Effects of Nefopam on Early Postoperative Hyperalgesia After Cardiac Surgery

Philippe Richebé, MD, PhD,* Walter Picard, MD,† Cyril Rivat, PhD,* Srdjan Jelacic, MD,*
Olivier Branchard, MSc,‡ Sandy Leproust, MSc,§ Alex Cahana, MD, DAAPM, FIPP, MAS,* and
Gérard Janvier, MD, PhD‡

Objective: **The purpose of this randomized, double-blind placebo-controlled study was to evaluate the effect of nefopam, a centrally acting antinociceptive compound, on the development of hyperalgesia after sternotomy. Preventive strategy giving nefopam from the early stage of anesthesia was compared with a postoperative strategy only and placebo.**

Design: **This study was double-blinded and randomized.**

Setting: **It was conducted in a single university hospital.**

Participants: **Ninety American Society of Anesthesiologists II to III patients scheduled for elective cardiac surgery.**

Interventions: **Patients were assigned randomly to receive a 0.3-mg/kg bolus of nefopam at the induction of anesthesia followed by a continuous infusion of 0.065 mg/kg/h for 48 hours (G1), a 0.3-mg/kg bolus of nefopam at the end of surgery followed by a continuous infusion of 0.065 mg/kg/h for 48 hours (G2), or a placebo (G3). Postoperative analgesia was based on morphine patient-controlled analgesia and rescue analgesia when necessary. Postoperative hyperalgesia, pain scores, morphine consumption, and postoperative cognitive dysfunction were assessed for the first 48 hours and thereafter on postoperative days 4 and 7.**

Measurements and Main Results: **The postoperative extent of dynamic hyperalgesia and the decrease of the nociceptive threshold evaluated by von Frey filaments at the sternal midline were smaller in group 1 and group 2 compared with the placebo group at the 24th hour. The primary objective was the extent of hyperalgesia at the midline given as the mean (standard deviation [SD]) (4.4 [2.5] cm for G1, 4.1 [2.7] for G2, and 6.1 [2.7] cm for G3. The punctuate is given as mean (SD) (64 [43] g for G1, 68 [40.8] g for G2, and 32 [27] g for G3; with $p < 0.05$ for the comparisons of extent and punctuate hyperalgesia between G1 and G3 and G2 and G3). The extent of hyperalgesia was not significantly different among the 3 groups on days 2, 4, and 7 after surgery. There were no significant differences in pain scores, morphine consumption, or postoperative cognitive dysfunctions.**

Conclusions: **Nefopam administered during the perioperative period slightly reduced acute hyperalgesia after cardiac surgery, but this was not associated with improved analgesic efficacy.**

KEY WORDS: postoperative hyperalgesia, cardiac surgery, nefopam, opioids, narcotics, analgesia, opioid tolerance, postoperative pain

POSTOPERATIVE ACUTE HYPERALGESIA that develops after major surgeries may initiate the development of chronic postoperative pain, and specific therapeutic modalities are limited.[1-3] Acute postoperative hyperalgesia refers to increased postoperative pain and larger perioperative morphine requirement[4,5] and is characterized by mapping nociceptive thresholds around the surgical wound.[6-8] An additional source of heterogeneity between reports on postoperative hyperalgesia is the nature of the surgical procedure (eg, abdominal, cardiac, knee, or laparoscopic procedure).[9] The need to optimize postoperative analgesia is made more compelling by studies suggesting a possible link between postoperative hyperalgesia and the risk of chronic postsurgical pain.[2,10]

Recently, animal[11] and clinical studies have shown the usefulness of perioperative ketamine infusion to prevent postsurgical hyperalgesia.[12,13] More recently, another nonopioid analgesic agent used in postoperative management, nefopam hydrochloride (Acupan; Biocodex, Compiegne, France), has received attention.[14-16] Nefopam is a centrally acting antinociceptive compound[17] that inhibits monoamine reuptake[4,14,15] with both supraspinal and spinal sites of action.[18] Animal studies suggested nefopam blocks voltage-sensitive calcium and sodium channels and consequently modulates glutamatergic transmission, leading to less activation of postsynaptic glutamatergic receptors, such as N-methyl-D-aspartate receptors,[19-21] which are involved in the development of hyperalgesia.[22] Nefopam has shown antihyperalgesic effects in different pain models[23] and clinical studies.[4,5]

The present study was designed as a prospective, randomized, double-blind placebo-controlled clinical trial to evaluate the effects of nefopam on postoperative hyperalgesia after cardiac surgery. A unique feature of the design is the inclusion of quantitative sensory testing using von Frey filaments to assess hyperalgesia and the nociceptive threshold to evaluate the level of central sensitization after surgery.[24,25]

METHODS

This was a randomized, double-blind, placebo-controlled trial that aimed at investigating the effect of nefopam infusion on postoperative hyperalgesia in patients undergoing cardiac surgery. The study was conducted over a 3-year period (March 2007-December 2009). Ethical approval for this study was provided by the local ethics committee.

