**Objective:** To determine whether injured patients who received a vagotomy would have worse outcomes after injury.

**Design:** Retrospective analysis of the Nationwide Inpatient Sample (NIS) database over 10 years.

**Patients:** Patients admitted for trauma (primary International Classification of Diseases, Ninth Revision [ICD-9] diagnosis codes 800-959) who had a vagotomy (ICD-9 procedure codes 44.00, 44.01, and 44.03) were included. A second cohort of injured patients without vagotomy was extracted and matched 3 to 1 on the following criteria: age, race, sex, concurrent splenectomy, survival risk ratio, payer status, comorbidities, and calendar year.

**Main Outcome Measures:** The primary outcome measured was in-hospital mortality. Secondary outcomes included septicemia, systemic inflammatory response syndrome, acute respiratory distress syndrome, ulcer disease, length of stay, and total charges.

**Results:** A total of 56 and 115 patients were included in the vagotomy and control groups, respectively, and were similar in demographic characteristics, comorbidities, and injury severity. We found that the vagotomy group had elevated mortality (27.27% vs 9.57% for controls; \( P = .003 \)). Patients who received vagotomy also had more septicemia (26.79% vs 3.48%; \( P < .001 \)) and ulcer disease (71.43% vs 2.61%; \( P < .001 \)) but not systemic inflammatory response syndrome or acute respiratory distress syndrome. Patients who received vagotomy also had an increased length of hospital stay (36.4 vs 9.6 mean days; \( P < .001 \)) and total cost ($211,899.90 vs $59,321.64; \( P < .001 \)).

**Conclusions:** Vagotomy after traumatic injury is associated with an increase in ulcer disease, septicemia, and mortality. This may reflect a loss of control over the systemic response to injury and warrants further study.


MULTIPLE ORGAN FAILURE has been a topic of intense research for several decades and is a continuous problem in the care of critically injured patients. Multiple organ failure after injury is thought to occur when damage-associated molecular patterns are released from injured cells and bind their ligand, Toll-like receptor 4, leading to activation of NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells) and increased expression of proinflammatory cytokines.1-3 When this occurs in the intestinal mucosa, it has been associated with a decrease in tight junction protein expression, resulting in breakdown of the intestinal mucosal barrier.4-5 This allows intraluminal bacteria and their products to traverse the wall of the intestine and activate inflammatory cells, leading to a massive inflammatory response, systemic cytokine expression, and ultimately, organ dysfunction and failure in tissues distant from the site of injury.5-9

Recently, the vagus nerve has been shown to have a reflexive role in modulating the proinflammatory signal produced after injury.10 The vagus nerve becomes activated, possibly by proinflammatory cytokines, and the afferent signal travels to the dorsal motor nucleus where it induces an efferent signal and the release of acetylcholine that then acts on the nicotinic α-7 receptor of macrophages and inflammatory cells.11,12 Several studies have demonstrated that blocking the nicotinic α-7 receptor leads to decreased local and systemic inflammation after injury.13,14 Our laboratory data have shown that stimulating the vagus nerve decreases inflammatory mediators in the intestine, improving intestinal barrier function and tightening intestinal protein expression, a process that can be blocked with vagotomy.15-17 Furthermore, we have also demonstrated in

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an animal model that vagal activation can have consequences beyond the intestinal epithelium; vagal-stimulated animals were shown to have improved measures of lung injury and pulmonary inflammation following a severe burn.17

For many decades, truncal vagotomy with pyloroplasty or antrectomy was the standard of care for peptic ulcer disease. After the advent of proton-pump inhibitors and the discovery of Helicobacter pylori, the treatment of ulcer disease has changed dramatically and these procedures are now most often reserved for patients with a complication of their ulcer disease, such as bleeding or perforation.18 No studies have been done to evaluate the potential consequences on the inflammatory response after vagotomy in the clinical setting. Evaluating the outcomes of traumatically injured patients who receive vagotomy following their injury provides us with an interesting view into the role the vagus nerve may play in modulating systemic inflammation outside of the laboratory setting. We hypothesized that vagotomy following a traumatic injury would be associated with an increased rate of systemic inflammation, septicemia, adult respiratory distress syndrome (ARDS), and mortality.

