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The impact of surgery on mortality and morbidity in patients with severe acute pancreatitis and intra-abdominal hypertension

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Abstract: Objectives: To determine the impact of surgery in mortality and morbidity in patients with severe acute pancreatitis (SAP) and intra-abdominal hypertension (IAH) or low abdominal perfusion pressure (APP). Materials and methods: We performed a case-control study of adult patients who presented with SAP and IAH or low APP defined as APP < 60 mmHg at the intensive care unit (ICU) of a tertiary care center. We evaluated the effect of surgery on mortality, morbidity, hospital and ICU length of stay. Results: We found 48 patients with IAH and 35 patients with low APP. We found no association with mortality. In the subgroup with IAH we found an association of protection for organ failure (adjusted OR = 0.17 [95% CI 0.41–0.69], p = 0.014), respiratory failure (adjusted OR = 0.15 [95% CI 0.04–0.62], p = 0.008) and renal failure (adjusted OR = 0.02 [95% CI 0.00–0.24], p = 0.002), and in the subgroup with low APP an association of protection for kidney failure (OR = 0.06 [95% CI 0.00–0.64], p = 0.012). In both subgroups, hospital and ICU length of stay were increased (p < 0.01). Conclusions: In patients with SAP, surgery seems protective for respiratory and kidney failures in the subgroup with IAH and for kidney failure in the subgroup with low APP, nonetheless, it increases hospital and ICU length of stay.
1. Introduction

Severe acute pancreatitis (SAP) is an important cause of mortality, morbidity and rise in health care costs globally. In our country, acute pancreatitis is the 20th leading cause of death with a rate of 1.7–2.2 deaths per 100,000 individuals (Información epidemiológica de morbilidad anual ejecutivo, 2010; Ledesma-Heyer & Arias, 2009; Panorama epidemiológico y estadístico de la mortalidad en México, 2010). According to the current Atlanta international consensus, diagnosis of acute pancreatitis requires the presence of two criteria from; characteristic abdominal pain, elevated levels of serum amylase or lipase and characteristic findings in imaging studies, and it’s further classified into mild when there is no presence of organ failure, local or systemic complication, moderate when there is a transient organ failure, local or systemic complication and severe when there is one or more persistent organ failure (Banks et al., 2013). The definition of organ failure is based on the modified Marshall scoring system (Marshall et al., 1995). The overall mortality of SAP is between 10 and 30% worldwide and it’s mainly attributed to the development of organ failures, local and infectious complications. In addition, mortality is related with the number and persistence of the organ failures (Banks & Freeman, 2006; Guzman & Rudnicki, 2006). For the treatment of acute pancreatitis, there is a broad spectrum of therapeutic measures. With regard to surgical treatment, a pancreatic necrosectomy is indicated in cases of infected or sterile but symptomatic pancreatic necrosis. (Büchler et al., 2000; Rattner, Legermate, Lee, Mueller, & Warshaw, 1992) Timing of surgery has long been debated, as early surgical procedures have been associated with increased morbidity and mortality and those than can be delayed for 3–4 weeks have been associated with decreased mortality (Hartwig et al., 2002; Mier, León, Castillo, Robledo, & Blanco, 1997; Tsiotos, Smith, & Starr, 1995). Some cases with walled off necrosis can be managed with percutaneous or endoscopic drainage (Bradley, Howard, van Sonnenberg, & Fotoohi, 2008; van Santvoort et al., 2010). Finally, in a recent prospective study, the step up approach compared with initial surgery demonstrated lower rates of organ failures and mortality (van Santvoort et al., 2010).

