

# Preliminary results of prolonged target controlled infusion of sufentanil adjusted to an effort pain score after cardiac surgery

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**Abstract** : Repeated boluses of IV morphine are often used for analgesia after cardiac surgery, but this procedure frequently provides inadequate pain relief. Target controlled infusion (TCI) of opioid drugs has been proposed as an alternative. The objective of this study was to evaluate the effects of prolonged sufentanil TCI adjusted to an effort pain score on the postoperative course after cardiac surgery. Twenty-six patients scheduled for cardiac surgery were anaesthetised using TCI of propofol and sufentanil, followed by early extubation. In the postoperative period, patients were randomly allocated to receive either boluses of IV morphine (Bolus group), adapted to a pain score at rest, or sufentanil TCI with a low target concentration (0.08-0.1 ng/ml), adapted to a pain score during deep inspiration (TCI group). Postoperative pain was assessed using a Verbal Numerical Score (VNS) before and during three stimuli : extubation, lateral positioning and physiotherapy. In 15 patients, inspiratory capacity was evaluated by incentive spirometry (IS) on postoperative day 1. Three patients in each group were withdrawn because of delayed extubation. Clinical characteristics, mean time to extubation and PaCO<sub>2</sub> were similar in both groups. Analgesia was adequate at rest in both groups as indicated by low pain scores. Pain intensity increased significantly during the three stimuli ( $p < 0.01$ ). VNS were lower in the TCI than in the Bolus group ( $3.8 \pm 0.5$  versus  $4.8 \pm 0.5$ ,  $p = 0.03$ ). Nine of 10 patients in the TCI group but only 4 of 10 patients in the bolus group gave a VNS below 5 during the stimuli. IS performance was better preserved in the TCI than in the Bolus group ( $53 \pm 5\%$  versus  $35 \pm 5\%$  of preoperative values,  $p < 0.05$ ). These observations indicate that after cardiac surgery, postoperative pain management with prolonged TCI of sufentanil adapted to a pain score during deep inspiration can achieve better analgesia during routine bedside procedures and higher pulmonary volumes than on-demand boluses of morphine.

**Key words** : Pain ; postoperative ; opioids ; TCI ; assessment ; cardiac surgery ; inspiratory capacity.

## INTRODUCTION

Pain management following cardiac surgery is a continuing challenge to ensure patient comfort

while limiting the risk of pulmonary complications. Cardiac surgery, especially with cardiopulmonary bypass, can induce changes in lung mechanics, increases in extravascular lung water (1) and reduction in lung volumes, leading to postoperative atelectasis (24, 14). Because pain can restrict the ability to breathe deeply and to clear secretions, adequate pain management is essential in the postoperative period, especially during physiotherapy and nursing care which can be particularly painful (19).

Fast track cardiac surgery that allows extubation within 6 hours after surgery is now regularly practised in many centres with no evidence of increased postoperative morbidity (8). Anaesthesia usually includes remifentanil or low doses of a long acting opioid agent such as sufentanil, associated with either propofol or a volatile anaesthetic agent. After tracheal extubation, physiotherapy and use of incentive spirometry (IS) are regularly performed. Pain in the postoperative period is usually managed with repeated doses of peripherally acting analgesics and centrally acting systemic opioids (21).

Target controlled infusion (TCI) has been successfully used not only during total intravenous general anaesthesia but also for postoperative analgesia (28). Such a system has been developed in our institution and is routinely used for cardiac anaesthesia combining propofol with sufentanil or remifentanil (3). The TCI system can be easily transferred into the ICU and prolonged for postoperative management, taking into account the total amount of drug given in the operating room. CHECKETTS *et al.* (7) showed that postoperative TCI

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of alfentanil provided a similar level of satisfaction when compared with a traditional patient-controlled analgesia (PCA) with morphine. However, the authors did not investigate postoperative pulmonary function or pain resulting from routine bedside procedures.

The present study was, therefore, undertaken after fast track cardiac surgery to compare the quality of analgesia at rest and also during painful stimuli using either a standard protocol of repeated IV boluses of morphine based on patient demand at rest, or by continuing sufentanil TCI administration adjusted to a pain score during deep inspiration. We also evaluated how the quality of analgesia may influence postoperative changes in lung volumes using incentive spirometry (IS) (4).

