The effects of electroacupuncture on intestinal integrity in a mouse model of total body irradiation

Harvey E. Ramirez1, Lauren Vaught2, Liangjie Li3, Karl Andrutis2, Sadasivin Vidyasagar1
1Animal Care Services, University of Florida, Gainesville, FL
2Department of Radiation Oncology, University of Florida, Gainesville, FL

Abstract

Total body irradiation (TBI) is a commonly used technique in murine bone marrow transplant research. However, during TBI all digestive activities are affected, including the cells of the gastrointestinal tract. Gastrintestinal (GI) cell damage decreases intestinal nutrient absorption and increases intestinal fluid loss; eventually leading to diarrhea, dehydration, bacterial translocation and death. Currently, there is no effective treatment to either prevent or successfully treat TBI-induced gastrointestinal damage. In this study, we evaluated the effectiveness of electroacupuncture (EA) in mitigating the GI cellular damage when applied right after TBI (3.5 Gy). Seven week old male mice (C57BL/6J strain, n=14/group) were randomly assigned to one of the following treatment groups: no TBI/EA, TBI/no EA, TBI/EA and TBI/EA. EA was administered 0.5 and 48 hours post TBI. Gastrintestinal tract was harvested 6 days post-TBI for analysis of GI function (paracellular and tight junction) and histology (H&E and BrdU labeling). Results showed that the TBI/EA group had a significant increase in increased ileal glucose current (p<0.01), suggesting an increase cellular activity when compared to TBI-EA. Histological analysis showed TBI/EA group had an increased number of crypts in addition to increased vilus length that showed a trend towards statistical significance when compared to TBI-EA group. EA did not have an effect on mice that did not receive TBI. Glucose conductance, a measure of paracellular permeability (intestinal leakiness), did not show a significant increase when compared to basal conductance measurements in the TBI-EA group, whereas a trend towards statistical significance could be seen in the TBI-IA group. This study suggests that EA may mitigate the intestinal damage caused post-TBI and potentially decrease GI clinical signs observed after TBI in mice. Additional studies are needed to confirm these findings.

Introduction

Total body irradiation (TBI) is a commonly used technique in murine bone marrow transplant research and other disease applications. However, the procedure does not discriminate between rapidly dividing bone marrow cells, the intended target cells, and other rapidly dividing cells in the body such as cells of the gastrointestinal tract. The direct injury to the gastrointestinal cells is known as acute gastrointestinal radiation syndrome and is characterized by anorexia, weakness, diarrhea, dehydration and general signs of malaise secondary to the systemic inflammatory response that occurs post-TBI(2). There are no effective treatments to minimize damage to the GI tract and most documented treatments are based on providing supportive care.

Acupuncture is an ancient therapeutic technique consisting of inserting sterile needles into defined acupuncture points on the body in order to stimulate physiologic balance through neural signaling. Electroacupuncture (EA) is a modern variation of this technique and uses an electrical current to stimulate acupoints. Electroacupuncture has been shown to modulate inflammatory(4, 5). In addition, electroacupuncture has been shown to decrease systemic inflammatory responses in rodent models of sepsis and ischemia reperfusion injury(6). The purpose of this experiment is to evaluate the effectiveness of electroacupuncture in preventing TBI induced damage in the intestinal epithelium.

Materials and Methods

TEST SUBJECTS AND HOUSING CONDITIONS Seven week old male mice (C57BL/6J strain, n=14/group) were randomly assigned to one of the following treatment groups: no TBI/EA, TBI/no EA, TBI/EA and TBI/EA. EA was administered 0.5 and 48 hours post TBI. Gastrintestinal tract was harvested 6 days post-TBI for analysis of GI function (paracellular and tight junction) and histology (H&E and BrdU labeling). Results showed that the TBI/EA group had a significant increase in increased ileal glucose current (p<0.01), suggesting an increase cellular activity when compared to TBI-IA. Histological analysis showed TBI/EA group had a significant increase in vilus length that showed a trend towards statistical significance when compared to TBI-IA group. EA did not have an effect on mice that did not receive TBI. Glucose conductance, a measure of paracellular permeability (intestinal leakiness), did not show a significant increase when compared to basal conductance measurements in the TBI-IA group, whereas a trend towards statistical significance could be seen in the TBI-IA group. This study suggests that EA may mitigate the intestinal damage caused post-TBI and potentially decrease GI clinical signs observed after TBI in mice. Additional studies are needed to confirm these findings.