During an episode of SAP there are several factors that can increase intra-abdominal pressure (IAP) such as pancreatic edema and necrosis, bleeding and fluid leakage into third space. Moreover, these patients usually receive aggressive intravenous hydration and often have systemic inflammatory response with multiple organ failures; each of these independent factors that further increase IAP. Currently, many studies have described the presence of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in patients with SAP. According to the current international consensus, IAH is defined as a sustained or repeated pathological elevation of IAP ≥ 12 mmHg, and the ACS is defined as an elevation of IAP > 20 mmHg, with or without abdominal perfusion pressure (APP) < 60 mmHg, but associated with a new organ failure. The APP is defined as the difference between the IAP and the mean arterial pressure (MAP) (Andrew et al., 2013). The presence of IAH, APP < 60 mmHg and ACS have been associated with increased mortality and morbidity in critically ill patients. The ACS has been associated with significant damage within the abdominal cavity, and in severe cases, a surgical decompressive laparotomy may be necessary as a therapeutic measure (Ke et al., 2012). Furthermore, it has been described that mortality in patients with IAH increases as the IAP rises too (Reintam, Parm, Kitus, & Starkopf, 2011). For the treatment of IAH and ACS there is also a wide therapeutic spectrum of measures. Surgical decompression is currently indicated in primary abdominal compartment syndrome, secondary or recurrent abdominal compartment syndrome with IAP > 25 mmHg and secondary or recurrent abdominal compartment syndrome and inability to maintain the APP ≥ 60 mmHg (Andrew et al., 2013).

Finally, acute pancreatitis itself is an independent risk factor for developing IAH, and it has been described that the IAH has an adverse impact in mortality and morbidity in patients with SAP.
There exist few recent studies that evaluate the relationship between SAP and IAH, some studies have described risk factors for the development of IAH in patients with SAP, such as a positive fluid balance, the number of intra-abdominal collections, the serum levels of calcium and amylase, the APACHE II and CT severity index scores, the presence and extension of pancreatic necrosis and the presence of organ failures (Zhao, Liao, Zhao, & Hu, 2014). Another study evaluated the outcomes of IAH in patients with SAP and reported increased mortality, in-hospital and intensive care unit (ICU) length of stay, multiple organ failures, local and systemic complications and requirement of surgical interventions (Ke et al., 2012).

In both, SAP and IAH, surgery has an important role in complicated cases, however, there are no current studies evaluating the impact of surgery on mortality and morbidity outcomes in selected groups of patients with both SAP and IAH, in whom surgery could be associated with better outcomes by disrupting multiple pathophysiological pathways that worsen patient status. The aim of this study was to determine the impact of surgery in mortality and morbidity outcomes in patients with SAP and IAH or low abdominal perfusion pressure defined as an APP < 60 mmHg.

2. Materials and methods

2.1. Study design

We performed a single-center case-control study in adult patients who were hospitalized in the ICU of the National Institute of Medical Science and Nutrition Salvador Zubiran with the diagnosis of SAP and IAH during the period of 2007–2014. We reviewed all medical records of patients of both sexes, aged 16 years or older, who met current criteria for SAP and with at least two IAP measures recorded prior to any surgical intervention. All SAP events were considered irrespective of the interstitial edematous, necrotizing or hemorrhagic type. From these patients, we finally included only those who also met current criteria for IAH. During the evaluated period, all IAP measurements were performed according to the current international consensus, except in those patients who were not intubated and thereby could not be paralyzed. The follow up period was of at least one year or until death, whichever came first. Of the patients included, two subgroups were formed for the analysis, one with SAP and IAH and another with SAP and low APP defined as APP < 60 mmHg. In each subgroup the effect of surgery on the mortality and morbidity outcomes was evaluated by bivariate and multivariate analyses if feasible by sample size. Demographic data recorded were age, gender and pancreatitis etiology. The surgical interventions evaluated were a composite of either pancreatic necrosectomy or decompressive laparotomy. Mortality and morbidity outcomes were evaluated in the overall follow-up period. Morbidity outcomes evaluated were local and systemic complications, persistent organ failures, and infectious complications such as intra-abdominal infections, urinary tract infections and hospital acquired pneumonia, we only considered those morbidity outcomes developed after admission for patients who were not operated and after first surgery for patients who were operated. Local and systemic complications considered were those described in the Atlanta international consensus of 2012. Organ failures were defined with the modified Marshal scoring system for organ dysfunction proposed in the same Atlanta international consensus. Organ failure was defined as a score of two or more in any respiratory, renal or cardiovascular system. Respiratory failure was defined as a PaO₂/FiO₂ ≤ 300, renal failure was defined as a serum creatinine > 1.8 mg/dL and cardiovascular failure was defined as a systolic blood pressure < 90 mmHg, not fluid responsive. The infectious complications were defined by the respective guidelines of the Infectious Diseases Society of America (IDSA). Co-variables evaluated in the multivariate analyses were known adverse risk factors for morbidity and mortality in critically ill patients (previous abdominal surgery, gastroparesis, ileus, distended abdominal wall, haemoperitoneum, positive fluid balance of >4 liters within 48 hours, multiple transfusions, age > 50 years old, coagulopathy, bacteraemia, sepsis, overweight or obesity, digestive hemorrhage, PEEP > 10 mmHg and SOFA > 12), all were individually assessed for each outcome in particular, and those with greater significance were
included in each multivariate analysis. The number of co-variables included on each multivariate analysis depended on the respective sample size. Hospital and ICU length of stay were also recorded and only the patients that survived until discharge were considered for this analysis. The local ethics committee approved this work.

