

CISATRACURIUM IN CARDIAC SURGERY

- Continuous Infusion vs. Bolus Administration -

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Abstract

The aim of this study was the comparison of infusion vs. intermittent bolus administration of cisatracurium (CA) following cardiac surgery with regard to total intraoperative dose and time of recovery from neuromuscular blockade.

From June 2005 to April 2006 sixty ASA II-III patients who were undergoing coronary bypass graft and valve replacement surgery, were equally divided and randomized to receive either intermittent bolus (Group A, n = 30) or continuous infusion (Group B, n = 30) of CA in Madani Heart Center in the Tabriz (Iran). Total intraoperative dose of CA and time to TOF ratio = 0.8 after operation were measured. Anesthesia technique in two groups was the same. All of the patients underwent cardiopulmonary bypass. Intensity of neuromuscular blockade maintained on one train-of-four (TOF) twitch response of adductor pollicis during operation.

Mean received dose of CA was 32.8 ± 20.6 μ /kg/hr in Group A and 89.7 ± 39.4 μ /kg/hr in Group B (p = 0.003). Total intraoperative dose of CA was 23.6 ± 4.9 mg in Group A and 39.2 ± 10.1 mg in

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Group B ($p = 0.001$). Spontaneous recovery from neuromuscular blockade in ICU (TOF ratio = 0.8) was reached in 43.8 ± 9.2 min in Group A, and 64.2 ± 15.1 min in Group B ($p = 0.0001$). Intubation time in ICU was not significantly different (Group A = 8.3 ± 5.1 hrs vs. Group B = 10.2 ± 6.2 hrs, $p = 0.256$).

These results support the intermittent bolus administration of cisatracurium in cardiac surgery following cardiopulmonary bypass.

Keywords: Cisatracurium, Continuous infusion, Intermittent administration, Cardiac surgery, Cardiopulmonary bypass.

Introduction

In comparison with intermittent bolus administration, the continuous infusion of intravenous anesthetic drugs provides greater control of anesthetic depth, thus ensuring better hemodynamic control, lower total drug doses, and more rapid return to an awake state¹. This is applicable for hypnotic and opioid drugs.

For muscle relaxants, however, reports in literature are controversial. For example Jellish WS et al.² (2000) found significant differences between continuous infusion and intermittent administration of cisatracurium, and rocuronium; and the recovery from neuromuscular blockade after infusion was slower than with intermittent administration². Whereas Cammu G et al.³ (2005) examined large bolus dose of cisatracurium vs. continuous infusion during cardiac surgery and concluded that consumption of the drug was greater in bolus administration³. In another study on patients undergoing intra-abdominal surgery, Secuk M et al.⁴ (2005) did not find any significant difference in recovery time from effects of cisatracurium between these two methods of administration⁴. It is generally agreed that the administration of muscle relaxants favors bolus rather than infusion technic in the ICU setting¹ though some studies use the infusion technic in the ICU⁵. No specific recommendation exists regarding the use of these drugs in prolonged operation such as cardiac surgery either as intermittent bolus or

continuous infusion.

The aim of the present study was to compare total intraoperative dose used and postoperative recovery time of cisatracurium in patients undergoing cardiopulmonary bypass (CPB), following the use of either intermittent bolus or continuous infusion of cisatracurium.

Methods and Materials

After procuring approval of the Committee on Human Rights in Research, and written patient informed consent, sixty patients (ASA II, III) to undergo coronary bypass graft and valve replacement surgery with cardiopulmonary bypass, were enrolled in the study. The study was done in Madani Heart Center in Tabriz in Iran and extended between June 2005 – April 2006.

Patients were equally divided and assigned randomly to receive cisatracurium either as intermittent bolus (Group A, n = 30) or continuous infusion (Group B, n = 30). The method of randomization was the “Randomly Permuted Blocks” performed by on-line software available in URL: <http://www.Randomization.com>.

Standard patient monitoring included: electrocardiography, invasive blood pressure, central venous pressure, pulse-oxymetry and temperature probe (nasopharyngeal). For assessing the intensity of neuromuscular blockade the ulnar nerve was stimulated every 15 min using train-of-four (TOF) supramaximal stimulation (50 mA), by the nerve stimulator and acceleromyograph (Organon TOF – watch SX) and recording the mechanical twitch response at the adductor pollicis muscle.

