

# A Clinical Evaluation Of Postoperative Alfentanil Infusion In Cardiac Surgical Patients: Effects On Hemodynamics, Sedation And Shivering

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## Abstract

We conducted a randomized prospective double-blind pilot study followed by an open main study to assess the effects of alfentanil infusion on postoperative hemodynamics, sedation and shivering following coronary artery bypass graft surgery. Two groups of 10 patients were randomized to receive 15 or 25mcg.kg<sup>-1</sup> alfentanil bolus. The 15mcg.kg<sup>-1</sup> dose caused less changes in heart rate and systolic arterial pressure (SAP) and was chosen for the main study. After admission to intensive therapy unit (ITU), 30 patients received alfentanil bolus followed by an infusion for 3 hours at a rate of 0.7±0.2mcg.kg<sup>-1</sup>.min<sup>-1</sup>. Changes from baseline in mean arterial pressure (MAP), cardiac index and pulmonary capillary wedge pressure were not significant during sedation and the early post-extubation periods, however, 30% of patients required nitroglycerin/nitroprusside infusions to avoid hypertension (SAP<140mmHg and/or MAP<95mmHg). Sedation was assessed on 0-6 grading scale. Sedation scores during alfentanil infusion were 4.9±0.8. Addition of midazolam was required in 16% of patients (4.8±1mg per patient). Shivering occurred in 20% of patients. Mean extubation time was 225±103min from the time of discontinuing alfentanil infusion. None of the patients required re-intubation. The ITU length of stay was confined to 24h period. In conclusion, postoperative administration of alfentanil achieved effective sedation, adequate cardiovascular stability, and provided good patient tolerance to ventilation and minimal shivering.

## INTRODUCTION

Following cardiac surgery patients are transferred to an intermediate care facility for postoperative monitoring, ventilatory support, sedation and analgesia. Postoperative sedation in the context of fast tracking cardiac surgery is usually limited to a 6-hour period. Its aim is to achieve anxiolysis, analgesia, amnesia and muscle relaxation as well as to reduce resistance to ventilation, decrease the incidence of shivering and promote smooth recovery. The optimal sedation and analgesia regimens minimise cardiovascular responses to stimulation and facilitate easy titratable levels of consciousness to ensure rapid awakening and tracheal extubation without increasing the incidence of myocardial ischaemia. During the early postoperative period, patients often develop hypertension requiring vasodilator therapy despite apparent adequate analgesia [1,2]. It is important to control postoperative hypertension to avoid potential adverse effects like bleeding, graft dehiscence, myocardial ischaemia, arrhythmias and cerebrovascular accidents. The initial treatment for postoperative hypertension usually

involves administration of opioid analgesics and sedatives. If this treatment fails to adequately control the blood pressure, then vasodilator therapy with nitroglycerin or sodium nitroprusside is initiated. Although the treatment is usually effective, the use of both maybe associated with decreased arterial oxygenation [3,4] and delay in weaning from mechanical ventilation [5].

We conducted a prospective, clinical trial to evaluate the hemodynamic and sedative effects of short acting opioid alfentanil, administered during the early postoperative period in patients undergoing elective coronary artery bypass graft (CABG) surgery.

## METHODS

### STUDY DESIGN AND PATIENT POPULATION

The study design consisted of an initial randomized double-blind pilot study to define the optimal bolus dose of alfentanil. It was followed by a prospective open clinical trial. With approval of the Institutional Ethics Committee

and informed consent, 50 patients age 40-75 years undergoing CABG surgery were recruited. The exclusion criteria were patients with a history of alcohol or drug abuse, preoperative left ventricular ejection fraction < 40%, significant valvular heart disease, abnormal liver, renal, cerebral, or hematological function, recent myocardial infarction (<3 months), cardiac index less than 2 L.min<sup>-1</sup>.m<sup>-2</sup> or requirements for mechanical and/or inotropic support upon arrival in the intensive therapy unit (ITU), postoperative bleeding greater than 200 ml.h<sup>-1</sup>, and known hypersensitivity to any of the trial drugs.

