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Iontophoretic transdermal system using fentanyl compared with patient-controlled intravenous analgesia using morphine for postoperative pain management†

S. Grond[1]*, J. Hall[2], A. Spacek[3], M. Hoppenbrouwers[4], U. Richarz[5] and F. Bonnet[6]

[1]Klinik für Anästhesiologie, Martin-Luther-Universität Halle-Wittenberg, Halle, Germany. [2]Anaesthetics and Intensive Care Medicine, Heath Park, Cardiff, UK. [3]Klinik für Anästhesie und Allgemeine Intensivmedizin, Medizinische Universität Wien, Wien, Austria. [4]SGS Medisearch International, Mechelen, Belgium. [5]Janssen-Cilag EMEA, Baar, Switzerland. [6]Département d'Anesthésie—Réanimation, Hôpital Tenon, Assistance Publique Hôpitaux de Paris, Université Paris VI, Paris, France

**Corresponding author: Klinik für Anästhesiologie, Martin-Luther-Universität Halle-Wittenberg, Ernst-Grube-Str. 40, 06097 Halle, Germany. E-mail: stefan.grond@Medizin.Uni-Halle.de*

Background. The fentanyl iontophoretic transdermal system (fentanyl ITS) enables needle-free, patient-controlled analgesia for postoperative pain management. This study compared the efficacy, safety, and ease of care of fentanyl ITS with patient-controlled, i.v. analgesia (PCIA) with morphine for postoperative pain management.

Methods. A prospective, randomized, multicentre trial enrolled patients in Europe after abdominal or orthopaedic surgery. Patients received fentanyl ITS (n=325; 40.0 μg fentanyl over 10 min) or morphine PCIA [n=335; bolus doses (standard at each hospital)] for ≤72 h. Supplemental i.v. morphine was available during the first 3 h. The primary efficacy measure was the patient global assessment (PGA) of the pain control method during the first 24 h.

Results. PGA ratings of 'good' or 'excellent' were reported by 86.2 and 87.5% of patients using fentanyl ITS or morphine PCIA, respectively (95% CI, −6.5 to 3.9%). Mean (SD) last pain intensity scores (numerical rating scale, 0–10) were 1.8 (1.77) and 1.9 (1.86) in the fentanyl ITS and morphine PCIA groups, respectively (95% CI, −0.38 to 0.18). More patients reported a system-related problem for fentanyl ITS than morphine PCIA (51.1 *vs* 17.9%, respectively). However, fewer of these problems interrupted pain control (4.4 *vs* 41.3%, respectively). Patients, nurses, and physiotherapists reported more favourable overall ease-of-care ratings for fentanyl ITS than morphine PCIA. Study termination rates and opioid-related side-effects were similar between groups.

Conclusion. Fentanyl ITS and morphine PCIA were comparably effective and safe.

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Patient-controlled intravenous analgesia (PCIA) is often considered the standard method of care for the treatment of acute postoperative pain.[1–7] However, the preparation of pumps, syringes, and lines requires considerable staff time and resources.[8] Patient mobility may also be restricted by the patient-controlled analgesia (PCA) pump and i.v. line, and programming errors, pump failures, and syringe errors may result in severe adverse events.[9] To overcome these problems, a new, needle-free fentanyl

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HCl iontophoretic transdermal system (fentanyl ITS, IONSYS™, Janssen-Cilag NV, Beerse, Belgium) has been developed that is pre-programmed to deliver a fixed dose of fentanyl (40.0 μg) across the skin, utilizing the process of iontophoresis.[10] It is compact, self-contained, and self-adhesive, and it is applied to the patient's upper outer arm or chest.

While previous trials have demonstrated the fentanyl ITS to be superior to placebo[11 12] and therapeutically comparable with a standard morphine PCIA dosing regimen for postoperative pain management,[13–15] other elements important to the process of patient care, such as the convenience of use and the associated levels of patient and provider satisfaction, have not been thoroughly assessed. The system was recently reviewed in this journal.[16] In this study, validated questionnaires were also included to assess the ease-of-care (EOC)/use and the level of satisfaction associated with each modality from the perspectives of patients, nurses, and physiotherapists.[17] This multicentre European study further evaluates the efficacy and safety of the two modalities in patients undergoing major abdominal or orthopaedic surgery to simulate its use in a standard clinical practice setting. The primary aim of this study was to determine whether fentanyl ITS was non-inferior to morphine PCIA for the management of postoperative pain using a patient global assessment (PGA) of the method of pain control 24 h after the initiation of treatment.