## METHODS

After obtaining Hospital Ethics Committee approval and each patient's informed consent, we enrolled 26 adult patients scheduled for fast track cardiac surgery. Preoperative exclusion criteria were an age greater than 75 years, a preoperative left ventricular ejection fraction less than 40%, and a history of drug addiction. All patients received the same anaesthetic technique allowing extubation within 6 hours after the arrival of the patient in the ICU. In the postoperative period, patients who required a dobutamine infusion at a dose greater than 5 µg/kg/min, who experienced bleeding at a rate higher than 100 ml/h, or who were still ventilated 6 hours after ICU admission were also excluded (8). The anaesthetic technique was standardised using a TCI infusion system for propofol and sufentanil administration developed at our institution (6) and using the pharmacokinetic models of MARSH *et al.* (16) and GEPTS *et al.* (12), respectively.

In the ICU, sedation in all patients was maintained using TCI of propofol which was adapted using a sedation score developed in our ICU department (10) (Table 1). The goal of the sedation was to have the patient awake only after strong stimulation (score 2). Propofol TCI was discontinued when the patient was judged able to be weaned from the ventilator, on the basis of a PaO<sub>2</sub>/FIO<sub>2</sub> > 160 mmHg, a stable haemodynamic status, and a body temperature > 36°C.

Patients were alternately allocated to two groups for pain therapy. In the Bolus group, TCI of sufentanil was discontinued on admission to the ICU and pain was controlled by the intravenous

Table 1

Brussels sedation score (14)

Score	Sedation
1	unrousable
1	arousable with strong stimulation
1	arousable with verbal stimulation
1	awake, quiet, co-operative
1	agitated

administration of repeated boluses of 1-2 mg morphine as required, to manage pain at rest, according to the usual analgesic routine used in the ICU department. In the TCI group, the sufentanil TCI used peroperatively was prolonged in the ICU (12). The targeted calculated plasma concentration of sufentanil was 0.08 to 0.1 ng/ml until tracheal extubation, titrated thereafter by 0.02 ng/ml step adjustments to maintain a verbal numerical pain score (VNS) < 3 during a deep inspiration. On the morning following extubation, sufentanil TCI was discontinued 2 hours before ICU discharge. In each group, propacetamol was infused at a dose of 2 g every 6 hours, starting immediately after ICU admission. The intensity of pain was assessed using a VNS (9) before and during 3 stimuli: extubation, nursing care in lateral position, and physiotherapy. The VNS had been explained to each patient by the anaesthetist, the day before surgery.

Arterial pressure, heart rate, central venous pressure and pulse oximetry were continuously recorded. Systolic arterial blood pressure (SAP) was obtained using a monitor (Siemens-SC9000, Erlangen, Germany) displaying data acquired every minute, by averaging data recorded during 8 min at rest, and during each stimulus. Arterial blood gases were measured 20 minutes (T1), 3 to 5 hours (T2), and 5 to 9 hours (T3) after tracheal extubation (analyser Radiometer, Copenhagen, Denmark).

In 8 patients in the Bolus group and in 7 patients in the TCI group, IS was performed using a volumetric spirometer (DHD Coach, Diemolding Healthcare Division, Canasotota, NY). The patient was instructed by the physiotherapist to use the IS as previously described (4) and preoperative performance was evaluated. The inspiratory capacity was expressed in relation to that obtained before surgery.

## Statistical analysis

Time course of SAP, PaCO<sub>2</sub>, calculated concentrations of sufentanil, and IS performance were analysed using an analysis of variance (ANOVA) for

Table 2

Patient characteristics and surgical procedures

	Bolus group	TCI group
Age (years)	63 ± 3	63 ± 4
Gender (M/F)	8/2	6/4
Duration of CPB (minutes)	102 ± 6	93 ± 5
Surgery : (numbers)		
CABG x 1	—	2
CABG x 2	2	1
CABG x 3	4	5
CABG x 1 and AVR	—	1
CABG x 1 and LVA	—	1
AVR	3	—
AC	1	—

CPB, cardiopulmonary bypass ; CABG, coronary artery bypass grafting ; AVR, aortic valve replacement ; AC, atrial communication ; LVA, left ventricular aneurysm.

repeated measurements. When the F ratio of the ANOVA reached the level of significance ( $p < 0.05$ ), pairwise comparisons were made using a modified t-test (29). Pain scores at rest and during stimulation were compared using a Wilcoxon signed rank test for within group comparisons between rest and stimulation, and a Mann-Whitney rank test for between groups comparisons at rest and during stimulation (26). Values at rest and during stimulation were the mean of triplicate measures recorded at rest and during the three stimuli for each patient. Data are presented as mean ± SEM.