2.2. Statistical analyses
For the demographic analysis, continuous normally distributed variables were represented as mean and standard deviation, as the distribution for age was normal, and categorical variables were summarized as number and percentage. To compare the means of continuous normally distributed variables between groups; the Student’s $t$-test was performed. To determine the distribution of categorical variables between groups; the Chi-squared test was performed. For outcomes of morbidity and mortality we determined the association with odds ratio (OR) and confidence interval (CI) 95% using contingency tables in the bivariate analysis and binary logistic regression in the multivariate analysis. For determination of statistical significance the chi-square or Fisher exact tests were performed as appropriate. For the hospital and ICU length of stay outcomes the Mann–Whitney U test was performed for determination of statistical significant differences. For all statistical tests, a $p < 0.05$ was considered statistical significant. All statistical analyses were performed using SPSS version 21 software.

3. Results

3.1. Sample size and patient background
We found 117 medical records that initially matched inclusion criteria, but after review, 69 cases didn’t fulfill current criteria for SAP and IAH. Finally, we obtained a sample of 48 patients with IAH and of 35 patients with low APP (Figure 1). There were no differences in mean age distribution among operated and not operated patients in both IAH and low APP subgroups. However, for both sex and etiology categories, there were no differences in their distribution among operated and not operated patients in the IAH subgroup, but there were differences in the low APP subgroup. The majority of patients were aged between 20–39 years old with predilection of the male gender in a ratio of 2/1 to 3/1. In order of decreasing frequency, the causes of SAP were biliary, hypertriglyceridemia, alcohol and other. All the patient demographics are summarized in Table 1. Of the 48 patients evaluated, 25 underwent surgery, of which 22 were pancreatic necrosectomies and the other three were decompressive laparotomies.

![Flow diagram of the patients included in the study](image)
3.2. Mortality outcomes among patients with SAP in both subgroups of IAH and low APP

Among the patients with IAH, the overall mortality was of 36% in those who were operated and of 26.1% in those who were not operated. However, this difference was not significant in the bivariate analysis (OR = 1.59 [95% CI 0.46–5.49], p = 0.459). Similarly, among the patients with low APP the overall mortality was of 39.2% in those who were operated and of 41.7% in those who were not operated. This difference was also not significant in the bivariate analysis (OR = 0.90 [95% CI 0.21–3.72], p = 0.884). Kaplan–Meier survival curves are shown in Figure 2.