Results

Gastrointestinal (GI) cell damage decreases intestinal nutrient absorption and increases intestinal fluid loss; eventually leading to diarrhea, dehydration, bacterial translocation and death. Currently, there is no effective treatment to either prevent or successfully treat TBI-induced gastrointestinal damage. In this study, we evaluated the effectiveness of electroacupuncture (EA) in mitigating the GI cellular damage when applied right after TBI (3.5 Gy). Seven week old male mice (C57BL/6J strain, n=14/group) were randomly assigned to one of the following treatment groups: no TBI/EA, TBI/no EA, TBI/EA and TBI/EA. EA was administered 0.5 and 48 hours post TBI. Gastrintestinal tract was harvested 6 days post-TBI for analysis of GI function (paracellular and tight junction) and histology (H&E and BrdU labeling). Results showed that the TBI/EA group had a significant increase in increased ileal glucose current (p<0.01), suggesting an increase cellular activity when compared to TBI-IA. Histological analysis showed TBI/EA group had an increased number of crypts in addition to increased vilus length that showed a trend towards statistical significance when compared to TBI-IA group. EA did not have an effect on mice that did not receive TBI. Glucose conductance, a measure of paracellular permeability (intestinal leakiness), did not show a significant increase when compared to basal conductance measurements in the TBI-IA group, whereas a trend towards statistical significance could be seen in the TBI-IA group. This study suggests that EA may mitigate the intestinal damage caused post-TBI and potentially decrease GI clinical signs observed after TBI in mice. Additional studies are needed to confirm these findings.

Conclusions

EA significantly increases short-circuit glucose current in ileal tissue of irradiated mice suggesting an increase in cellular activity and enhanced repair mechanism of ileal tissue after TBI.

• Number of crypt cells and villus length is higher in tissue from animals that received EA as a treatment after TBI.

• Paracellular permeability, and therefore intestinal leakiness, may or may not be improved by the enhanced cellular activity when measured six days post TBI.

• Further studies are needed to:
  - Evaluate the mechanism of action of EA in the treatment of acute gastrointestinal radiation syndrome in mice.
  - Evaluate the clinical effects of EA alone or in combination with other treatments at higher irradiation levels.
  - Evaluate other acupuncture point combinations in an attempt to obtain the most effective EA treatment.

References


Figure 1. Effect of EA on short-circuit current of murine ileal tissue after TBI.

Figure 2. Effect of EA in number of crypts of murine ileal tissue after TBI.

Figure 3. Effect of EA in villus length of murine ileal tissue after TBI.

Figure 4. Assessment of cellular proliferation of ileal tissue by BrdU staining. Sample photomicrographs of ileal tissue obtained from group 0Gy+EA, 3Gy+EA (A), 3.5Gy-EA (C), 3.5Gy+EA (D), Magnification 13 µm at the ST36 (Zusanli) acupuncture of both limbs. The point is located 23mm lateral to the anterior tubercle of the ilium and 4 mm distal to the lateral aspect of the iliac crest in the iliacus stran of muscle. Needles were inserted to a depth of 3mm and connected to an electrical stimulus (PENS electrostimulator 120, Pro, Pantheon Research, Venice, CA). Electrical stimulation was delivered in a continuous mode with a current of 30 mA, frequency of 10 Hz for 30 minutes during each treatment.

Figure 5. Comparison between basal and glucose conductance measurements. A p-value of 0.05 is considered significant. Data is presented in mean±SEM.