Methods

This international, multicentre, open-label, randomized, comparative, parallel-treatment, phase IIIb study was conducted from June 14, 2004, to June 15, 2005, at 51 sites in 11 European countries (Austria, Belgium, Denmark, France, Germany, Italy, Ireland, Spain, Sweden, Switzerland, and the UK). The study protocol was approved by ethical committees in each country, and patients provided written consent during the screening process.

Prospective patients were screened within 2 weeks before surgery, and medical history, physical examination, and informed consent were obtained. Patients were instructed in the use of the fentanyl ITS and morphine PCIA pump, and were provided with education regarding pain management and pain assessment. To determine the patient's pain management goal, they were asked to indicate the postoperative pain score (0='no pain' to 10='worst possible pain') that they felt would not interfere with required activities, so that recovery could occur more quickly. Eligible patients were ≥18 yr of age; ASA status I, II, or III; and scheduled to undergo general or regional anaesthesia (i.e. spinal anaesthetic with ≤4 h duration of action) for elective major orthopaedic or abdominal surgery requiring parenteral opioids for moderate or severe pain for at least 24 h after surgery.

Patients were screened in the recovery room after the operation, and included in the study if they were awake, alert, and breathing spontaneously for at least 30 min, with a ventilatory frequency of 10–24 breaths min^{-1} and a pulse oximetry reading (Sp_{O_2}) of at least 90% (with or without supplemental oxygen), and able to answer questions and follow commands. Patients had to be comfortable [pain intensity ≤4 out of 10 on a verbal numerical rating scale (NRS)].

Patients were excluded from the study if they were known or expected to be opioid-dependent, had a chronic pain disorder, had an active skin disease, were pregnant or breast-feeding, were expected to require intensive care after the operation, or would be likely to require additional surgical procedures within 72 h.

Patients who satisfied the above requirements were randomized (1:1) to receive either the fentanyl ITS or morphine PCIA, utilizing an interactive voice response system implemented before the study. Randomization was stratified by country and by surgery type (orthopaedic surgery of the lower extremities, lower abdominal surgery, upper abdominal surgery, or pelvic surgery). Patients were considered enrolled after the first application of the fentanyl ITS or after the attachment and enabling of the morphine PCIA pump, which occurred in the recovery room immediately after baseline assessments at Hour 0.

In the recovery room, if required, they were titrated to an acceptable level of comfort with i.v. bolus doses of morphine. After at least 30 min, the study entry criteria were assessed, and qualifying patients were randomized to receive either fentanyl ITS or morphine PCIA. Pain management with fentanyl ITS or morphine PCIA continued for up to 72 h. The treatment and assessment schedule is described in Figure 1.

Fentanyl ITS was applied to the patient's upper outer arm or chest, and was activated when the patient pressed the recessed, on-demand dosing button twice within 3 s. An audible beep and the flash of a red light-emitting diode (LED) indicated the initiation of dosing. The system is pre-programmed and used an imperceptible electrical field to deliver 40 μg fentanyl over 10 min, allowing up to six doses per hour for 24 h or a maximum of 80 doses, whichever occurred first. At the end of each 24 h period or after 80 doses, the fentanyl ITS was removed from the patient and a new system was applied to a different application site. During delivery of each fentanyl dose, the system did not respond to additional requests for dosing delivery.

PCA pumps were programmed for a specific dose and lock-out period according to the standard practice of each participating hospital. Across hospitals, the patient initiated the delivery of a bolus dose of morphine (up to 20 mg per 2 h and a maximum of 240 mg per 24 h) by pressing the PCA dosing button.

Supplemental analgesia (i.v. morphine bolus administration after the routine practice of each hospital) was available to patients in both the fentanyl ITS and the