### Table 1. Patient demographics

| Values                  | Patients with SAP and IAH | Patients with SAP and low APP and low APP |
|-------------------------|---------------------------|-------------------------------------------|
| Age, years (SD)         | All patients n = 48       | Operated n = 25                           |
|                         | Not operated n = 23       | p                                         |
| Age range               | 46.7 ± 18.5               | 45.3 ± 18.1                               |
| <20 years, n (%)        | 0.584ab                   | 48.3 ± 19.2                               |
| 20–39 years, n (%)      | 1 (4)                     | 1 (4.3)                                   |
| 40–59 years, n (%)      | 17 (35.4)                 | 11 (31.4)                                 |
| ≥60 years, n (%)        | 12 (25.1)                 | 11 (31.4)                                 |
| Males, n (%)            | 32 (66.6)                 | 24 (68.5)                                 |
| Etiology                | Age, years (SD)           | 17 (73.9)                                 |
| Biliary, n (%)          | 46.7 ± 18.5               | 0.307ab                                   |
| Alcohol, n (%)          | 19 (39.5)                 | 15 (42.8)                                 |
| Hypertriglyceridemia, n (%) | 3 (12)                 | 9 (39.1)                                  |
| Post-ERCP, n (%)        | 4 (8.3)                   | 4 (11.4)                                  |
| Other, n (%)            | 15 (31.2)                 | 4 (11.4)                                  |
|                         |                           | 7 (28)                                    |
|                         |                           | 8 (34.7)                                  |
|                         |                           | 9 (25.7)                                  |
|                         |                           | 7 (30.4)                                  |
|                         |                           | 2 (5.7)                                   |
|                         |                           | 2 (8.6)                                   |
|                         |                           | 3 (6.2)                                   |
|                         |                           | 3 (12)                                    |
|                         |                           | 0 (0)                                     |
|                         |                           | 2 (6)                                     |
|                         |                           | 5 (21.9)                                  |
|                         |                           | 5 (14.4)                                  |
|                         |                           | 2 (8.9)                                   |
|                         |                           | 3 (14.8)                                  |
|                         |                           | 2 (8)                                     |
|                         |                           | 5 (21.9)                                  |
|                         |                           | 5 (14.4)                                  |
|                         |                           | 2 (8.9)                                   |
|                         |                           | 3 (25)                                    |

Notes: APP—abdominal-perfusion pressure; ERCP—endoscopic retrograde cholangiopancreatogram; IAH—intra-abdominal hypertension; SAP—severe acute pancreatitis.

*Student’s t-test.

χ² test.

Figure 2. Kaplan–Meier survival curves for both sub-groups of SAP with IAH and low APP.

Notes: SAP—severe acute pancreatitis; IAH—intra-abdominal hypertension; APP—abdominal perfusion pressure.
3.3. Morbidity outcomes in patients with SAP and IAH

In the bivariate analysis there was an association of risk for intra-abdominal infections (OR = 4.44 [95% CI 1.03–19.01], p = 0.036) and an association of protection for organ failure (OR = 0.18 [95% CI 0.52–0.66], p = 0.007), respiratory failure (OR = 0.16 [95% CI 0.04–0.58], p = 0.004) and renal failure (OR = 0.04 [95% CI 0.00–0.39], p = 0.0001). From these outcomes, in the multivariate analysis only an association of protection for organ failure (adjusted OR = 0.17 [95% CI 0.41–0.69], p = 0.014), respiratory failure (adjusted OR = 0.15 [95% CI 0.04–0.62], p = 0.008) and renal failure (adjusted OR = 0.02 [95% CI 0.00–0.24], p = 0.002) remained with statistical significance. The analysis for the systemic complications could not be performed as no single patient presented one. The multivariate analysis was performed only for the outcomes that achieved statistical significance in the bivariate analysis. All the analyses made in this subgroup are shown in Table 2. Otherwise, in this subgroup the surgical procedures significantly increased both the hospital and ICU length of stay (Figure 3).

Table 2. Outcomes in operated patients with severe acute pancreatitis and intra-abdominal hypertension

