Elucidation of the Detrimental Synergy of Intestinal Surgery Followed by an Abdominal Sepsis – the Septic Surgical Patient.

Isaac T. Prows, Mindy L. Prows, Hannah R. Thompson, P. Bryan Hankey and Anthony J.M. Bauer

Liberty University College of Osteopathic Medicine, Liberty University, Lynchburg, VA 24502, USA

Introduction: Clinically, surgery is unfortunately commonly followed by an iatrogenic-induced or nosocomial-associated bacterial infection. We have shown that surgical manipulation of the intestine triggers a complex molecular cascade of transcription factor activation (MAPK p38, Egr-1, NF-κB, etc.) and the subsequence induction of multiple pro-inflammatory mediators (MCP-1, IL-6, TNF-α, iNOS) that cause the recruitment/extravasation of numerous circulating leukocytes into the intestinal muscularis externa, which together result in the development of clinical postoperative ileus (POI). Previously, we have also shown that sustained pre-exposure to bacterial lipopolysaccharide (LPS) dramatically “prevents” the development of POI. And, additionally, we published that mild hemorrhagic shock “beneficially” pre-conditions the gut to a subsequent polymicrobial sepsis. Our study is designed to elucidate the intestinal molecular, cellular and functional alterations that occur during the detrimental clinical scenario of a surgical patient acquiring an infection using a rodent model.

Methods: A standardized POI rodent model utilizing mild non-traumatic intestinal manipulation (IM) followed by a 24hr delayed intraperitoneal injection of low dose LPS (0.5mg/kg) will be used and compared to controls, IM alone and LPS alone at specified time points. In vivo gastrointestinal transit (GIT) will be measured using non-digestible, orally administered FITC-labeled dextran (70kD MW) and jejunal circular muscle strips will be functionally evaluated using organ bath recordings after IM (48hrs), LPS (24hrs) and combined IM+LPS (48hrs). Myeloperoxidase (MPO+) staining of jejunal muscularis whole-mounts will assess leukocyte infiltration, qPCR will be used to quantify induction of pro-inflammatory genes, and Luminex analysis will measure tissue and serum cytokines/chemokines.

Results: Individually, mild IM or low dose LPS (0.5 mg/kg) treatment minimally suppressed in vivo GIT compared to control (calculated transit geometric center measurements: control=10.6±0.3, IM=9.2±2.00, LPS=7.3±0.09 alone vs. IM+LPS=5.6±0.37 (N=2-3 each). Similar synergistic results of IM+LPS on jejunal circular muscle contractility has been observed using in vitro muscle strip organ bath recording experiments. The synergistically delayed transit was accompanied by a significant recruitment of leukocytes into the intestinal muscularis (control=2±0.3, IM=7±1.6, LPS=3±0.6 alone vs. IM+LPS=25±2.4 (MPO+ PMNs/200X field N=4 each). The induction of pro-inflammatory genes by qPCR and cytokine/chemokine Luminex analysis is pending.

Conclusion: We conclude that mild IM followed by a simulated infection potentiates the inflammatory response within the intestinal muscularis leading to a synergistic aggravation of POI. Thus, instead of being a protective pre-conditioning response – intestinal responses to surgery are potentiated by a subsequent septic event, which explains the detrimental clinical morbidity and mortality associated with the septic surgical patient.