METHODS

We performed a matched case-control retrospective analysis of the Nationwide Inpatient Sample (NIS), a database sponsored by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project, which provides a representative 20% sample of hospital discharge records from 37 states.19 We searched the most recent 10 years available, 1998 through 2007. Trauma patients 18 years or older were identified by International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes of 800 through 959 in the primary position, excluding 905 to 909 (late effects of injury), 930 to 939 (foreign body), 940 to 949 (burns), and 958 (early complications of trauma). From this cohort we identified patients who underwent vagotomy not otherwise specified, truncal vagotomy, or other selective vagotomy (ICD-9 codes 44.00, 44.01, and 44.03) during the same hospital stay. We excluded patients who underwent highly selective vagotomy, as these patients were likely to have an intact vagal connection to the small and large intestine.

A 3-to-1 matched control cohort of patients was then constructed from the same pool of patients who were admitted for the primary diagnosis of trauma identified earlier. Patients who received vagotomy were matched to the control cohort on the following criteria: age (within 10-year windows), race, sex, payer status, year of discharge, extent of injury, and presence of comorbidities. In addition, patients were matched for splenectomy performed during their hospital stay, as the spleen has been implicated in modulating the inflammatory response to injury.12,20 Matches were identical unless specified otherwise.

The data obtained from the NIS database were enriched in 2 ways. First, to estimate the extent of injury for the patients included in our study, we extracted the independent and traditional Survival Risk Ratio per International Commission on Intervention and State Sovereignty methods from the patients’ available ICD-9 diagnosis codes.21 Several studies have demonstrated that the Survival Risk Ratio is an excellent estimate of the Injury Severity Score when obtaining data from administrative databases.22,23 Second, we enriched our data by calculating the comorbidities of patients using the Charlson Index per Deyo et al24 adaptation for administrative data sets.

The primary outcome variable measured was in-hospital mortality. Secondary outcomes evaluated included a concomitant diagnosis of septicemia (ICD-9 code 38), Systemic Inflammatory Response Syndrome (SIRS) or sepsis (ICD-9 code 995), ARDS (ICD-9 codes 518.82 and 518.5), and ulcer disease (ICD-9 codes 531 to 535), in addition to length of hospital stay and total charges assessed. Bivariate analysis was performed with $\chi^2$ for categorical dependent variables (death, septicemia, SIRS/sepsis, ARDS, and ulcer disease) and $t$ tests, for continuous dependent variables (length of hospital stay and total hospital charges). Statistical analysis was performed in Stata MP 11 (StataCorp LP, College Station, Texas). Statistical significance was defined as $P < .05$.

RESULTS

A total of 3,016,627 patients who met our initial inclusion criteria were identified. Of these patients, 36 were identified as having undergone vagotomy during their hospital stay (14 patients had vagotomy not otherwise specified; 29, truncal vagotomy; and 13, other selective vagotomy). Of the patients who received vagotomy, 14 (25%) were unable to be matched on any variable to a patient in the control cohort, 4 (7.1%) were matched to only 1 control patient, and 3 (5.4%) were matched to only 2 control patients. We identified a total of 115 patients for the matched-control cohort.

There was no statistically significant difference in demographic data between the control and vagotomy cohorts (Table 1). The mean (SD) age of the controls was 56.6 (23) years vs 56.7 (22) years for the vagotomy group ($P = .98$). Table 2 displays the injury severity and comorbidity measures of the groups in terms of Survival Risk Ratio scores and average Charlson Index scores, which were also found to be similar. The lack of significant differences in injury severity and comorbidities between the vagotomy and control cohorts demonstrates the success of our matching.

