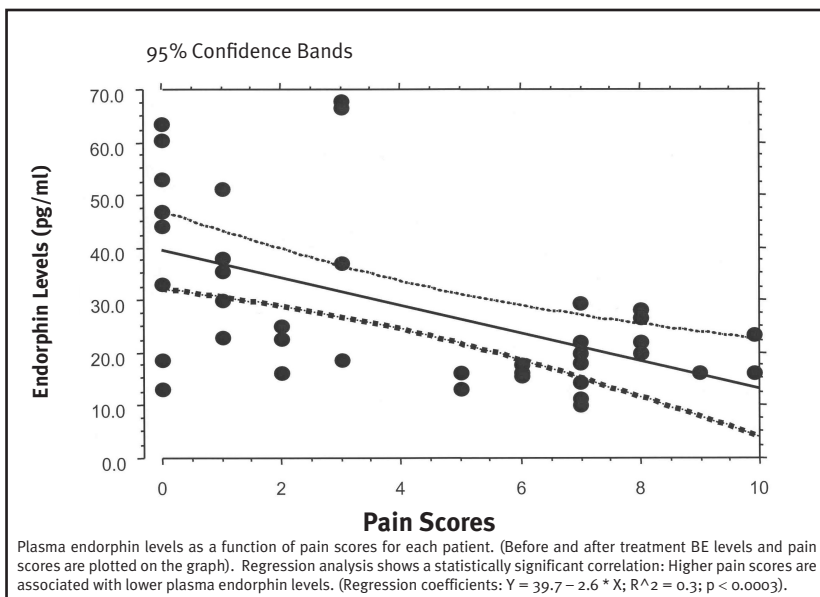


Fig 3. Endorphin levels and pain scores.

of those studies used analgesic techniques that did not involve opioids. Similarly, Befon and colleagues (5) found that treatment with subcutaneous octreotide, a somatostatin analogue, improved pain due to gastrointestinal cancers and resulted in increases levels of plasma BE.

In our study, patients received oral or parenteral opioids, either as the primary or supplemental analgesic. Although the role of plasma BE in pain pathophysiology is unclear, it appears that pain relief *per se*, and not the analgesic technique, mod-

ulates plasma BE levels. This is evident because pain relief from parenteral opioids, epidurally-administered opioids and local anesthetic infusions correlated with increased plasma BE levels. Moreover, contrary to conventional wisdom, analgesic techniques that used oral or epidural morphine did not suppress BE levels. Intuitively, one might have predicted a fall in endogenous endorphins with administration of exogenous opioids, which was not the case in the present study.

The relevance of β endorphins in

pain control remains unclear, although it is assumed that plasma endorphin levels correlate with CSF levels. Opioid receptors are pharmacologically classified as μ , δ , κ and ϵ . The epsilon opioid receptor system appears to be stimulated supraspinally by the endogenous opioid peptide β endorphin (6). Stimulation of the epsilon receptor induces the release of met-enkephalin, which then acts on spinal delta opioid receptors to produce analgesia. The epsilon receptor-mediated descending system appears to be distinct from the μ opioid receptor system. This suggests that the endorphin system is a parallel analgesic system, and in some manner plasma endorphin levels reflect the current levels of pain or analgesia.

CONCLUSION

In summary, this study confirms that plasma BE levels increase with improved pain control in upper abdominal gastrointestinal malignancy. This suggests that plasma BE levels may serve as an objective measure of cancer pain severity and corroborate the patient's report of pain relief.

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