## **ANESTHESIA AND SURGERY**

All routine cardiac medication was continued up to the morning of surgery. Premedication included 1-3 mg of lorazepam two hours prior to surgery. Following preoxygenation, induction of anaesthesia was achieved with sufentanil 5 ug.kg<sup>-1</sup> and thiopentone 1-3 mg.kg<sup>-1</sup>. Pancuronium was used to facilitate muscle relaxation. Lungs were ventilated with air/oxygen mixture and anaesthesia was maintained with isoflurane. Routine monitoring was applied. A conventional CABG procedure with cardiopulmonary bypass (CPB) was performed. A combination of intermittent cold (40C) crystalloid and blood cardioplegia (range 32-340C) was applied. No topical cooling was used. Following surgery all patients were transferred to ITU.

## **DOSE FINDING STUDY**

Pilot study included 20 patients who were randomly allocated to receive either 15 or 25 (g.kg<sup>-1</sup> alfentanil bolus within 15-20 min of arrival in the ITU. The purpose of the pilot study was to determine systolic arterial pressure (SAP) and heart rate (HR) response to two different bolus doses of alfentanil. The measurements were recorded at baseline prior to administration of alfentanil bolus and then at 5, 10, 15, 30 and 60 min intervals. The dose that produced the least hemodynamic changes was chosen for the open main study.

## **HEMODYNAMIC AND SEDATION STUDY**

In the main study, 30 patients received 'the optimal' alfentanil bolus followed by a variable rate of alfentanil infusion starting at 0.25(g.kg<sup>-1</sup>.min<sup>-1</sup> and maximum increase to 2(g.kg<sup>-1</sup>.min<sup>-1</sup>. The rate of infusion was reassessed every 30 min and adjusted accordingly to ensure the minimum infusion rate necessary to maintain haemodynamic stability. The alfentanil infusion was continued for the duration of 3 hours after administration of the initial alfentanil bolus. The HR, SBP, mean arterial

(MAP) and pulmonary capillary wedge pressures (PCWP), cardiac index (CI) as well as sedation scores were recorded at predetermined time intervals: (baseline, 5, 60, 180 min, 60 min after cessation of sedation, immediately prior to extubation, 15 min post-extubation, and 30 min post-extubation).

Patients who were hypertensive (SAP > 140mmHg and/or MAP > 95mmHg) received a bolus of alfentanil 20 ug.kg<sup>-1</sup> followed by incremental increase of the infusion rate by 0.25 (g.kg<sup>-1</sup>.min<sup>-1</sup>. A maximum of up to 3 boluses and 2 (g.kg<sup>-1</sup>.min<sup>-1</sup> of alfentanil infusion was allowed according to the protocol. If the patient remained hypertensive a 'rescue medication' in the form of nitroglycerin and/or sodium nitroprusside was commenced. If hypotension (SAP < 90mmHg) occurred, the alfentanil infusion rate was reduced by decrements of 0.25 (g.kg<sup>-1</sup>.min<sup>-1</sup>. The PCWP was maintained > 8 mmHg at all times. If the patient remained hypotensive despite stopping the alfentanil infusion, vasopressor and/or inotropic therapy was initiated as appropriate.

The level of sedation was assessed according to the Ramsay Sedation scale: 0 – agitated, 1 – awake, 2 – asleep (eyes open to surroundings), 3 – asleep (eyes open to name), 4 – asleep (eyes open to moderate tap on shoulder), 5 – asleep (moves and reacts to moderate tap on shoulder), 6 – unconscious and unarousable [6]. Target sedation score was 3-5.

Shivering was assessed on a scale 0 to 3 (0 - no shivering, 1 – mild, involving only head and neck, 2 – moderate, only upper body, 3 - generalized shivering) during the study period. Treatment consisted of administration of pethidine 10-25 mg bolus per episode, up to a maximum of two doses. If shivering continued muscle relaxation with pancuronium was initiated.

Patients were assessed for extubation 30 min after cessation of the alfentanil infusion and reassessed every 30 min thereafter until extubation criteria were satisfied [7,8].

