Title: CONTROLLED IONTOPHORETIC DELIVERY OF MORPHINE HCL FOR POST-OPERATIVE PAIN RELIEF

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Introduction. There is an increasing interest in the administration of medications by other than the classical intravenous, intramuscular, inhalational or enteral routes. The painless, non-invasive administration of concentrated, potent opioids will contribute to the perioperative management of surgical patients and also to many patients with persistent pain syndromes. Iontophoresis is a method of transdermal application of ionizable drugs in which electrically charged molecules are propelled through the skin by an external electric field. Iontophoresis of morphine HCl on healthy human volunteers can lead to pharmacologically active systemic levels of the drug after only 20 minutes of treatment. The objective of this study was to determine the effectiveness of iontophoretically delivered morphine HCl for the control of significant post-operative pain.

Methods. Twelve patients, ASA classification I-III, who were scheduled for total knee replacement or total knee arthroplasty have been studied. Informed consent was obtained on the night before surgery and the patient was instructed on the use of the Bard PCA pump. The patients were placed on the PCA pump during the study period to document the effectiveness of iontophoretically delivered morphine HCl and to ensure the patient's pain was adequately controlled throughout the study. On arrival to the recovery room following surgery, the patient was reinstructed on the use of the PCA infusion pump. Pain in the recovery room was controlled with IV meperidine and PCA pump therapy was begun using meperidine as the analgesic. Meperidine was administered in a 2 mg/cc concentration with an initial dose of 10 mg IV per dose with a lockout period of 15 minutes. Dose was adjusted as necessary to provide satisfactory analgesia; the lockout period remained the same throughout the study. The number of patient requests and the dose (mg) administered by the PCA pump was recorded on an hourly basis throughout the study. On the morning following surgery, the patient was placed on the iontophoresor, receiving either morphine HCl or saline in a randomized, blinded fashion. The iontophoresis delivery current was adjusted to provide a dose of morphine that was equianalgesic to the average dose of meperidine required during the previous two hours. Venous blood samples for determination of morphine levels were obtained every thirty minutes during iontophoresis, then every 60 minutes for six hours. The patient remained on the iontophoresor for six hours; during this period PCA analgesia remained available. After six hours, the iontophoresor was discontinued. The patient continued to have access to the PCA pump for pain control for at least six hours following iontophoresis.

Comparison of the PCA use between the saline and the morphine iontophoresis group was made. In addition, PCA use during the six hours before and after iontophoresis was compared to the six hour iontophoresis period as a measure of the ability of iontophoresis to provide systemic analgesic levels of morphine. Any adverse effects and patient acceptance of iontophoresis was documented.

Results. Twelve patients, seven receiving iontophoresed morphine, five receiving iontophoresed saline, have completed the study. In the morphine iontophoresis group, there was a significant difference between PCA use during the six hours before iontophoresis as compared to the six hours of iontophoresis ($P<0.05$). However, there was no significant difference between PCA use during iontophoresis compared to the first six hours following iontophoresis. Analgesic levels of morphine which varied with the iontophoresis current were obtained in those patients receiving iontophoresed morphine (figure 1). In patients receiving iontophoresed saline, no change in PCA use was noted throughout the study. Patients accepted PCA therapy and iontophoresis well. No adverse effects related to PCA therapy or iontophoresis were reported.

Discussion. Iontophoresis can systemically deliver morphine HCl in high enough concentrations to provide early post-operative pain relief in patients undergoing total knee replacements or total hip arthroplasties, as shown by the significant decrease in PCA use during the morphine iontophoresis and the analgesic blood levels obtained. We feel that the continuing analgesic effect of the iontophoresed morphine after the discontinuation of iontophoresis accounts for the lack of a significant difference in PCA use between the six hours of iontophoresis and the first six hours following iontophoresis. Additional patients are necessary to further document use differences between these time periods and between the saline and morphine groups. Further investigation into iontophoretically delivered morphine HCl and other narcotics for post-operative and chronic pain control is warranted.

Figure 1. Free morphine blood levels in iontophoresis.