## RESULTS

Of the 26 patients enrolled in the study, 6 patients were withdrawn (3 in each group) because of delayed extubation (3 with bleeding and 1 with significant metabolic acidosis), inappropriate TCI management (1) and administration of a non-steroidal anti-inflammatory agent (1). The clinical data and the surgical procedures are listed in Table 2.

As expected, the calculated propofol serum concentration was very low at the time of extubation. On admission to the ICU, the mean calculated concentrations of sufentanil were similar in both groups (Table 3), but decreased to lower levels in the Bolus group than in the TCI group (Table 3 and figure 1). Despite this difference, the mean time to extubation was similar in the two groups (Bolus :  $279 \pm 38$  min versus TCI :  $276 \pm 32$  min,  $p = \text{NS}$ ). The total amount of propofol infused during the

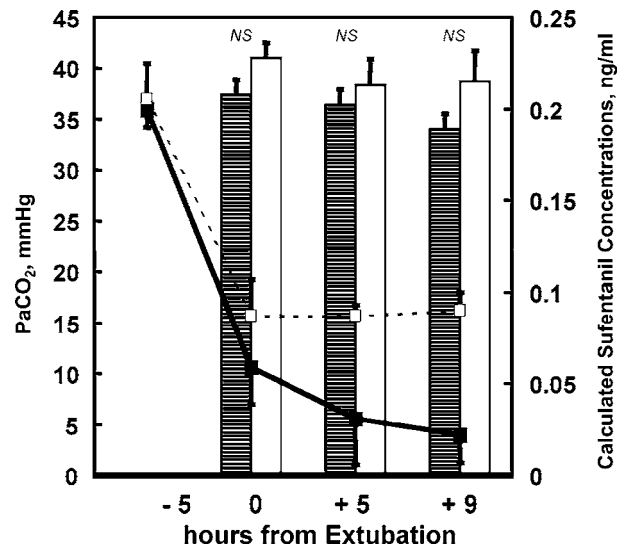


Fig. 1. — Time course evolution of PaCO<sub>2</sub> and calculated sufentanil concentrations in the Bolus group (solid bars and solid line) and in the TCI group (open bars and dashed line).

per- and postoperative periods was similar in both groups, but the total amount of sufentanil was higher in the TCI group than in the Bolus group. Interestingly, PaCO<sub>2</sub> did not change significantly and never exceeded 45 mmHg (Fig. 1). The total amount of morphine until ICU discharge was only  $3.8 \pm 1.1$  mg in the Bolus group (Table 3).

Analgesia was adequate at rest in both groups as indicated by low pain scores (VNS =  $1.6 \pm 0.4$  vs  $1.1 \pm 0.4$ ). Pain intensity increased significantly during the three stimuli (extubation, lateral position and physiotherapy) ( $p < 0.01$ ). Nevertheless, VNS were lower in the TCI group than in the Bolus group ( $3.8 \pm 0.5$  versus  $4.8 \pm 0.5$ ,  $p = 0.03$ ) (Fig. 2). Furthermore, 9 of 10 patients in the TCI group but only 4 of 10 in the Bolus group gave a VNS below 5 during the 3 stimuli (Fig. 2). There was no significant difference between the 2 groups in SaO<sub>2</sub> and respiratory rate values (Table 4).

IS performance was evaluated in only 15 patients because preoperative values could not be obtained in 2 patients in the bolus group and in 3 patients in the TCI group. Importantly, in the 15 patients who were evaluated, IS performances on the first postoperative day were higher in the TCI group than in the Bolus group ( $53 \pm 5\%$  versus  $35 \pm 5\%$  of preoperative values,  $p < 0.05$ ) (Fig. 3).