Induction of general anesthesia in all patients was done by intravenous midazolam 0.15 mg/kg, sufentanil 1.5 µg/kg, and cisatracurium 0.2 mg/kg (tracheal intubating dose). Maintenance of anesthesia was established with continuous infusion of midazolam 1.0 µg/kg/min and sufentanil 0.5 µg/kg/h.

Patients in Group A received intermittent doses of 0.02 mg/kg cisatracurium when needed (at least in 15 min intervals) to maintain one

TOF twitch response. Patients in Group B received 2 $\mu\text{g}/\text{kg}/\text{min}$ cisatracurium as continuous infusion. The intensity of neuromuscular blockade was monitored every 15 min to maintain one twitch response of TOF. When the neuromuscular blockade was more intense than one TOF twitch response (no response), the rate of cisatracurium infusion was reduced 30%, and when the blockade level reached two TOF twitch responses, rate of infusion increased 30%. Cisatracurium administration was stopped at sternal closure.

Following surgery, spontaneous recovery from neuromuscular blockade was monitored every 5 min until appearance of all TOF twitch responses and TOF ratio (T4: T1 ratio) reached to 0.8 (as a determinant of sufficient recovery). Patient's trachea was extubated after patient was fully awake and met the standard criteria of extubation (respiratory and hemodynamic stability, no acid-base and electrolyte abnormality, and no bleeding). During CPB with hypothermia (29-30°C) monitoring of neuromuscular blockade was stopped until rewarming to peripheral (thumb) temperature to 35°C.

Data were processed by the SPSS v. 13.0 statistical package. Continuous variables were expressed as mean \pm SD. Comparisons between the two groups of patients was performed by using two-sided independent samples *t*-test for continuous variables and the Chi-square test (or Fisher's exact test when appropriate) for discrete variables. Repeated measures ANOVA was done to assess the variations in TOF twitch response numbers and TOF ratios with time, in ICU. Statistical significance was inferred at $P =$ or <0.05 .

Results

Patients' demographic data, the preoperative medication that may have some impact on neuromuscular transmission and blockade, and the intraoperative variables, were similar between the two groups (Table 1).

Table 1
Patients' demographic characteristics, preoperative and intraoperative data

| | Intermittent bolus (Group A) (n = 30) | Infusion (Group B) (n = 30) | P |
|------------------------------|---------------------------------------------|-----------------------------------|-------|
| Age (yr) | 52 ± 10 | 53 ± 12 | 0.769 |
| Sex (M/F) | 22/8 | 22/8 | 1.000 |
| Weight (kg) | 71 ± 12 | 73 ± 12 | 0.558 |
| ASA physical status (II/III) | 12/15 | 13/16 | 1.000 |
| Operation (CABG/Valve) | 24/6 | 22/8 | 0.517 |
| Preoperative medications: | | | |
| Beta-blocker | 22 | 20 | 0.778 |
| Calcium channel blocker | 11 | 7 | 0.398 |
| ACEI | 12 | 7 | 0.349 |
| Operation time (min) | 293 ± 60 | 270 ± 69 | 0.181 |
| CPB time (min) | 108 ± 50 | 110 ± 37 | 0.880 |

Values are shown as number of patients or mean ± SD.

CABG = coronary artery bypass graft surgery; CPB = cardiopulmonary bypass;

ACEI = angiotensin converting enzyme inhibitor.

Mean intraoperative dose of cisatracurium in intermittent bolus (Group A) was 32.8 ± 20.6 µg/kg/hr, whereas in Group B mean infusion was 89.7 ± 39.4 µg/kg/hr ($P = 0.003$). Also total intraoperative dose in Group A was significantly lower than Group B (Table 2).

