

The Effect of Intraoperative Alkali Treatment on Recovery from Atracurium-Induced Neuromuscular Blockade in Renal Transplantation: A Randomized Trial

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Abstract

Background: Intraoperative care and anesthesia method in patients undergoing allograft renal transplantation surgery are very necessary. Acid-base imbalance can alter neuromuscular blockade and recovery time.

Objectives: The aim of the present study was to investigate the effect of acid-base balance on atracurium blockade in renal transplantation.

Methods: In this randomized-controlled trial, 31 end-stage renal disease (ESRD) patients undergoing renal transplantation were randomly assigned into two equal groups. The case group received intravenous sodium bicarbonate based on base excess in the first ABG sample, while the control group received sterile water for injection during the interval between anesthesia and beginning of surgery. Arterial blood gas (ABG) sample was drawn first prior to surgery and again at declamping time. Train-of-four (TOF) was measured before anesthesia and repeatedly after declamping time until acceptable recovery (TOF 3 of 4). The time of achieving TOF 3 was recorded and compared between the groups.

Results: There was no significant difference in blood pH between the groups in the first evaluation ($P = 0.649$). The pH and base excess (BE) in the case group significantly increased after the intervention. There was a significant decrease in after-surgery measurement of pH in the control group ($P = 0.011$). The mean time to achieve TOF = 3 was 23.75 ± 5.32 and 41.80 ± 5.2 minutes after declamping in the case and control groups, respectively. Patients in the sodium bicarbonate group achieved TOF = 3 significantly faster than the control group.

Conclusions: Based on our results, intraoperative alkali and acid-base imbalance treatment can reduce neuromuscular blockade and recovery time, and it can be regarded as a potential casual factor to enhance transplantation outcome.

Keywords: ESRD, Kidney Transplantation, Acid-Base Imbalance, Sodium Bicarbonate

1. Background

Renal transplantation is improving as an acceptable treatment for end-stage renal disease (ESRD). Metabolic acidosis is a relatively common complication in patients with pre-ESRD or ESRD, as well as in those with renal replacement therapy as a result of the inability to produce sodium bicarbonate and impaired kidney buffering system (1-3). Chronic metabolic acidosis is associated with morbidity and mortality in chronic kidney disease (CKD) and transplantation practice (2, 4). Recently, the body of evidence regarding the efficacy of alkali treatment in these patients is growing (5-8).

Intraoperative care and anesthesia method in patients undergoing allograft renal transplantation surgery are very important. Transplanted kidney viability is associated with hemodynamic stability and early, enhanced vascular perfusion (9-11). Some studies have been carried out to as-

sess different anesthesia methods and medication and also find out the best of them to improve transplant outcome (12, 13); however, there is still limited information.

Hughes (14) in his animal study indicated that acid-base imbalance can alter neuromuscular blockade duration. In metabolic or respiratory acidosis (blood pH < 7.35), the duration of blockade increased and recovery from anesthesia was prolonged, which could affect the outcome of renal transplantation as a result of prolonged muscle relaxation, hypoxemia, hypertension, tachycardia, and apnea.

2. Objectives

The aim of the present study was to investigate the effect of acid-base balance on neuromuscular blockade in renal transplantation.

3. Methods

In this randomized-controlled trial conducted at Shahid Modarres hospital, Tehran, Iran, 31 ESRD patients who were candidate for elective renal transplantation from live donors were randomly selected and divided into case (n = 16) and control groups (n = 15). This clinical trial was registered in the Iranian registry of clinical trial (IRCT2015092612203N3). Written informed consent was obtained from all the patients.

Inclusion criteria included ASA functional class III and age of 18 - 70 years. Exclusion criteria included advanced cardiovascular disease (ASA functional class \geq IV), potassium concentration $>$ 5.5 mEq/L at admission, metabolic acidosis (pH $<$ 7.15), axillary body temperature $<$ 35°C or $>$ 38.5°C before or during the surgery, need for blood transfusion during the surgery, and cadaveric renal transplantation. Patients with ischemic time $>$ 30 minutes or the duration of surgery above 150 minutes were excluded from our study.

