Original Article

Comparison of continuous infusion and intermittent bolus administration of Cisatracurium in cardiac surgery: a randomized clinical trial

Moosa Mirinejad, Ali Reza Yaghoubi, Rasoul Azarfarin, Azin Alizadeh Asl

From Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Correspondence: Dr. Moosa Mirinejad MD, Department of Anesthesiology, Madani Heart Center, Daneshgah Street, Tabriz, Iran PO Box: 51665 - 404
E-Mail: mmmirinejad@yahoo.com

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Abstract

Objective: The aim of this study was to compare continuous infusion and intermittent bolus administration of cisatracurium (CA) with respect to total intraoperative dose and time of recovery from neuromuscular blockade after cardiac surgery.

Methods: From June 2005 to April 2006 sixty patients who undergoing coronary bypass graft and valve replacement surgery were randomized to receive either intermittent bolus (Group A, n=30) or continuous infusion (Group B, n=30) of CA in Madni heart center in Tabriz, Iran. Total intraoperative dose of CA and time to train–of–four (TOF) ratio=0.8 after operation were measured. Anesthesia technique in two groups was the same. Intensity of neuromuscular blockade maintained on one TOF twitch response of adductor pollicis during operation.

Results: Mean received dose of CA was 32.8±20.6 µ/kg/hr in Group A and 89.7±39.4µ/kg/hr in Group B (p=0.003). Total intraoperative dose of CA was 23.6±4.9mg in Group A and 39.2±10.1mg in 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±15.1min in Group B (p=0.0001). Intubation time in ICU was not significantly different (Group A=8.3±5.1hrs vs. Group B=10.2±6.2hrs, p=0.256).

Conclusions: Intermittent bolus administration of cisatracurium in cardiac surgery with cardiopulmonary bypass used lower intraoperative dose and gave shorter
postoperative recovery time as compared to continuous infusion. (Rawal Med J 2007;32:63-66)

**Key Words:** 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 state. Recovery from neuromuscular blockade after infusion was found slower than intermittent administration although consumption of the drug was reported to be greater in bolus administration. In other study on patients undergoing intra-abdominal surgery no significant difference in recovery time from effects of Cisatracurium between these two administration methods was found. In general, administration of muscle relaxants favors bolus rather than infusion in the ICU setting but in some studies these drugs used as infusion in ICU. However, recommendations exist about using these drugs in prolonged operation such as cardiac surgery either as intermittent bolus or continuous infusion. The aim of this study was comparison of total intraoperative dose and postoperative recovery time of cisatracurium after either intermittent bolus or continuous infusion in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

**METHODS**

After obtaining approval from our committee on human rights in research, and written informed consent from each patient, sixty patients with American Society of Anesthesiology (ASA) physical status II–III, undergoing CABG and valve replacement surgery with cardiopulmonary bypass, entered into the study. The study was done from June 2005 to April 2006 in Madani heart center in Tabriz, Iran. Patients were 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 “Randomly Permutated Blocks” that performed by on-line software available in URL: http://WWW.Randomization.com. All of the patients were blinded for the method of the drug administration (single blinded trial). Standard patients 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 15min using train-of-four (TOF) supramaximal stimulation (50mA), 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 0.15mg/kg, sufentanil 1.5µg/kg, and cisatracurium 0.2mg/kg (tracheal intubating dose). Maintenance of anesthesia was established with continuous infusion of midazolam 1.0µg/kg/min and sufentanil 0.5µg/kg/h. Patients in Group A received intermittent doses of 0.02mg/kg cisatracurium when needed (at least in 15min intervals) to maintain one TOF twitch response. Patients in Group B received 2µ/kg/min Cisatracurium as continuous infusion, and intensity of neuromuscular blockade was monitored every 15min for maintain one twitch response of TOF. If the neuromuscular blockade was more intense than one TOF twitch response (no response), the rate of cisatracurium infusion reduced 30%, and when blockade level reach two TOF twitch responses, rate of infusion increased 30%. Cisatracurium administration was stopped at sternal closure.

Table1. Patients demographic characteristics, and preoperative and intraoperative data.