## **STATISTICAL ANALYSIS**

Data analysis was performed with chi-squared or Fisher's exact probability tests, as well as T-tests and ANOVA as appropriate (Systat, Evanston statistical software package). A p value of less than 0.05 was considered statistically significant. Data was expressed as mean ( standard deviation.

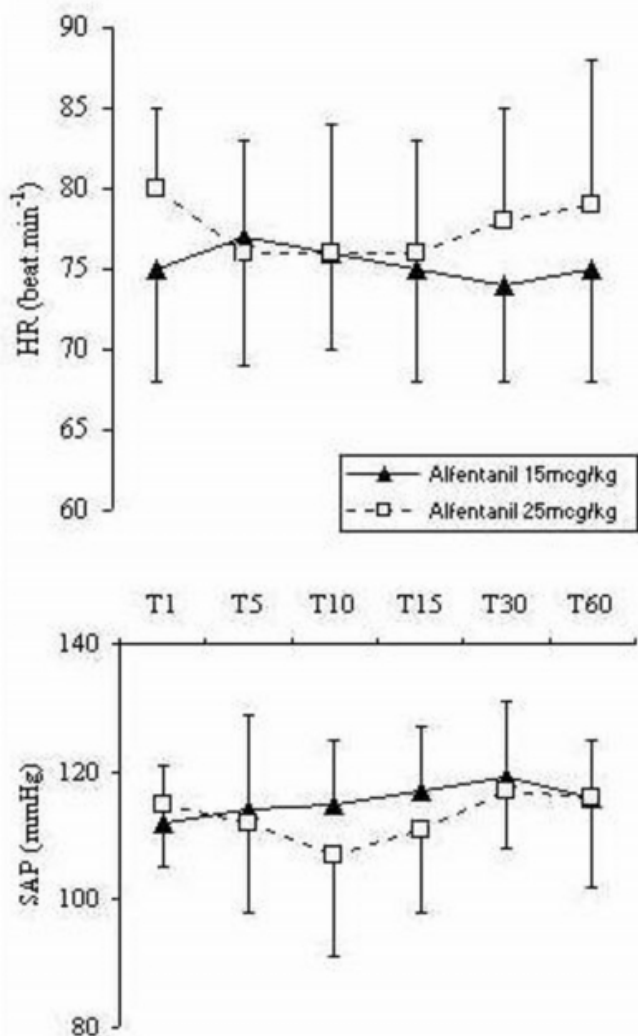
**RESULTS**

**DOSE FINDING**

Both groups of patients in the dose study were similar in respect to their demographic data, preoperative medication and left ventricular ejection fraction. Following administration of alfentanil bolus all patients had stable hemodynamic profile (Figure 1). The higher dose (25(g.kg-1) of alfentanil caused a 5% reduction in HR and 9% decrease in SAP. For the lower dose (15(g.kg-1) of alfentanil the change in HR and SAP was 3% and 6% respectively and consequently the lower bolus dose of alfentanil was chosen for the main study. There was no statistically significant difference between the groups in respect to changes in SAP and HR.

**Figure 1**

Figure 1: Hemodynamic profile



**MAIN STUDY**

A total of 29 male and 1 female patients with the mean age

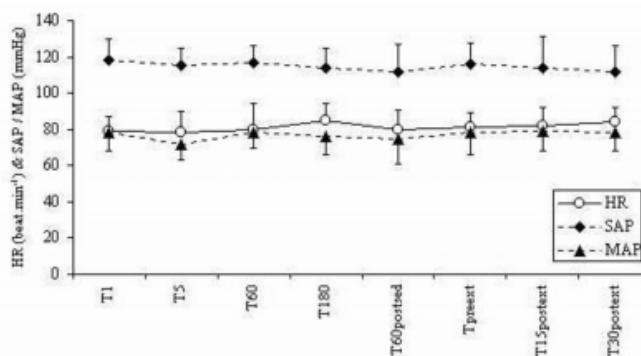
57 ( 8 years, weight 84 ( 10 kg, height 173 ( 7cm were recruited into the main prospective study. Preoperative medication included nitrates, (-blockers, angiotensin-converting enzyme inhibitors, Ca-antagonists, cholesterol lowering agents and aspirin. The mean CPB time was 75 ( 28 min with the mean number of grafts 3.4 ( 0.9 per patient. Intraoperative nasopharyngeal temperature range was 33-35°C. All patients were actively rewarmed to 37-38°C before separation from CPB. Warming blankets were applied postoperatively to maintain an adequate body temperature.