Our primary and secondary outcome results are shown in Table 3. The vagotomy group had more in-hospital mortality, with 27.27% of patients dying vs 9.57% in the control group ($P = .003$). There were no differences in the rate of SIRS/sepsis or ARDS between the 2 groups; however, the vagotomy group had more septicemia than the control group (26.79% vs 3.48%; $P < .001$) as well as ulcer disease (71.43% vs 2.61%; $P < .001$). To account for the bias that may have been introduced by the uneven distribution of ulcer disease, we ran a separate analysis and matched the control cohort for incidence of ulcer diagnosis. In doing so, we were unable to match 25 (44.6%) of the patients who received vagotomy on any criteria, and the rate of ulcer diagnosis between the vagotomy and control cohorts still remained uneven (71.43% vs 50.63%; $P = .02$). We continued to demonstrate a significant difference in our primary outcome measure; in-hospital mortality was increased in the vagotomy group compared with controls when matched for ulcer disease (27.27% vs 3.80%; $P < .001$). We elected to abandon these data and proceed without matching for ulcer disease, as this matching strategy was less optimal.

Table 4 shows our additional secondary outcome data. The vagotomy group had a significantly longer hospital
course (36.9 vs 9.6 days; \( P < .001 \)), resulting in increased charges ($211 899.90 vs $59 321.64; \( P < .001 \)).

To evaluate for possible confounders contributing to our mortality results, we compiled the most frequently occurring diagnoses in the vagotomy group (data not shown). As may be expected, 44.65% of patients who received vagotomy had a diagnosis of upper gastrointestinal ulcer with hemorrhage, either duodenal or gastric.

Our study demonstrates that vagotomy performed after admission for traumatic injury is associated with a significantly increased risk of in-hospital mortality and septicemia, resulting in increased length of stay and hospital charges. Using a retrospective review of a national sample of inpatients, we demonstrated that patients who underwent vagotomy following admission for traumatic injuries had a nearly 3-fold increased risk of in-hospital mortality. Septicemia in these patients was also significantly increased, more than 8 times the rate seen in control patients.

The increased incidence of ulcer disease among patients who received vagotomy that was seen in our study likely reflects the reason for undergoing vagotomy and may be a manifestation of their physiologic derangement. It is possible that the mortality differences seen in our study are a consequence of ulcer disease and its complications, such as hemorrhage and perforation, independent of the vagotomy procedure. We feel that this is unlikely, as our efforts to account for this and match the groups for ulcer disease still resulted in significantly increased mortality in the vagotomy group.

Our study is not without several significant limitations. Our use of the NIS database, an administrative database sampling a large percentage of inpatient admissions, allowed us to identify an infrequently occurring patient population—patients undergoing vagotomy after traumatic injury—to understand how the anti-inflammatory reflex pathway may be involved in postinjury systemic inflammation. However, the NIS database does not provide information on the timing of procedures or diagnoses made during the hospitalization. This is an important limitation for our study because we cannot definitively conclude that the increased mortality or septicemia found in our study occurred as a direct result of the vagotomy procedure since we do not know the chronological order of events. Furthermore, the NIS database does not provide information on the timing of procedures or diagnoses made during the hospitalization. This is an important limitation for our study because we cannot definitively conclude that the increased mortality or septicemia found in our study occurred as a direct result of the vagotomy procedure since we do not know the chronological order of events. Furthermore, the NIS database does not provide information on the timing of procedures or diagnoses made during the hospitalization. This is an important limitation for our study because we cannot definitively conclude that the increased mortality or septicemia found in our study occurred as a direct result of the vagotomy procedure since we do not know the chronological order of events.
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ruption and shown to be similar to the burn injury group.\(^1\)\(^6\),\(^1\)\(^7\) Our laboratory has shown a protective effect of vagal stimulation up to 90 minutes following injury, providing a potential therapeutic window during which intestinal inflammation can be modulated.\(^1\)\(^7\)