SAP did not change significantly during stimuli in the TCI group but increased in the Bolus group from  $128 \pm 3$  to  $133 \pm 4$  mmHg ( $p < 0.01$ ).

Table 3  
Sedative and analgesic agents

	Bolus group	TCI group	p
Calculated serum concentration :			
☐ propofol at extubation (µg/ml)	0.19 ± 0.02	0.26 ± 0.02	NS
☐ sufentanil at ICU admission (ng/ml)	0.21 ± 0.01	0.20 ± 0.02	NS
☐ sufentanil at extubation (ng/ml)	0.06 ± 0.02	0.09 ± 0.02	NS
☐ sufentanil 5 hours post extubation (ng/ml)	0.03 ± 0.03	0.09 ± 0.006	0.04
☐ sufentanil 9 hours post extubation (ng/ml)	0.02 ± 0.02	0.09 ± 0.01	0.01
Total doses (until ICU discharge) :			
☐ propofol (mg)	1250 ± 140	1500 ± 100	NS
☐ propacetamol (g)	6.8 ± 0.4	6.2 ± 0.6	NS
☐ sufentanil (µg)	195 ± 10	308 ± 31	0.001
☐ morphine (mg)	3.75 ± 1.1	—	

Table 4  
SpO2 and respiratory rate

	Bolus group	TCI group	p
SpO2			
✓ at rest	96.9 ± 0.4%	96.4 ± 0.4%	NS
✓ Stimuli	96.7 ± 0.4%	96.9 ± 0.9%	NS
RR			
✓ at rest	17.0 ± 0.4 b/min	18.9 ± 0.9 b/min	NS
✓ Stimuli	22.4 ± 1.3 b/min	22.1 ± 1.3 b/min	NS

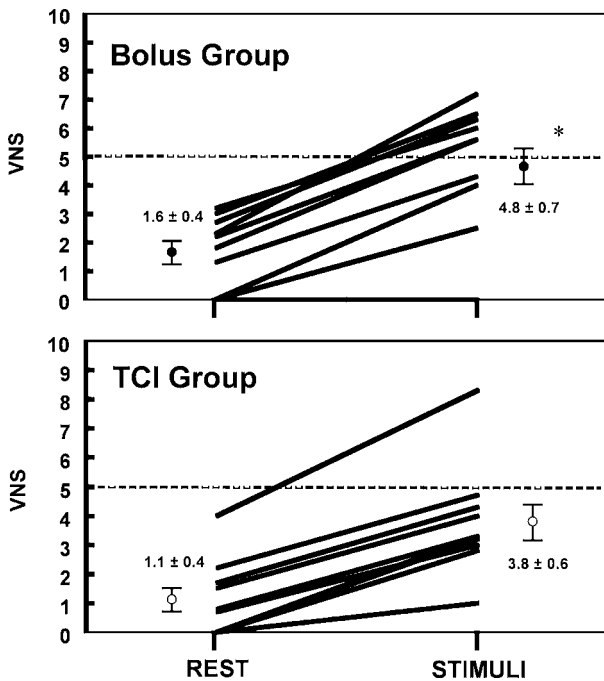


Fig. 2. — Verbal numerical pain scores (VNS) obtained at rest and during the 3 stimuli (extubation, nursing care in lateral position and physiotherapy) in the bolus group (upper graph) and in the TCI group (lower graph). Values at rest and during stimulation were the mean of triplicate measures recorded at rest and during stimuli for each patient. \*, p = 0.03, TCI group vs Bolus group during stimuli.

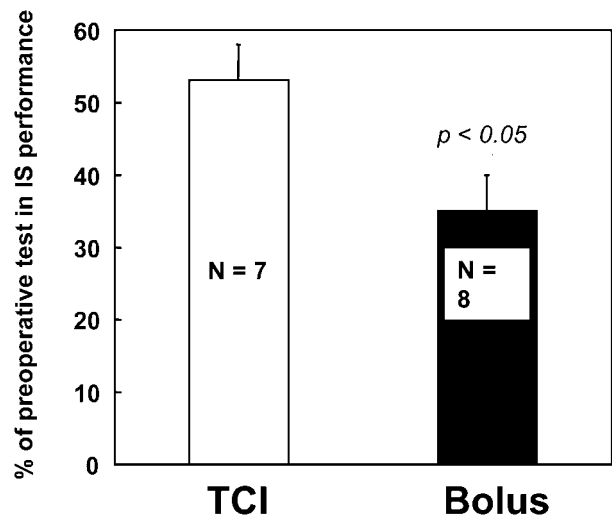


Fig. 3. — Inspiratory capacity estimated by incentive spirometry performance realised on POD1 and expressed as percentage of the pre-operative test.

