

Kiran Reddy, M.B.
Wellcome-Wolfson Institute for Experimental Medicine
Queen's University Belfast
Belfast, Ireland

Charles Corey Hardin, Ph.D.
Department of Medicine
Massachusetts General Hospital and Harvard Medical School
Boston, Massachusetts

Daniel Francis McAuley, M.D.
Wellcome-Wolfson Institute for Experimental Medicine
Queen's University Belfast
Belfast, Ireland

and
Regional Intensive Care Unit
Royal Victoria Hospital
Belfast, Ireland

ORCID ID: 0000-0002-1621-1481 (K.R.).

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Ⓐ New Insights into the Comparative Effectiveness of Fentanyl and Morphine Infusions in ICU Patients

Invasively mechanically ventilated ICU patients often receive opioids to alleviate pain and discomfort. Fentanyl and morphine are the

opioids used most commonly for this purpose. These medicines are often given by infusion in combination with sedatives. The comparative effectiveness of these drugs on ventilator-free days in invasively mechanically ventilated adults has not been evaluated previously.

In this issue of the *Journal*, Casamento and colleagues (pp. 1286–1294) report the findings of an open-label, two-center, cluster crossover randomized clinical trial comparing the effect of using morphine infusions versus fentanyl infusions on alive ventilator-free days to Day 28 (1). A total of 681 patients from two

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Table 1. Main Opioids Used for Analgosedation in the ICU

Drug	Time to Onset (min)	Half-life (h)	Metabolism	Presence of Active Metabolites	Elimination	Risk of Accumulation
Morphine	5–10	3–5	Glucuronidation in the liver	+++	Renal fecal	Yes with hepatic or renal impairment
Fentanyl	1–2	1–4	CYP3A enzymes in the liver	+/-	Renal	Yes with hepatic impairment
Sufentanil	1–3	0.5–2	Liver and enterocytes of the small intestines	—	Renal and biliary	Yes with hepatic impairment
Remifentanyl	1–3	<1 (3–10 min)	Hydrolysis by plasma esterases	—	Plasma esterases	No

Australian ICUs were included in the primary analysis, with 344 assigned to fentanyl and 337 assigned to morphine. At Day 28 after ICU admission, median ventilator-free days were 26.1 (20.7–27.3) and 25.3 (19.1–27.2) for fentanyl and morphine patients, respectively (median difference, 0.79 [95% confidence interval, 0.31–1.28]; $P = 0.001$). This effect appeared to be driven by a greater number of days spent alive and ventilator-free among older patients and those with renal impairment who were allocated to fentanyl. Despite heterogeneity of treatment effect, there were no patient subgroups in which point estimates of the effect on ventilator-free days favored morphine. In-hospital mortality to Day 28 was lower in patients assigned to fentanyl, although not statistically significantly so.

For trials that compare the effectiveness of standard therapies, subtle shifts in the probability that one treatment is superior to another may be sufficient to favor one treatment over another (2). Accordingly, as no patient groups seemed to do better with morphine, the data from this trial provide a reasonable basis for using fentanyl infusions in preference to morphine in invasively mechanically ventilated adults in ICU who require such drugs by infusion. However, the choice of the two drugs studied can be debated. Morphine is conjugated in the liver to biologically active metabolites, which are cleared by the kidney. Fentanyl is distributed to lipid-rich tissues and can accumulate prolonging its elimination. Although differences in pharmacokinetic profiles of morphine and fentanyl (3) might explain the observed differences in the current trial, both morphine and fentanyl have relatively long elimination half-lives when administered by infusion for prolonged periods. Shorter-acting opioids such as sufentanil or remifentanyl may provide more rapid recovery after prolonged intravenous infusion because of their shorter elimination half-life (4).

In several countries, sufentanil and fentanyl are the drugs most used for sedation in adult ICU patients (5–7). For clinicians in these countries, who do not use morphine infusions in adult ICU patients, the current study has limited relevance. However, in most countries, as outlined by the authors (1), morphine and fentanyl are by far the most commonly used agents for analgosedation (8). The main characteristics of opioids (time to onset, half-life, metabolism, presence of active metabolites,

elimination, and risk of accumulation) used for sedation worldwide are detailed in Table 1.