The mechanism of the anti-inflammatory pathway has yet to be fully elucidated. Huston et al\(^1\)\(^3\) demonstrated, using an endotoxemia model, that vagal stimulation in animals that received splenectomy failed to decrease serum levels of tumor necrosis factor beyond splenectomy alone. On the contrary, work in our laboratory has shown that intestinal permeability following burn injury in rodents without the spleen was improved with vagal stimulation and returned to levels similar to those in sham animals, whereas animals that receive splenectomy alone had significant barrier breakdown following burn injury.\(^1\)\(^6\) Our findings suggest that the vagus nerve’s preservation of the intestinal barrier after burn injury has a component that is independent of the spleen. For the purposes of our current study, we elected to match patients for splenectomy owing to the potential infectious complications that may arise in the later postoperative period, thereby controlling for a potential source of bias.

An interesting finding in this study is the lack of difference in SIRS and ARDS between the vagotomy and control groups. Given our laboratory research, which has demonstrated a lung protective effect of vagal stimulation, we hypothesized that the vagotomy group would have a higher rate of ARDS and systemic SIRS. This result may be owing to our small sample size and the relatively low incidence of documented SIRS in both groups. However, our experimental data show that an abdomi-

nal vagotomy abolishes the protective effects of vagus nerve stimulation in the lung, confirming the importance of an “impermeable” intestinal barrier in the pre-

vention of acute lung injury in our model.\(^1\)\(^7\)

There is a considerable amount of research yet to be conducted on the intricacies of the vagal nerve and the anti-

inflammatory response. Future animal study is needed to determine the mechanism as well as important cell types and signaling molecules. In addition, the development of a vagomimetic drug candidate to activate the anti-

inflammatory response may be an important advance and is currently an ongoing project in our laboratory. Prospec-

cive clinical research evaluating patients who receive a va-

gal stimulus is needed and may provide more definitive answers. Ultimately, vagal stimulation may provide clinicians with a therapy that can be easily applied after injury to ameliorate systemic inflammation and could potentially save an untold number of lives.

We have shown that patients admitted for traumatic injuries who undergo vagotomy during hospitalization have increased mortality and rate of sepsis com-

pared with matched control patients without vagotomy. This supports our hypothesis that the vagus nerve may be implicated in the systemic inflammatory response, and vagal activation can act as an anti-inflammatory modulator.
Vagotomy, Inflammation, and the Injured Patient

This fascinating article presents a novel hypothesis and interpretation of observed data combining bench research and clinical experience. The basic premise of the hypothesis is that the presence of an intact vagus nerve and gut innervations will decrease the postinjury inflammatory response and that patients who happen to have had a vagotomy sometime during their admission for a traumatic injury will have worse inflammatory-mediated outcomes. The basic science supporting the importance of an intact vagal signal in downregulating the inflammatory response, particularly decreasing intestinal permeability, is well referenced. Peterson et al have done a nice job of using the NIS database to test this hypothesis, identifying trauma patients who had a vagotomy and matching them as best as possible to a similar cohort who did not have a vagotomy but had similar demographics and injury severity pattern. There certainly are problems with this approach, but these are clearly stated in the “Comments” section. As far as I know, this is a novel look at the role of vagotomy and outcome in injured patients. However, the basic criticism of this article is that the higher incidence of inflammatory-mediated adverse outcomes (ARDS, SIRS/sepsis, septicemia) and hospital mortality is not the result of the vagotomy dis inhibiting the inflammatory response but rather a consequence of severe injury, gut ischemia, development of a gastrointestinal ulcer and bleeding, and the subsequent necessity for gastrectomy and vagotomy. Peterson et al acknowledge this and made an effort to control for it, primarily by adjusting for the comorbidity of ulcer disease, but this was not particularly effective. Nonetheless, the article is well written, concise, creative, and consistent with previous study by some of the authors. I suspect it will be educational to many readers, and while seriously flawed, Peterson et al are very clear on this and not overreaching in their discussion and conclusions.

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REFERENCES