Table 2
Dose requirements, intensity of neuromuscular blockade and recovery
time of cisatracurium in Group A, B.

| | Intermittent bolus (Group A) (n = 30) | Infusion (Group B) (n = 30) | P |
|-------------------------------------|---------------------------------------------|-----------------------------------|---------|
| Mean intraoperative dose (µg/kg/hr) | 32.8 ± 20.6 | 89.7 ± 39.4 | 0.003 |
| Total intraoperative dose (mg) | 23.6 ± 4.9 | 39.2 ± 10.1 | <0.001 |
| Mean TOF twitch response* | 1.1 ± 0.3 | 0.8 ± 0.6 | 0.272 |
| Time to TOF ratio 0.8 in ICU (min) | 43.8 ± 9.2 | 64.2 ± 15.1 | <0.0001 |
| Intubation time in ICU (hrs) | 10.2 ± 6.2 | 8.3 ± 5.1 | 0.256 |

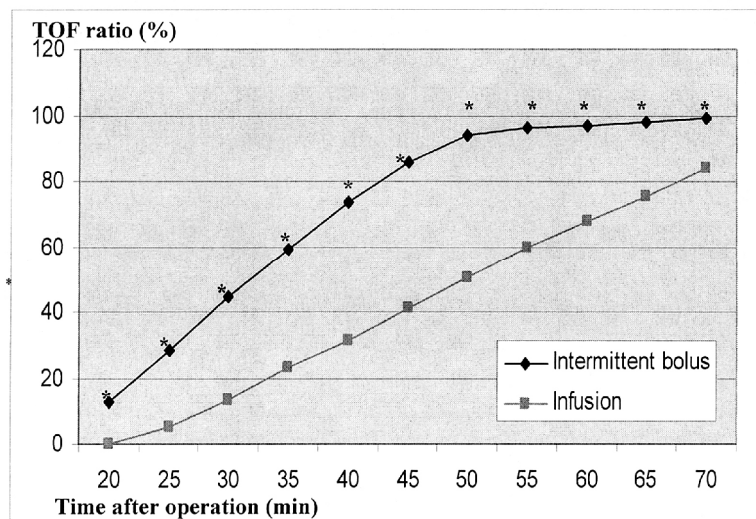
Values are shown as mean ± SD.

TOF = train-of-four.

* During operation.

In the postoperative period, patients in Group A had shorter recovery time to TOF ratio 0.8 (43.8 ± 9.2 min) than those in Group B (64.2 ± 15.1 min). Recovery characteristics of cisatracurium in ICU are shown in Figures 1 (number of TOF twitch responses and Fig. 2 percentage of TOF ratio). Patients in Group A had statistically significant – lower neuromuscular blockade intensity even in 5 min after arriving in ICU, than Group B (Fig. 1).

Fig. 1
Number of TOF twitch responses in ICU in the two groups
(Intermittent Bolus & Infusion).

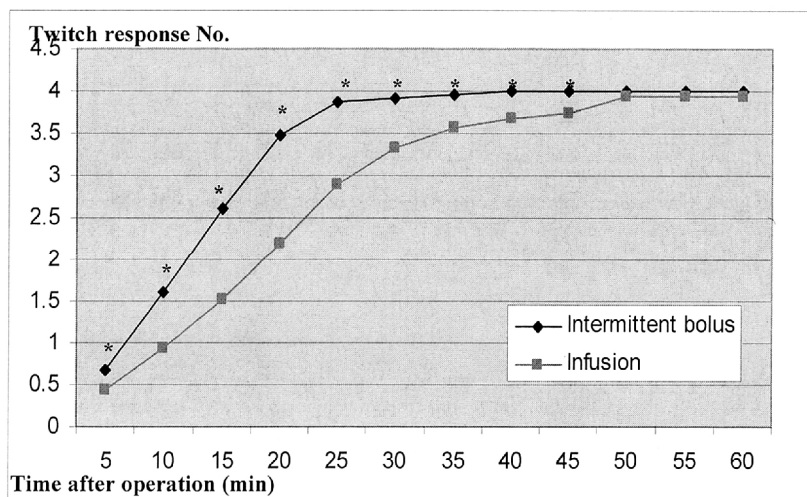


TOF = Train-of-four

* P < 0.05 in comparison between the two groups.

Repeated measures ANOVA test results in Group A for TOF twitch response count in ICU was: F (11,319) = 194.0, p = 0.0001; and for TOF ratio was: F (10,290) = 103.7, p = 0.0001. In Group B for TOF twitch response count in ICU was: F (11,264) = 249.0, p = 0.0001; and for TOF ratio was: F (10,240) = 252.8, p = 0.0001. Despite of the difference in recovery time of cisatracurium, the patients in the two groups had similar intubation time in ICU (Table 2).