DISCUSSION

The present study indicates that using TCI of sufentanil adapted to a pain score can achieve better analgesia during routine bedside procedures after cardiac surgery than on-demand boluses of morphine adapted to pain at rest. The use of TCI titrated with a pain score of sufentanil was also associated with higher postoperative pulmonary volumes during IS on the first postoperative day.

Early extubation after cardiac surgery can facilitate early mobilisation, reduce complications associated with mechanical ventilation (8, 15) and improve utilisation of ICU resources. As sedation is discontinued early after fast track cardiac surgery, adequate postoperative pain management is essential to improve comfort and limit the stress response (21, 11). Several methods have been proposed to improve postoperative analgesia after cardiac

surgery. Epidural analgesia used during general anaesthesia for coronary surgery can improve control of perioperative hypertension and tachycardia (27) and attenuate the reduction in lung volume after major surgery (25), but is not widely used in cardiac surgery due to the risk of epidural hematoma when the epidural is not inserted the day before surgery (22). PCA after cardiac surgery has resulted in inconclusive results, showing either a better control of postoperative pain as assessed by pain scores at rest (23, 5), or no difference as compared with nurse-controlled opiate administration (17, 18). The effects of PCA on postoperative pulmonary function are also inconsistent (23, 5). In fact, the adequate use of PCA depends on the degree of alertness of the patient, especially in the early postoperative period in elderly or confused patients. Actually, there is no real consensus concerning the optimal method of analgesia.

In the present study, we used the pharmacokinetic models published by MARSH *et al.* (16) for propofol and GEPTS *et al.* (12) for sufentanil because these models have demonstrated an acceptable accuracy and precision in healthy adults (20) and in cardiac surgery patients (3, 2). Fortunately, the TCI system used was mobile and can be easily transferred from the operating room to the ICU, taking into account the amounts of propofol and sufentanil administered during anaesthesia and in the postoperative period, thus maintaining a continuum between the operating room and the ICU.

The routine morphine administration 'on demand' was associated with a VNS at rest of  $1.6 \pm 0.4$  which implies that patients were comfortable, at rest from extubation to discharge of ICU. An anaesthetic technique including 3 µg/kg Sufentanil per-operatively followed by IV morphine 'on demand' of around 4 mg is then able to provide comfort at rest. The sufentanil TCI allows to closely adjust analgesic agents to an effort pain score (deep inspiration). As a consequence, doses of analgesics were higher, with a lower VNS during extubation, physiotherapy or nursing procedures than in bolus group but with similar pain scores at rest. Although pain scores at rest were similar in both groups of patients, pain during routine bedside procedures (extubation, nursing care in lateral position, physiotherapy) was significantly reduced when the peroperative TCI of sufentanil was continued and adapted to an effort pain score. In the current practice of postoperative pain management, the administration of analgesics is too rarely adapted according to pain score obtained during a deep

inspiration. Our data emphasise the advantage of adapting analgesia to a painful stimulus, i.e., deep inspiration. Such a method can limit the degree of pain felt during events such as nursing care or physiotherapy, and can promote spontaneous deep inspiration.

We did not adjust morphine administration to an effort pain score because of its slow onset of action; the peak analgesia effect of morphine takes at least 20 min, whereas it is only 5 min for sufentanil.

Furthermore, the use of such a postoperative TCI of an opioid adapted to maintain theoretical analgesic concentrations did not delay tracheal extubation and allowed better preservation of the inspiratory capacity on the first postoperative day, with no respiratory depression.