All demographic and clinical information was recorded before the surgery. The patients were pre-oxygenated by 100% O₂ for 3 minutes and received 0.02 mg/kg midazolam + 12 μ g/kg fentanyl as premedication followed by 5 mg/kg thiopental sodium for induction of anesthesia. A dose of 0.5 mg/kg atracurium was administered as muscle relaxant. Additional dose of atracurium was administered if needed. Last dose of atracurium was administered at declamping time. Anesthesia was maintained using 0.6% - 1% isoflurane and 50% nitrous oxide. All patients received 3 mg/kg furosemide and 0.5 mg/kg mannitol.

Invasive radial artery catheter was administered after positive Allen test for the measurement of blood pressure. Central vein pressure (CVP) was calculated repeatedly and maintained at 10 - 12 cm H₂O (by infusion of fluid if needed) and body temperature was preserved at 36°C (using nasopharyngeal thermometer). Arterial pressure of O₂, and CO₂ (P_aO₂, P_aCO₂), HCO₃, base excess (BE), and pH were studied on arterial blood gas (ABG) sample prior to the surgery and at declamping time. Train-of-four (TOF) was measured prior to anesthesia and then every 15 minutes during the surgery (to assess the need for further atracurium, TOF = 3 was our threshold for administration of additional dose of atracurium), 15 minutes after declamping time, and every 2 minutes until acceptable recovery (TOF 3 of 4). The time of achieving TOF 3 was recorded and compared between the groups. In all patients, the controlled mode of ventilator was used. Ventilator setting during operation was as follows: RR = 12, TV = 5 - 6 cc / kg, and Pmax = 35. The rate of ventilation was raised in respiratory acidosis.

Patients in the case group received sodium bicarbonate based on base excess in the first ABG sample, during the interval between anesthesia and initiation of surgery. The dose of sodium bicarbonate was calculated as follows: (base excess \times 0.3 \times body weight)/2. Patients in the control group received 50 mL of sterile water for injection.

All data were gathered in a report sheet and analyzed by SPSS 12 (SPSS Inc. Chicago, IL, USA). Descriptive statistics was expressed as mean \pm SD. Inferential statistics of chi-square and independent-test were used to analyze the data. Sample size was calculated based on power of 80 %. P value less than 0.05 was considered statistically significant.

4. Results

Thirty one ESRD patients in the sodium bicarbonate group (n = 16) with mean age of 41.18 \pm 13.18 years and control group (n = 15) with 39.0 \pm 13.30 years were studied during 2 months. Twenty two of them were male (71.0%). The mean duration of ESRD was 29.31 \pm 27.45 and 23.06 \pm 13.56 months in the case and control groups, respectively. Ischemic time, warm and cold, in the case and control groups was 19.71 \pm 8.13 and 20.01 \pm 9.42 minutes, respectively (P = 0.62). The duration of surgery in the case and control groups was 103.91 \pm 21.53 and 100.07 \pm 24.33 minutes, respectively, which was not different between the two groups (P = 0.42). There were no significant differences between the groups in age, gender, and duration of ESRD (P $>$ 0.05).

ABG variables are summarized in Table 1. There was no significant difference in pH between the groups in the first evaluation (P = 0.649). The pH and BE in the case group significantly increased after the intervention. There was a significant reduction in after-surgery measurement of pH and BE in the control group (P = 0.011). In other variables, the primary data were significantly different between the groups. We calculated the difference of secondary and primary data in each group (diff: secondary measurement - primary measurement) and compared the obtained data between the case and control groups to prove the significant effect of the intervention.

The mean time to achieve TOF = 3 was 23.75 \pm 5.32 and 41.80 \pm 5.2 minutes after declamping in the case and control groups, respectively. Patients in the sodium bicarbonate group achieved TOF = 3 significantly faster than those in the control group.