The alfentanil infusion rate ranged from 0.25-1.25(g.kg-1.min-1 with the average of 0.7 ( 0.2 (g.kg-1.min-1 during the 3 hour sedation period. All patients required incremental adjustment of alfentanil infusion. The average number of alfentanil boluses were 2.7 ( 1.2 per patient. A total dose of alfentanil was 15.3 ( 4.7mg per patient.

The HR, SAP, and MAP remained very stable during the sedation as well as the early post-extubation periods (Figure 2). The upward trend in PCWP was noted during sedation period, however, this increase was not statistically significant when compared to baseline; the changes in CI were insignificant (Figure 3). Thirty percent of patients required nitroglycerin infusion and half of them needed an addition of sodium nitroprusside to control hypertension. None of the patients required administration of vasopressors during the alfentanil infusion.

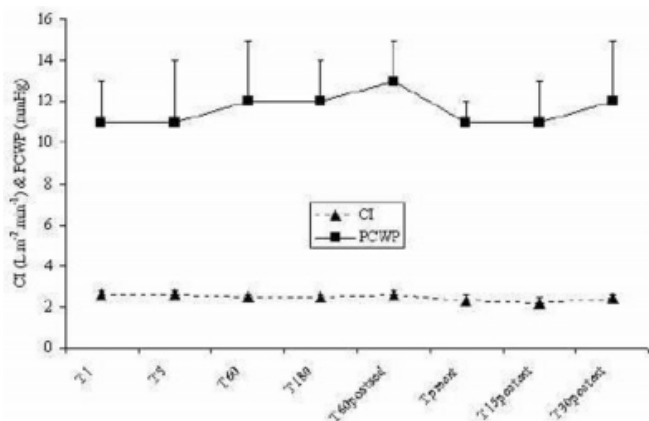
**Figure 2**

Figure 2: Hemodynamics I



**Figure 3**

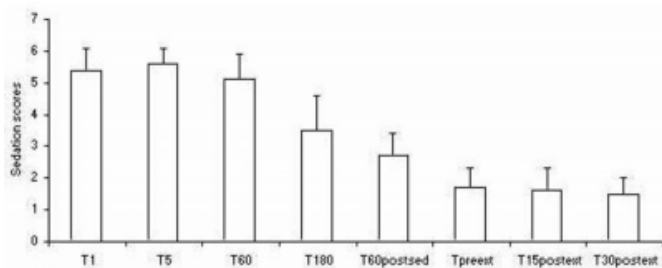
Figure 3: Hemodynamics II



Sedation scores are reflected in Figure 4. A total of 5 (16%) patients required addition of midazolam to achieve adequate sedation scores. On average, 2 boluses of midazolam were administered per patient (4.8 ( 1 mg). Shivering occurred in 6 (20%) patients. One patient experienced mild, three moderate and two generalized shivering. All patients responded successfully to administration of pethidine, with an average dose of 28 ( 18 mg per patient. There was no significant difference in alfentanil requirements for patients needing midazolam and pethidine.

**Figure 4**

Figure 4: Sedation scores



Mean extubation time was 225 ( 103 min from the time of discontinuing alfentanil infusion. The time for readiness of extubation and actual time of extubation was identical. None of the patients required re-intubation. The ITU length of stay was confined to 24 h period. There was no incidence of perioperative myocardial infarction, major respiratory, renal, hematological, hepatic or cerebral complications.