Fig. 2
TOF ratio of patient in two groups in ICU
(Intermittent Bolus & Infusion)



TOF = Train-of-four

* P < 0.05 in comparison between the two groups.

Discussion

Cisatracurium has been shown to be primarily cleared from the body (77%) by Hoffman degradation with a 16% renal excretion². Although a large intragroup variability was noted in recovery time of cisatracurium under differing anesthetic conditions^{6,7}, cisatracurium may be the muscle relaxant of choice for prolonged procedures because its recovery is least affected by length of infusion^{2,7}.

Recovery from neuromuscular blockade after a single dose is primarily attributed to redistribution. Long infusions will reduce the ability to redistribute drug because the peripheral compartment will become saturated over time, making recovery totally dependent on elimination. Repeated bolus dosing, rather than infusion, produces similar results⁸. Reported recovery characteristics of cisatracurium infusion was variable in most previous studies in different anesthetic and surgical settings^{2,5,9,10}. For example, Jellish WS et al. noted a prolonged recovery

index (time required for the first twitch (T1) of TOF to recovery from 25% to 75% of baseline) after the infusion of cisatracurium compared with bolus dosing under TIVA anesthesia². This is in contrast to the results obtained by Belmont et al. who demonstrate no difference in recovery index between bolus or continuous infusion of cisatracurium¹⁰.

In our study we noted spontaneous sufficient recovery of cisatracurium (defined as mean time interval from 25% T1 recovery to a T4:T1 = 0.8)¹¹ in bolus dosing group significantly shorter than infusion group (43.8 ± 9.2 vs. 64.2 ± 15.1 min). Recovery times in our study was relatively longer than some other studies^{11,12}. For example, Phringer et al. noted 31.7 ± 10 min to TOF ratio 0.8 in elderly patients¹¹, and Jellish WS et al. showed 33.5 min to TOF ration 0.75 in bolus and 38 min in infusion of cisatracurium in prolonged procedures (more than 300 min), but Carroll et al.¹³ report spontaneous recovery of 74 min to TOF ratio 0.8 in one study and 65 min in another study¹⁴. These differences may be somewhat related to hypothermic CPB in our patients; because Hoffman's degradation of cisatracurium is temperature dependent and hypothermic CPB may reduce the required dose of cisatracurium up to 50%¹⁵. We adjusted the dosing of cisatracurium by monitoring with nerve stimulator to maintain one twitch response after CPB, and the patients received this drug no more than needed, and no accumulation occurred to prolong recovery time in ICU.

Although in the intermittent bolus method less intensity of neuromuscular blockade was observed, no patient movement or respiratory changes during operation were noted. In addition significantly lower mean intraoperative dose (as $\mu\text{g}/\text{kg}/\text{h}$) and total intraoperative dose (as mg) was noted in comparison to the continuous infusion method.

We conclude that, choosing the intermittent bolus method of administration and maintaining less intensity of neuromuscular blockade, is not problematic for patient or surgeon. This method reduces the mean and total dosage of the drug used with faster postoperative recovery. Cammu G et al.³ used large bolus dose of cisatracurium ($8 \times \text{ED95}$) and added doses when patients moved during operation, and found out that bolus administration method uses more drug than continuous infusion.

Selcuk M et al.⁴ showed no significant difference in recovery time between the two administration methods of cisatracurium, but the study consisted of only 20 and 18 patients in each groups (low study power).

The mechanical ventilation time of patients in the ICU was not different between the two study groups. Time of 8-10 hours for tracheal extubation is similar to study of Ouattara et al. on fast-track cardiac surgery, who showed that 83% of patients' trachea were extubated in 8 hour after stopping of cisatracurium infusion¹⁶. Our results on recovery and mechanical ventilation times, confirm previous reports in the suitability of cisatracurium for operations with CPB¹⁷, without any cumulative effect of drug¹⁸.

In conclusion, this study support the intermittent bolus administration of cisatracurium during cardiac surgery (with CPB) with respect to lowering intraoperative dose and shorter postoperative recovery time.

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