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The effects of beta blockade and clonidine on persistent injury-associated anemia

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ABSTRACT

Background: Nonselective beta blockade (BB) and clonidine may abrogate catecholamine-mediated persistent injury-associated anemia. We hypothesized that critically ill trauma patients who received BB or clonidine would have favorable hemoglobin (Hb) trends when adjusting for operative blood loss (OBL), phlebotomy blood loss (PBL), and red blood cell (RBC) transfusion volumes, and that the effect would be greatest among the elderly, who have higher catecholamine levels.

Methods: We performed a 4-y retrospective cohort analysis of 280 consecutive trauma patients with ICU stay ≥48 h and moderate/severe anemia. Patients who received BB or clonidine for ≥25% of their hospital stay were grouped as the BB/clonidine cohort ($n = 84$); all other patients served as controls ($n = 196$). Admission and discharge Hb were used to calculate ΔHb. OBL, PBL, and RBC volume were used to calculate adjusted ΔHb assuming 300 mL RBC = 1 g/dL Hb.

Results: BB/clonidine and control patients had similar age, injury severity, comorbid illness, and admission Hb. BB/clonidine patients received fewer RBCs despite greater OBL, though neither association was statistically significant. BB/clonidine patients had higher discharge Hb (9.9 *versus* 9.5, $P = 0.029$) and adjusted ΔHb (+1.0 *versus* −0.8, $P = 0.003$). Hb curves separated after hospital day 10. The difference in adjusted ΔHb between groups increased with advanced age (all patients: 1.7, ≥50 y: 1.8, ≥60 y: 2.4, ≥70 y: 3.7).

Conclusions: Critically ill trauma patients receiving BB or clonidine had favorable Hb trends when accounting for OBL, PBL, and RBC transfusions. These findings support the hypothesis that BB and clonidine alleviate persistent injury-associated anemia, with strongest effects among the elderly.

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Introduction

Anemia affects about 95% of patients who remain critically ill for 3 or more days.[1] Fifty-five percent of critically ill trauma patients receive a red blood cell (RBC) transfusion during their intensive care unit (ICU) stay, and about half of all transfusions are given after 4 d in the ICU.[2] Anemia of critical illness involves reduced iron bioavailability, suppression of erythropoiesis by inflammatory cytokines, hemodilution, and blood loss.[1,3-5] Persistent injury-associated anemia is a unique subtype of anemia of critical illness that is observed in critically ill trauma patients, characterized by a prolonged hypercatecholamine state mediating bone marrow dysfunction that manifests as decreased red blood cell production with low reticulocyte counts despite adequate iron stores and erythropoietin levels in the peripheral blood.[6-8] Following traumatic injury, high levels of inflammatory mediators and circulating catecholamines compromise iron metabolism and inhibit erythropoiesis.[1,4-6,9] Persistent injury-associated anemia may disproportionately affect the elderly, based on evidence that plasma norepinephrine levels rise with increasing age in humans and that older mice are unable to replace lost erythrocytes as quickly as younger controls following hemorrhage.[10-12] These factors compound baseline anemia in the elderly, which affects approximately 10% of subjects aged ≥65 y and approximately 20% of subjects aged ≥85 y.[13,14]

Preclinical studies in rodents indicate that interruption of hypercatecholamine pathways and the neuroendocrine stress response via nonselective beta-adrenergic receptor blockade (BB) or by sympathetic nervous system outflow inhibition with the alpha-2 agonist clonidine effectively restores bone marrow production of erythroid progenitors and alleviates persistent injury-associated anemia.[7,8,15] However, clinical translation has been difficult to establish, partly due to heterogeneity in practice patterns.[9] The purpose of this study was to examine the effects of BB and clonidine on persistent injury-associated anemia among critically ill trauma patients while accounting for confounding impact of operative blood loss (OBL), phlebotomy blood loss (PBL), and RBC transfusions on serial hemoglobin (Hb) levels. We hypothesized that critically ill trauma patients who received BB and clonidine would have improved Hb trends compared with control patients with similar injury severity.

Methods

We performed a retrospective cohort analysis of 280 trauma patients presenting to our level 1 trauma center during a 4-year period ending September 1st, 2015. Patients were identified by searching our trauma database for all adults (age ≥ 18 y) who were admitted to the ICU for ≥48 h and had moderate (<11 g/dL for adults) or severe (<8 g/dL for adults) anemia per World Health Organization criteria.[16] This study population was chosen to simulate the rodent model of lung contusion, hemorrhage, and chronic stress that established the pathophysiology of persistent injury-associated anemia and identified BB and clonidine as potential treatment options. We excluded burn patients, outside hospital transfers, and patients with unmeasured blood loss that was unrelated to their initial injury (e.g., gastrointestinal bleed, postoperative hemorrhage). Institutional review board approval was obtained before study initiation and chart review.

Clinicopathologic variables were collected from our prospective institutional trauma database and retrospective review of the electronic medical record, including age, sex, Charlson Comorbidity Index, outpatient prescriptions for BB or clonidine, blunt *versus* penetrating trauma, injury severity score, head abbreviated injury scale, Glasgow Coma Scale score, intubation on arrival to the emergency department, vital signs, laboratory values, operations during admission, BB and clonidine administration, operative blood loss, red blood cell transfusions, and length of stay in the hospital and in the ICU.

For each patient, hospital length of stay was divided by the number of days on nonselective BB (e.g., propranolol, labetalol, carvedilol) or clonidine. BB and clonidine were administered at the discretion of the treating physicians. Patients who received BB or clonidine for ≥25% of their hospital stay were allocated to the BB/clonidine group ($n = 84$); all other patients were allocated to the control group ($n = 196$). BB and clonidine were considered in a single group because separation into BB, clonidine, and BB + clonidine groups would have created prohibitively small cohorts and reduced statistical power. Of the 84 patients in the BB/clonidine group, 68 received BB alone (81% of the BB/clonidine group, 24% of all patients), six patients received clonidine alone (7% of the BB/clonidine group, 2% of all patients), and 10 patients received BB and clonidine (12% of the BB/clonidine group, 4% of all patients). The average interval from admission to initial administration of BB or clonidine was 4.4 (3.7-5.1) d, range 0-18 d. The number of days on which subjects in the BB/clonidine group received BB ranged from 0-152 d. The number of days on which subjects in the BB/clonidine group received clonidine ranged from 0-34 d. The 25% cutoff was chosen based on observations that a 5-6 d course of BB or clonidine is sufficient to improve persistent injury-associated anemia in rodents, and the average hospital length of stay in this study was 19 d. The raw number of days on BB/clonidine may not have accurately represented medication effects, i.e., a patient who receives 5 d of BB/clonidine during a 1 wk admission is different than a patient who receives 5 d of BB/clonidine over the course of 1 mo in the ICU and 2 wk of rehabilitation on a hospital ward. Although a higher cutoff value may have magnified the effects of BB/clonidine on postinjury erythropoiesis, the size of the BB/clonidine group would have decreased at higher cutoff values, eroding statistical power.

Admission and discharge Hb levels were used to calculate the change in hemoglobin (ΔHb) for each patient. To account for the effects of OBL, PBL, and RBC transfusions on Hb levels, we recorded these variables for each patient. PBL was estimated by a three-step process. First, the amount of blood drawn for laboratory tests was determined. At our institution during the study period, basic metabolic panels and complete blood counts required 5-7 mL of blood, arterial blood gases required 2 mL of blood, and blood cultures required 8-10 mL of blood. Next, the number of laboratory tests performed daily for ICU and floor patients was ascertained from previous