## DISCUSSION

Postoperative hemodynamic and sedation control is an important component of perioperative care for cardiac surgical patients. In conjunction with analgesia optimal sedation regimen should facilitate ventilatory support and

adequate gas exchange whilst maintaining cardiovascular stability. The primary objective of this study was assessment of hemodynamic profile and efficacy of sedation with alfentanil during the early postoperative period in patients undergoing coronary revascularization surgery. The pharmacokinetic profile of alfentanil, which is represented by a rapid onset and short duration of action is an appealing choice of postoperative analgesia and sedation in fast track cardiac surgical recovery. The alfentanil infusion produces reliable plasma concentration levels and decreases the plasma catecholamine concentrations after surgery [9]. Furthermore, both analgesia and sedation can be achieved with the administration of a single drug effectively reducing the need for midazolam and propofol which use has been associated with hypotension and reduction in cardiac output after cardiac surgery [10,11,12]. Consequently, Carrasco et al highlighted the advantages of synergistic treatment with propofol and midazolam administered together for postoperative sedation after CABG surgery. This regimen achieved better hemodynamic stability by reducing the maintenance dosage of solo-therapy and resulting in lower pharmaceutical cost [13]. However, an addition of opioid analgesics still would be required to provide optimal postoperative pain relief.

It has been shown that after discontinuing sedation to facilitate tracheal extubation many patients develop tachycardia, hypertension [14] and myocardial ischemia [15] after cardiac surgery requiring either re-sedation or institution of additional treatment [16]. A Southampton group suggested that patients should be extubated on continuing sedation to minimize hemodynamic disturbance and reduce the incidence of myocardial ischaemia associated with tracheal extubation [17]. Furthermore, a recent study by Checketts et al [18] outlined a potential for alfentanil to be continued after extubation in spontaneously breathing patient following cardiac surgery. The authors identified that target-controlled infusion of alfentanil delivered high-quality analgesia with adequate overall sedation scores and low incidence of hemodynamic instability, myocardial ischaemia or hypoxaemia [18].

It is noteworthy, that in our study, following the initial bolus and throughout the continuous infusion of alfentanil patients' hemodynamic parameters remained close to the baseline. The transition period from sedation with alfentanil to extubation was very smooth and resulted in no significant increase in either blood pressure or heart rate. Left

ventricular performance as assessed by cardiac index and pulmonary capillary wedge pressure remained very stable.

One of the requirements for tracheal extubation is an awake, co-operative patient. The initial three-hour period of alfentanil infusion was intended to assess the ease of hemodynamic and sedation control. It may have resulted in delay of awakening of patients for assessment of earlier extubation. However, the extubation times were confined to a less than 4-hour period from the time of discontinuing the medication. This study demonstrated that continuous infusion of alfentanil provided easily controllable level of analgesia, sedation, good tolerance of endotracheal tube in postoperative cardiac surgery.

Postoperative shivering is a common complication after cardiac surgery. Although both pethidine and alfentanil have been shown to reduce the incidence of postoperative shivering when compared to placebo [19], it is generally accepted that pethidine is superior in abolishing shivering [20]. Our results were in line with a general agreement that effects of alfentanil are short lived and that the majority of patients would require further administration of pethidine to effectively control postoperative shivering.

The obvious limitation of our study was the lack of control group which prevented a comparative assessment of alfentanil and its effects on requirements for antihypertensives and postoperative shivering. However, we performed a qualitative assessment of the bolus dose of alfentanil and effects of alfentanil infusion on the quality of postoperative sedation and shivering.

In the era of monitored performance and financial restraint it is important to address the issue of cost. A recent study by Manley et al [21] compared the alfentanil/propofol versus morphine/midazolam sedation regimens in critically ill patients. The shorter recovery characteristics and reduced intensive care length of stay resulted in overall reduction in costs with alfentanil/propofol regimen [21]. At a current rate of \$14.93 per 5ml (2.5mg) of alfentanil an average cost of alfentanil in our study was \$91.4 ( 28 per patient [22]. Further comparative studies are warranted to assess the pharmacoeconomic profile of alfentanil sedation after cardiac surgery.

In conclusion, postoperative administration of alfentanil (15ug.kg-1 bolus and 0.25-1.25 ug.kg-1.min-1 infusion) achieved effective sedation and good cardiovascular stability

after CABG surgery. Alfentanil infusion provided good patient tolerance to ventilation and minimal shivering. Further work is necessary for comparative evaluation of alfentanil and other currently used sedation regimens in cardiac surgical patients.

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