| Outcomes                  | Operated n = 25 | Not operated n = 23 | Bivariate analyses | Multivariate analyses |
|---------------------------|-----------------|---------------------|--------------------|----------------------|
|                           |                 |                     | OR                 | p                    | Adjusted OR | p         |
| Mortality                 | 9 (36%)         | 6 (26.1%)           | 1.59 (95% CI 0.46–5.49) | 0.459                |
| Local complication        | 11 (44%)        | 14 (60.9%)          | 0.50 (95% CI 0.16–1.59) | 0.243                |
| Infectious complication   | 15 (60%)        | 15 (65.3%)          | 0.80 (95% CI 0.24–2.58) | 0.709                |
| Intra-abdominal infection | 10 (40%)        | 3 (13.1%)           | 4.44 (95% CI 1.03–19.01) | 0.036 | 4.00 (95% CI 0.90–17.73) | 0.068 |
| Hospital acquired pneumonia| 10 (40%)    | 12 (52.2%)          | 0.61 (95% CI 0.19–1.91) | 0.398                |
| Urinary tract infection   | 9 (36%)         | 6 (26.1%)           | 1.59 (95% CI 0.46–5.49) | 0.459                |
| Organic failure           | 10 (40%)        | 18 (78.3%)          | 0.18 (95% CI 0.52–0.66) | 0.007 | 0.17 (95% CI 0.41–0.69) | 0.014 |
| Respiratory failure       | 5 (20%)         | 14 (60.9%)          | 0.16 (95% CI 0.04–0.58) | 0.004 | 0.15 (95% CI 0.04–0.62) | 0.008 |
| Cardiovascular failure    | 8 (32%)         | 9 (39.2%)           | 0.73 (95% CI 0.22–2.39) | 0.606                |
| Renal failure             | 1 (4%)          | 11 (47.8%)          | 0.04 (95% CI 0.00–0.39) | 0.0001 | 0.02 (95% CI 0.00–0.24) | 0.002 |

Notes: CI—confidence interval; IAH—intra-abdominal hypertension; OR—odds ratio; SAP—severe acute pancreatitis.
3.4. Morbidity outcomes in patients with SAP and low APP

In the bivariate analysis there was only an association of risk for renal failure (OR = 0.06 [95% CI 0.00–0.64], \( p = 0.012 \)). In this subgroup the multivariate analysis couldn’t be performed because of the small sample size. All the analyses made in this subgroup are shown in Table 3. Finally, in this subgroup the surgical procedures also significantly increased both the hospital and ICU length of stay (Figure 4).

### Table 3. Outcomes in operated patients with severe acute pancreatitis and low abdominal perfusion pressure

| Outcomes                      | Operated \( n = 23 \) | Not operated \( n = 12 \) | Bivariate analyses |
|-------------------------------|-----------------------|--------------------------|-------------------|
| Mortality                     | 9 (39.2%)             | 5 (41.7%)                | 0.90 (95% CI 0.21–3.72) | 0.884 |
| Local complication            | 10 (43.4%)            | 6 (50%)                  | 0.76 (95% CI 0.19–3.12) | 0.713 |
| Infectious complication       | 13 (56.6%)            | 6 (50%)                  | 1.30 (95% CI 0.32–5.27) | 0.713 |
| Intra-abdominal infection     | 9 (39.2%)             | 2 (16.7%)                | 3.21 (95% CI 0.56–18.20) | 0.174 |
| Hospital acquired pneumonia  | 8 (34.8%)             | 5 (41.7%)                | 0.74 (95% CI 0.17–3.12) | 0.689 |
| Urinary tract infection       | 8 (34.8%)             | 2 (16.7%)                | 2.66 (95% CI 0.46–15.25) | 0.260 |
| Organic failure               | 9 (39.2%)             | 8 (66.7%)                | 0.32 (95% CI 0.07–1.38) | 0.122 |
| Respiratory failure           | 4 (17.4%)             | 3 (25%)                  | 0.63 (95% CI 0.11–3.43) | 0.670 |
| Cardiovascular failure        | 7 (30.5%)             | 7 (58.3%)                | 0.31 (95% CI 0.07–1.33) | 0.110 |
| Renal failure                 | 1 (4.4%)              | 5 (41.7%)                | 0.06 (95% CI 0.00–0.64) | 0.012 |

Notes: APP—abdominal perfusion pressure; CI—confidence interval; OR—odds ratio; SAP—severe acute pancreatitis.
4. Discussion
From the results obtained, we can estimate that the surgical interventions have no association with mortality in both subgroups studied.