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

CABG=coronary artery bypass graft surgery; CPB= cardiopulmonary bypass; ACEI= angiotensin converting enzyme inhibitor

After surgery, spontaneous recovery from neuromuscular blockade monitored every 5 min until appearance of all TOF twitch responses and TOF ratio (T4:T1 ratio) reach to
0.8 (as a determinant of sufficient recovery). Patient’s trachea was extubated after fully awaking and meeting standard criteria of extubation. During CPB with hypothermia monitoring of neuromuscular blockade was stopped until re-warming to peripheral (thumb) temperature.

Data were processed by the SPSS v.13.0 statistical package. Continuous variables were expressed as mean ±SD. Comparisons between patient of two groups 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=<0.05.

RESULTS
Patients demographic data, and preoperative medication that may be have some effects on neuromuscular transmission and blockade, and intraoperative variables were similar between the two groups (table 1). Mean intraoperative dose of cisatracurium in intermittent bolus (Group A) was 32.8 ±20.6µg/kg/hr, whereas in Group B mean infusion was 89.7±39.4µg/kg/hr (P=0.003). Also total intraoperative dose in Group A was significantly lower than Group B (Table 2).

<table>
<thead>
<tr>
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<th>Infusion (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean intraoperative dose (µg/kg/hr)</td>
<td>32.8±20.6</td>
<td>89.7±39.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Total intraoperative dose (mg)</td>
<td>23.6±4.9</td>
<td>39.2±10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean TOF twitch response*</td>
<td>1.1±0.3</td>
<td>0.8±0.6</td>
<td>0.272</td>
</tr>
<tr>
<td>Time to TOF ratio 0.8 in ICU (min)</td>
<td>43.8±9.2</td>
<td>64.2±15.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intubation time in ICU (hrs)</td>
<td>10.2±6.2</td>
<td>8.3±5.1</td>
<td>0.256</td>
</tr>
</tbody>
</table>

TOF=train–of–four.*During operation

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

**Figure 1. Number of TOF twitch responses in ICU in the two groups**

![Graph showing TOF twitch responses in ICU](image)

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. This test results 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 difference in recovery time of cisatracurium, the patients in the two groups had similar intubation time in ICU (Table 2).

**DISCUSSION**

Cisatracurium has been shown to be primarily cleared from the body (77%) by Hoffman degradation with a 16% renal excretion. 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. Repeated bolus dosing, rather than infusion have produced similar results. Reported recovery characteristics of cisatracurium infusion was variable in most previous studies in
different anesthetic and surgical setting.\textsuperscript{2,5,9,10} Prolonged recovery index after the infusion of cisatracurium compared with bolus dosing under TIVA anesthesia have been noted,\textsuperscript{2} while no difference in recovery index between bolus or continuous infusion of cisatracurium have been reported.\textsuperscript{10}

Figure 2. TOF ratio of patients in two groups in ICU.

![Figure 2](image)

TOF=Train-of-four\textsuperscript{*} P<0.05 in comparison between the two groups.

In our study, we noted spontaneous sufficient recovery of cisatracurium 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.\textsuperscript{11,12} Carrol et al.\textsuperscript{13} reported spontaneous recovery of 74 min to TOF ratio 0.8 in one study and 65 min in another study.\textsuperscript{14} These differences may be somewhat related to hypothermic CPB in our patients; because Haffman degradation of cisatracurium is temperature dependent and hypothermic CPB reduce the required dose of cisatracurium up to 50%.\textsuperscript{15} Although in the intermittent bolus method we observed less intensity of neuromuscular blockade through operation, we did not encounter any patient movement or respiration during procedure.

Mechanical ventilation time of our patients in 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.\textsuperscript{16} Our results on recovery and mechanical ventilation times, emphasize the previous reports on suitability of cisatracurium use with CPB\textsuperscript{17} without any cumulative effect of drug.\textsuperscript{18} In conclusion, this study results support the intermittent bolus administration of Cisatracurium during cardiac surgery with CPB with respect to lower intraoperative dose and shorter postoperative recovery time.

REFERENCES