Finally, during the periods of extubation and of nursing care in the lateral position, the systolic arterial pressure increased only in the Bolus group, suggesting better analgesia in the TCI group. This observation could have some clinical implications because an increase in arterial pressure during weaning from mechanical ventilation after CABG may be associated with an increased risk of postoperative bleeding and myocardial lactate production (13).

This study has its limitations. Inherent to the study design, different analgesic agents were used in the groups and the dosage of analgesics was adapted to a painful stimulus in only one group. The study could not be blinded and thus remains prone to bias. To evaluate the impact of this regimen on outcome and morbidity, much larger patient populations would be necessary.

In conclusion, when compared to routine IV boluses of morphine administered according to pain at rest, TCI of sufentanil titrated following pain assessed during deep inspiration improve pain relief and IS performance after cardiac surgery without delaying tracheal extubation or increasing PaCO<sub>2</sub> after tracheal extubation. This technique also preserves haemodynamic stability during extubation and during nursing care. We cannot separate if this adequate analgesia is mainly due to the TCI system itself or to the adjustment of analgesic agents to an effort pain score or to the combination of two.

## References

1. Barnas G. M., Watson R. J., Green M. D., Sequeira A. J., Gilbert T. B., Kent J., Villamater E., *Lung and chest wall*

- mechanical properties before and after cardiac surgery with cardiopulmonary bypass*, J. APPL. PHYSIOL., **76**, 166-175, 1994.
2. Barvais L., Rausin I., Glen J. B., Hunter S. C., D'Hulster D., Cantraine F., d'Hollander A., *Administration of propofol by target-controlled infusion in patients undergoing coronary artery surgery*, J. CARDIOTHORAC. VASC. ANESTH., **10**, 877-883, 1996.
  3. Barvais L., Heitz D., Schmartz D., Coussaert E., Cantraine F., d'Hollander A., *Pharmacokinetic model-driven infusion of sufentanil and midazolam during cardiac surgery: assessment of the prospective predictive accuracy and the quality of anesthesia*, J. CARDIOTHORAC. VASC. ANESTH., **14**, 402-408, 2000.
  4. Bastin R., Moraine J. J., Bardocsky G., Kahn R. J., Mélot C., *Incentive spirometry performance. A reliable indicator of pulmonary function in the early postoperative period after lobectomy ?*, CHEST, **111**, 559-563, 1997.
  5. Boldt J., Thaler E., Lehmann A., Papsdorf M., Isgro F., *Pain management in cardiac surgery patients: comparison between standard therapy and patient controlled analgesia regimen*, J. CARDIOTHORAC. VASC. ANESTH., **12**, 654-8, 1998.
  6. Cantraine F., Coussaert E., *The first object oriented monitor for intravenous anesthesia*, J. CLIN. MONIT. COMPUT., **16**, 3-10, 2000.
  7. Checketts M. R., Gilhooly C. J., Kenny G. N., *Patient-maintained analgesia with target-controlled alfentanil infusion after cardiac surgery: a comparison with morphine PCA*, BR. J. ANAESTH., **80**, 748-751, 1998.
  8. Cheng D. C., Karski J., Peniston C., Asokumar B., Raveendran G., Caroll J., Nierenberg H., Roger S., Mickle D., Tong J., Zelovitsky I., David T., Sandler A., *Morbidity outcome in early versus conventional tracheal extubation after coronary artery bypass grafting: a prospective randomized controlled trial*, J. THORAC. CARDIOVASC. SURG., **112**, 755-64, 1996.
  9. Deloach L. J., Higgins M. S., Caplan A. B., Stiff J. L., *The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale*, ANESTH. ANALG., **86**, 102-106, 1998.