*From the *Department of Anesthesiology and Pain Medicine, University of Washington Medical Center, Seattle, WA; †Intensive Care Medicine, Centre Hospitalier François Mitterrand, Pau, France; ‡Department of Anesthesiology and Intensive Care II, Centre Hospitalier et Universitaire de Bordeaux, Pessac, France; and §University Hospital of Bordeaux, Clinical Epidemiology Unit, Bordeaux, France.*

Supported by the University Hospital of Bordeaux and the University Victor Segalen of Bordeaux 2. The drug nefopam was supplied by the pharmaceutical company BIOCODEX (France) for this study only and no other financial support was provided by this company. This study was registered in a public trials registry: http://clinicaltrials.gov identifier NCT00413257.

Address reprint requests to Philippe Richebé, MD, PhD, Department of Anesthesiology and Pain Medicine, University of Washington Medical Center, Campus Box 356640, 1959 NE Pacific Street, BB1459, Seattle, WA 98195-6540. E-mail: prichebe@u.washington.edu

1053-0770/2703-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2012.08.015

The clinical schedule of surgeons was reviewed electronically on a daily basis for patients meeting the inclusion criteria. On the evening before the surgery, the principal investigator and/or coinvestigators reviewed the study with the patient and obtained informed consent.

Ninety adult patients scheduled to undergo cardiac surgery for coronary artery bypass graft (CABG) surgery or valve replacement with sternotomy and cardiopulmonary bypass were expected to be enrolled in this trial. They had to be between 55 and 75 years of age and have an American Society of Anesthesiologists status of I to III.

Patients were not included in the study if they (1) regularly used analgesics or opioids within 12 hours of surgery; (2) had a history of drug or alcohol abuse, had a psychiatric disorder, or were obese (>130% of ideal body weight); (3) had contraindications to the self-administration of opioids (eg, unable to understand the patient-controlled analgesia [PCA] device); (4) had any contraindication to any drug used in the study; or (5) had any hepatic, kidney, or pulmonary dysfunction (ASAT and ALAT above 2 N or any history of liver disease or failure, creatinine >1.4 mg/mL or creatinine clearance < 50 mL/min, asthma, or chronic obstructive pulmonary disease history, respectively). Patients requiring hemostatic surgery within the first 7 days after the initial cardiac surgery were excluded from the analysis.

Before surgery, patients were instructed in the use of a 4-point verbal rating scale (VRS) for pain (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain), the 100-mm horizontal visual analog scale (VAS) for pain (0 = no pain to 100 = worst pain), and the PCA device (Master PCA; Vial Fresenius, Brezin, France). Quantitative sensory testing on the sternal skin area was performed during this visit to get preoperative basal nociceptive threshold values. Patients were premedicated with oral hydroxyzine (1 mg/kg) the night before and oral midazolam (0.1 mg/kg) 1 hour before surgery.

A standardized anesthesia technique was used for all patients. In the operating room, intravenous and arterial catheters were inserted, and standard monitoring was used including a BIS monitor (Version XP; Aspect Medical Systems BV, Leiden, The Netherlands). The anesthetic doses were calculated according to body weight, except for propofol. The latter was administered using target-controlled infusion (Diprifusor; AstraZeneca, Wedel, Germany) according to the model of Schnider et al.[26] Anesthesia was induced with a propofol target-controlled infusion to a target concentration of 2 μg/mL, and a 1-μg/kg initial dose of remifentanil was administered over 120 seconds. Anesthesia was maintained with remifentanil at a fixed rate of 0.3 μg/kg/min, and propofol infusion rates were adjusted to achieve a BIS value of 40 to 50 during the whole surgical procedure.

Baseline heart rate, arterial pressure, and BIS values were measured immediately before induction. The intraoperative parameters (ie, heart rate, arterial pressure, pulse oximetry, BIS, temperature, and end-tidal carbon dioxide) were recorded during anesthesia. Volume expansion and catecholamines were recorded during the pre- and postoperative periods. The total doses of remifentanil and propofol given in the operating room were recorded.