Interestingly, there was a marked difference in the rate of respiratory failures between patients with IAH (60.9%) and those with low APP (25%) that were not operated. This could be explained by the fact that IAH implies two main pathophysiological mechanisms; one that involves restriction of the thoracic compliance and another that involves lowering the APP, on the other hand, low APP mainly involves the second mechanism as a result of lower MAP’s. Further, the surgical interventions seem to have a protective association for the development of respiratory and renal failures in the subgroup with IAH and only for the development of renal failures in the subgroup with low APP. This could be explained in a similar way by a therapeutic role of surgical procedures in the disruption of some particular pathophysiological mechanisms related to elevated intra-abdominal pressure, as in the subgroup of patients with IAH the elevated IAP causes restriction for the ventilation, and therefore, it’s possible that the release of the abdominal pressure by surgery have resulted in reduction in the pulmonary restriction making less likely the development of further respiratory failures. Otherwise, in the subgroup of patients with low APP the circulation of the kidneys is compromised and this increases the risk for the development of renal failures, so the improvement in the renal perfusion pressure secondary to the therapeutic effect of the surgical procedures in lowering the IAP may have been the reason why this subgroup of patients presented lower rates of new renal failures. However, regarding all the morbidity results, the associations found should be considered as weak since as a bias of this study, many patients had a shorter time of follow up because of early and significant mortality (30–40%).
As this is a retrospective study, the patients that we included originally underwent surgery following a particular indication such as the presence of infected pancreatic necrosis or an abdominal compartment syndrome, and it is possible that the effect of surgery made under these particular indications had been the real cause of the organ failure prevention.

For this reason, we performed a multivariate sub-analysis including the co-variables of infected pancreatic necrosis and abdominal compartment syndrome for the outcomes of respiratory and renal failures. The analysis could only be performed in the IAH subgroup because of the sample size. Among the 48 patients that had IAH, 25 of them underwent surgery and from this operated patients, 21 had infected pancreatic necrosis. When we performed the multivariate sub-analysis with the variables of surgery and infected pancreatic necrosis, we found that the presence of infected pancreatic necrosis acted as a confounding factor for the respiratory failure outcome and both as a confounding and interacting factor for the renal failure outcome. From the same 25 patients with IAH that underwent surgery, eight of them had abdominal compartment syndrome. In the multivariate sub-analysis with the variables of surgery and abdominal compartment syndrome, we found that the presence of an abdominal compartment syndrome acted as an interacting factor for the renal failure outcome. So it seems that the surgical procedures made under the indication of infected pancreatic necrosis could have been the reason for the lower rates of respiratory and renal failures, and made under both the indications of infected pancreatic necrosis and abdominal compartment syndrome could have been an additional factor contributing to the lower rates of renal failures.

As a practical summary of our findings, it seems that performing surgical procedures in patients with SAP and IAH or low APP does not seem to be a recommended approach. Although it apparently can result in lower rates of respiratory and renal failures, it doesn’t decrease the mortality but increases the hospital and ICU length of stay. So for the time being in patients with SAP and IAH it would be more reasonably to perform surgery case by case following the current guidelines by the indications of infected pancreatic necrosis and/or abdominal compartment syndrome.

Several limitations are evident with our study design. First, as this is a case-control study of retrospective nature, in general our results have low strength of association and evidence, however, it was intended as an exploratory study as there are no similar studies performed previously, and because of the low incidence of such severe cases, a case-control study represented an appropriate design for this purpose. Secondly, due to the small sample size, it was not possible to evaluate whether there were differences between groups of patients with different degrees of IAH, so that patients with a higher degree of IAH hypothetically may have had better benefits from surgical procedures. Finally, as well as in other studies in critically ill patients, it is possible that some variables with significant impact on the outcomes have not been considered in the analysis, so that a specific association cannot be demonstrated.

In conclusion, among patients with SAP surgery seems to be protective for the development of new respiratory and kidney failures in the subgroup with IAH and only for the development of new kidney failures in the subgroup with low APP, nonetheless it has no impact on overall mortality and it does significantly increases the hospital and ICU length of stay in both subgroups.
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