  10. Detriche O., Berré J., Massaut J., Vincent J. L., *The Brussels sedation scale: use of a simple clinical sedation scale can avoid excessive sedation in patients undergoing mechanical ventilation in the intensive care unit*, BR. J. ANAESTH., **83**, 698-701, 1999.
  11. Flacke J. W., Bloor B. C., Flacke W. E., *Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery*, ANESTHESIOLOGY, **67**, 11-19, 1987.
  12. Gepts E., Shafer S. L., Camu F., Stanski D. R., Woestenborghs R., Van Peer A., Heykants J. J., *Linearity of pharmacokinetics and model estimation of sufentanil*, ANESTHESIOLOGY, **83**, 1194-1204, 1995.
  13. Hall R. I., *Anaesthesia for coronary artery surgery - a plea for a goal-directed approach*, CAN. J. ANAESTH., **40**, 1178-1194, 1993.
  14. Johnson D., Hurst T., Thomson D., Mycyk T., Burbridge B., To T., Mayers I., *Respiratory function after cardiac surgery*, J. CARDIOTHORAC. VASC. ANESTHESIA, **10**, 571-577, 1996.
  15. Johnson D., Thomson D., Mycyk T., Burbridge B., To T., Mayers I., *Respiratory outcomes with early extubation after coronary artery bypass surgery*, J. CARDIOTHORAC. VASC. ANESTH., **11**, 474-480, 1997.
  16. Marsh B., White M., Morton N., Kenny G. N., *Pharmacokinetic model driven infusion of propofol in children*, BR. J. ANAESTH., **67**, 41-48, 1991.
  17. Munro A. J., Long G. T., Sleight J. W., *Nurse-administered subcutaneous morphine is a satisfactory alternative to intravenous patient-controlled analgesia morphine after cardiac surgery*, ANESTH. ANALG., **87**, 11-15, 1998.
  18. Myles P. S., Buckland M. R., Cannon G. B., Bujor M. A., Langley M., Breaden A., Salamonsen R. F., Davis B. B., *Comparison of patient-controlled analgesia and nurse-controlled infusion analgesia after cardiac surgery*, ANAESTH. INTENSIVE CARE, **22**, 672-678, 1994.
  19. Paiement B., Boulanger M., Jones C. W., Roy M., *Intubation and other experiences in cardiac surgery: the consumer's views*, CAN. ANAESTH. SOC. J., **26**, 173-180, 1979.
  20. Pandin P. C., Cantraine F., Ewalenko P., Deneu S. C., Coussaert E., d'Hollander A. A., *Predictive accuracy of target-controlled propofol and sufentanil coinfusion in long-lasting surgery*, ANESTHESIOLOGY, **93**, 653-661, 2000.
  21. Rawal N., *Analgesia technique and postoperative morbidity*, EUR. J. ANAESTHESIOLOGY, **12** (suppl 10): 47-52, 1995.
  22. Sanchez R., Nygard E., *Epidural anesthesia in cardiac surgery: is there increased risk ?*, J. CARDIOTHORAC. VASC. ANESTH., **12**, 170-173, 1998.
  23. Searle N. R., Roy M., Bergeron G., Perrault J., Roof J., Heermans C., Courtemanche M., Demers C., Cartier R., *Hydromorphone patient-controlled analgesia (PCA) after coronary artery bypass surgery*, CAN. J. ANAESTH., **41**, 198-205, 1994.
  24. Shenkman Z., Shir Y., Weiss Y. G., Bleiberg B., Gross D., *The effects of cardiac surgery on early and late pulmonary function*, ACTA ANAESTHESIOLOGY SCAND., **41**, 1193-1199, 1997.
  25. Shulman M., Sandler A. N., Bradley J. W., Young P. S., Brebner J., *Postthoracotomy pain and pulmonary function following epidural and systemic morphine*, ANESTHESIOLOGY, **61**, 569-575, 1984.
  26. Siegel S., Castellan N. J. Jr., *Non parametric statistics for the behavioral sciences*, New York: McGraw-Hill, 1988.
  27. Stenseth R., Bjella L., Bradley J. W., Young P. S., Brebner J., *Thoracic epidural analgesia in aortocoronary bypass surgery. I: Haemodynamic effects*, ACTA ANAESTHESIOLOGY SCAND., **38**, 826-833, 1994.
  28. van den Nieuwenhuyzen M. C., Engbers F. H., Burm A. G., Lemmens H. J., Vletter A. A., Van Kleef J. W., Bovill J. G., *Computer-controlled infusion of alfentanil for postoperative analgesia. A pharmacokinetic and pharmacodynamic evaluation*, ANESTHESIOLOGY, **79**, 481-492, 1993.
  29. Winer B. J., *Statistical Principles in Experimental Design*, Second edition. New York: McGraw-Hill, 1971.