Patients were assigned randomly to 1 of 3 groups (30 patients per group). Before the study began, a computer-generated block randomization scheme was used to randomize patients in groups of 9 to 1 of the 3 treatment regimens. On the morning of the surgery, a nurse not involved in any part of the study prepared nefopam or saline solution syringes in line with information she got from the electronic randomization list. None of the investigators involved in patient management or data collection were aware of the group assignment. In case of emergency, the anesthesiologist could break the code.

The 3 treatment groups were as follows:

1. Group 1: Perioperative nefopam: patients were given a 0.3-mg/kg bolus of nefopam at induction over 5 minutes followed by an intraoperative continuous infusion of 0.065 mg/kg/h. At the end of the surgery, a placebo bolus was given over 5 minutes. Nefopam infusion was continued for 48 hours at the same rate as the intraoperative rate.
2. Group 2: Postoperative nefopam: patients were given a bolus of placebo at induction and an infusion of placebo during surgery; a 0.3-mg/kg bolus of nefopam was administered over 5 minutes at the end of surgery followed by a continuous infusion of nefopam, 0.065 mg/kg/h, for 48 hours.
3. Group 3: Placebo: patients were given saline solution (placebo: as a bolus at induction, then an intraoperative infusion, bolus at the end of surgery, and followed by a continuous infusion for 48 hours).

Thirty minutes before the anticipated end of surgery, a 0.15-mg/kg morphine chloride bolus was given intravenously. After skin closure, remifentanil was discontinued, and propofol was infused at a rate of 1.5 mg/kg/h. This infusion was continued in the cardiac surgical intensive care unit (CSICU) until a temperature of >36.5°C was reached. The trachea was extubated in the CSICU as soon as hemodynamic parameters were satisfactory and when patients responded to verbal commands and the spontaneous respiratory rate exceeded 12 breaths/min. They stayed in the surgical intensive care unit for 2 days.

Postoperative pain initially was treated in the CSICU with morphine chloride (a 3-mg bolus) every 5 minutes until the pain score VAS was <40 or the VRS was <2. After morphine titration was completed, patients were connected to a PCA device containing morphine chloride, 1 mg/mL, programmed to deliver a 1-mg intravenous bolus with a 5-minute lockout interval without continuous infusion. This PCA regimen was continued for 48 hours after tracheal extubation. Rescue analgesia was allowed, if necessary, first with intravenous acetaminophen, second with intravenous ketoprofen, and last with a 3-mg intravenous morphine bolus. The total amount of rescue medication was recorded. Forty-eight hours after surgery, intravenous analgesic treatment was discontinued, and acetaminophen and tramadol were administered orally per patient request.

Patients assessed pain intensity by giving both VAS and VRS scores at 15-minute intervals during the first hour and then hourly for 3 hours. Subsequently, pain was evaluated with VAS/VRS at 4-hour intervals for an additional 44 hours. Opioid consumptions from the PCA device and rescue analgesics were recorded for 48 hours.

First, the pain threshold (static hyperalgesia) was determined with von Frey filaments 2 cm to the right at the top, middle, and bottom of the surgical wound. Only the right side of the sternum was chosen for evaluation because dysesthesias have been reported on the left side when patients undergo CABG surgery with dissection of the left internal mammary artery. The nociceptive threshold for mechanical static stimuli was assessed by using calibrated von Frey filaments (0.06-180 g). Patients were instructed to close their eyes during the procedure. Care was taken to avoid stroking the skin with the hair and to apply only a pressure stimulus. Filaments were applied to the designated point for approximately 1 second. These actions were performed at intervals of at least 30 seconds to reduce the likelihood of anticipatory responses. They were applied in ascending order of stiffness. The tactile nociceptive threshold was defined as the smallest force (in grams) necessary to bend a von Frey filament, which was just perceived as painful. Three determinations with an interval of 30 seconds were made at each assessment, and a mean was calculated.

Second, the extent of mechanical hyperalgesia (dynamic hyperalgesia) to von Frey filament stimulation (pressure = 100 g) was assessed according to a previously reported method.[25] The extent of hyperalgesia (in centimeters) was determined on the right side of the sternal wound by stimulating along 3 linear paths at right angles to the top, middle, and bottom of the surgical incision starting 10 cm outside the midline and going to the midline in steps of 5 mm at 1-second intervals. Stimulations continued toward the incision until patients reported a clear change in sensation (eg, burning, tenderness, or more intense pricking).