As one would expect, uncertainties remain, and this trial provides only a piece of the puzzle. Irrespective of the opioid chosen, it is worth noting that the use of adjuvant analgesia might help provide effective analgesia while minimizing unwanted side effects (9), and the use of such adjuvant analgesia was not detailed in the current trial (1). Furthermore, if the observed 4.7–percentage point lower frequency of opioid use at hospital discharge for patients assigned to morphine was demonstrated to represent the true treatment effect in an appropriately powered trial, this finding would certainly be clinically important in the context of the current epidemic of opioid abuse (10). If such findings were confirmed, they might well mean that morphine would be a better choice than fentanyl, particularly for younger patients and those without renal impairment. Despite not generating a definitive answer on this point, this study is a great example of how it is possible to generate practice-informing data efficiently using novel trial designs.

Evaluating commonly used treatments and using cluster randomization instead of individual patient randomization allowed for rapid recruitment of trial participants. Nevertheless, only two centers participated. Although the number of clusters is an important determinant of power in a cluster trial (11), incorporating a crossover (i.e., allowing each site to sequentially enroll patients into each treatment arm) markedly increases power compared with not incorporating a crossover (12). Irrespective of such considerations, having more clusters would have been desirable to increase the generalizability of the results.

Lack of blinding is another weakness of the trial. Knowing the type of analgesia being used may have influenced the clinicians in their management of analgosedation because they decided the dose of medication to administer to each patient.

Compared with using study case report forms and collecting data from individual patient's health records, obtaining information from existing registry data sources would have substantially reduced costs associated with data acquisition. Because the trial was approved with a waiver of consent for one site and with an opt-out process for the other site, personnel costs associated with trial conduct would likely have been small.

All of these factors, combined with cluster randomization and associated rapid recruitment, have implications for future research. Collectively, they may make research that informs clinical practice feasible in hospitals in which it otherwise would not be. Particularly in situations in which idiosyncratic practice variation is exposing patients to a range of treatments in usual practice, trials like this have tremendous potential to improve the quality of care through standardization and to advance knowledge. ■

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Paul J. Young, M.B. Ch.B. B.Sc., Ph.D.
Intensive Care Unit
Wellington Hospital
Wellington, New Zealand

Intensive Care Programme
Medical Research Institute of New Zealand
Wellington, New Zealand

and
Australian and New Zealand Intensive Care Research Centre
Monash University
Melbourne, Victoria, Australia

Audrey De Jong, M.D., Ph.D.
Department of Anaesthesia and Critical Care
University of Montpellier
Montpellier, France

ORCID ID: 0000-0002-3428-3083 (P.J.Y.).

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Two Steps Forward: Improving the Management of Cystic Fibrosis Pulmonary Exacerbations

In this issue of the *Journal*, Goss and colleagues (pp. 1295–1305) report the findings of the STOP2 (Standardized Treatment of Pulmonary Exacerbations) study, a randomized trial of antimicrobial duration for cystic fibrosis (CF) pulmonary exacerbation (PEX) treatment (1). Adults with CF experiencing PEXs treated with intravenous antibiotics were enrolled at presentation and assessed at an interim time point (7–10 days into antibiotic therapy) for clinical

response based on lung function and symptom improvement. Early responders were randomized to either 10 or 14 days of total antibiotic treatment duration, whereas non-early responders were randomized to 14 or 21 days' duration. The primary outcome was the change in FEV₁ from the start of antibiotics to 2 weeks after antibiotic cessation. Almost 1,000 patients with CF were randomized in the study; among the approximate one-third of early responders, 10 days was not inferior to 14 days of antibiotics, and among the remaining non-early responders, 21 days was not shown to be superior to 14 days of antimicrobial therapy.

The STOP2 trial represents a landmark study in the treatment of CF pulmonary exacerbations as it is the first to be adequately powered to compare varying lengths of antibiotic courses. The choice of antibiotic duration in the treatment of infectious diseases is frequently guided by clinical experience or observational studies

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