5. Discussion

The results of the present study revealed a significant reduction in the duration of muscle relaxation of

Table 1. The Comparison of ABG Variables and TOF Before (1) and After (2) Intervention in Sodium Bicarbonate and Control Groups^a

| Variable | | Group | | P Value |
|------------------|---------|--------------------|--------------------|--------------------|
| | | Case (n = 16) | Control (n = 15) | |
| PH | 1 | 7.32 (± 0.97) | 7.37 (± 0.06) | 0.115 |
| | 2 | 7.38 (± 0.08) | 7.30 (± 0.13) | 0.040 ^b |
| | P value | 0.001 ^b | 0.011 ^b | - |
| HCO ₃ | 1 | 14.01 (± 4.06) | 18.67 (± 3.57) | 0.002 ^b |
| | 2 | 18.72 (± 4.68) | 13.55 (± 3.58) | 0.002 ^b |
| | P value | 0.004 ^b | 0.001 ^b | - |
| pCO ₂ | 1 | 27.1250 (± 7.27) | 33.46 (± 6.63) | 0.017 ^b |
| | 2 | 30.68 (± 6.09) | 27.73 (± 6.54) | 0.203 |
| | P value | 0.122 | 0.011 ^b | - |
| BE | 1 | -11.28 (± 5.05) | -6.28 (± 3.74) | 0.004 ^b |
| | 2 | -5.84 (± 5.03) | -12.77 (± 5.20) | 0.001 ^b |
| | P value | 0.003 ^b | 0.001 ^b | - |
| TOF | | 23.75 (± 5.32) | 41.80 (± 5.2) | 0.000 ^b |

^aValue are expressed as mean (SD).

^bStatistically significant.

Atracurium and about two-time faster recovery due to treatment of acid-base imbalance by sodium bicarbonate. The decompensated metabolic acidosis in the case group was amended and BE increased as a result of using sodium bicarbonate. On the other hand, the compensated metabolic acidosis in the control group changed to manifest metabolic acidosis, and BE reduced during the surgery. Some of the primary data were significantly different between the groups, which may be due to a bias in sample selection. We calculated the difference of secondary and primary data in each group (diff: secondary measurement - primary measurement) and compared the new data between the case and control groups to prove the significant effect of the intervention applied in the case group.

The aim of this study was to assess the effect of intraoperative correction of acid-base imbalance on recovery duration; therefore, we did not focus on post-surgical hemodynamic situation and buffering system.

Hughes (14) in his study revealed that acid-base imbalance can alter the duration of neuromuscular blockade. In metabolic or respiratory acidosis (blood pH < 7.35), the duration of blockade increased and recovery from anesthesia prolonged. After his investigation, several researchers focused on acid-base balance on pharmacokinetics and pharmacodynamics of muscle relaxants (15, 16). Teng (15) in his randomized controlled trial (RCT) revealed prolonged spontaneous and reversal (after small doses of neostigmine) recovery time of rocuronium in patients with el-

evated P_aCO₂. The emphasis of all these studies was on pH-dependent clearance of muscle relaxant agents such as rocuronium and atracurium. The clearance of Atracurium was found to be greater and its neuromuscular blockade effect evaluated in respiratory alkalosis (17). Yamauchi showed the prolonged duration of action and faster rate of recovery index of vecuronium by hypercapnia-induced acidosis (16).

Reduction of blood pH increases the affinity of atracurium for the anionic acetylcholine receptors, while prolonged muscle relaxant metabolism can occur as a result of reduced muscular blood perfusion in acidotic environment (15).

Prolonged neuromuscular blockade has different side effects such as aspiration, diminished response to hypoxia, upper airway obstruction, and sometimes longer hospital and ICU stay and more hours of mechanical ventilation, which can cause administration of reversal medication in some patients (18). Reversal medications such as neostigmine, gamma cyclodextrin, and sugammadex also have side effects (19). Given the risks of prolonged neuromuscular blockade or reversal medications, any intervention to decrease the duration of blockade and recovery time is important and considerable as an adjuvant to enhance the outcome of medical and surgical procedures. In conclusion, intraoperative alkali treatment can amend acid-base imbalance and decrease spontaneous recovery time of atracurium in renal transplantation. Further investiga-

tions are needed to confirm the result of our study with longer follow-up.

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Footnotes

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