Intra-Abdominal Pressure in the Early Phase of Severe Acute Pancreatitis: Canary in a Coal Mine? Results from a Rigorous Validation Protocol

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Background/Aims: Intra-abdominal hypertension (IAH) is being increasingly reported in patients with severe acute pancreatitis (SAP) with worsened outcomes. The present study was undertaken to evaluate intra-abdominal pressure (IAP) as a marker of severity in the entire spectrum of acute pancreatitis and to ascertain the relationship between IAP and development of complications in patients with SAP.

Methods: IAP was measured via the transvesical route by measurements performed at admission, once after controlling pain and then every 4 hours. Data were collected on the length of the hospital stay, the development of systemic inflammatory response syndrome (SIRS), multiorgan failure, the extent of necrosis, the presence of infection, pleural effusion, and mortality.

Results: In total, 40 patients were enrolled and followed up for 30 days. The development of IAH was exclusively associated with SAP with an APACHE II score ≥8 and/or persistent SIRS, identifying all patients who were going to develop abdominal compartment syndrome (ACS). The presence of ACS was associated with a significantly increased extent of pancreatic necrosis, multiple organ failure, and mortality. The mean admission IAP value did not differ significantly from the value obtained after pain control or the maximum IAP measured in the first 5 days.

Conclusions: IAH is a reliable marker of severe disease, and patients who manifest organ failure, persistent SIRS, or an Acute Physiology and Chronic health Evaluation II score ≥8 should be offered IAP surveillance. Severe pancreatitis is not a homogenous entity.

Key Words: Intra-abdominal hypertension; Pancreatitis

INTRODUCTION

Pancreatitis remains a disease whose unpredictable course can humble even the most astute physicians and hence the quintessential search for prognostic factors remains. While newer molecular markers for predicting disease severity offer hope, but they provide little by means as a point of intervention frustrating care givers and patients alike. There have been significant advances in the past decade about our knowledge of the natural course and underlying pathophysiology of the disease and similarities between manifestations of fulminant acute pancreatitis (an early disease course characterised by pulmonary, cardiovascular, and renal insufficiency which may lead to rapidly progressive multiple organ dysfunction syndrome) and abdominal compartment syndrome (ACS) has increasingly drawn investigators to study relationship between the two. While conservative treatment still remains as standard of care in the initial phase of disease yet increasing evidence offers that a subgroup of patients with early severe disease may benefit from specific surgical/interventional procedures. While offering a much elusive point of therapeutic intervention, evidence is still scarce whether intra-abdominal pressure (IAP) measurements should be routine in all patients with acute pancreatitis or can some selectivity be maintained and how can the patient at risk for developing intra-abdominal hypertension (IAH) and ACS be identified at the earliest. Scarcity of data from patients with mild disease, less than rigorous adherence to guidelines framed by World Society of Abdominal Compartment Syndrome (WSACS) in the measurement of IAP, retrospective study designs with measurements obtained in selected individuals, recent change in guidelines for IAP measurement by WSACS in 2006 added to the difference in the way severe disease is defined between various workers are few of the issues in many previous studies adding much to the
dilemma of treating physician in interpreting results from previous literature. This study was undertaken with a prospective design with an aim to evaluate IAP as a marker of severity in acute pancreatitis and to ascertain the relationship between IAP and development of complications in patients with severe acute pancreatitis (SAP) following a rigorous validation protocol in accordance with up to date guidelines at the time of beginning this study in January 2009.

MATERIALS AND METHODS

1. Subjects

After obtaining Institutional and University ethical committee approval (the work awarded as theses for grant of postgraduate degree to one of the authors, with all patients providing written informed consent and work being in accordance with the Declaration of Helsinki (2000) of the World Medical Association; all individuals more than 18 years of age and duration of symptoms less than 72 hours admitted to Safdarjung Hospital surgical emergency with diagnosis of acute pancreatitis were included in this prospective study carried from January 2009 till March 2010 with 40 patients finally included in study population after appropriate exclusions. Any two of the following three features were used to diagnose acute pancreatitis: 1) abdominal pain suggestive strongly of acute pancreatitis; 2) serum amylase and/or lipase activity at least three times greater than the upper limit of normal; and 3) characteristic findings of acute pancreatitis on transabdominal ultrasonography or on contrast enhanced computed tomography (CECT) scan, or magnetic resonance imaging.

Classification of a case as mild or SAP was based on standard criteria as defined by Atlanta Symposium 1992. Acute Physiology and Chronic health Evaluation II (APACHE II) score ≥8 (calculated during the first 24 hours) was used only as predictive marker for SAP and not actual severe disease. Pregnant females and individuals with significant comorbid conditions like renal failure, cardiac disease, chronic abdominal pathology, and immunosuppression were excluded from the study.

2. IAP measurement and monitoring protocol

To determine IAP a Foley catheter inserted into the bladder and instilled with 25 mL sterile saline (1 mm Hg=1.36 cmH2O) with mid axillary line as level 0 was used. We followed a modification of low cost transvesical technique described by Basu (JIPMER India); to measure the IAP after further pretesting it independently in five patients undergoing laparoscopic elective cholecystectomy (by using tubing connected to a central venous pressure manometer obviating the need of a ruler to improve reproducibility). IAP was measured at immediate admission and after control of severe acute pain by optimal use of analgesics (including paracetamol, nonsteroidal anti-inflammatory drugs, fentanyl, tramadol hydrochloride, and morphine as necessary in individual case) to minimize the possible confounding effect of pain on IAP measurement. Pain control was assessed by visual analogue scale (VAS) targeted to values ≤4 (on a scale from 1 to 10) in awake patients or Richmond Agitation Sedation Scale 0 in intubated patients. Care was taken to delay IAP measurement by 30 minutes in case any procedure possibly causing pain was done and VAS was reassessed immediately prior to IAP assessment to avoid confounding by breakthrough pain of any intervention. Further IAP measurements were done every 4 hourly. IAP measurements were done hourly for those with ACS.

Maximum IAP was defined as the maximum pressure recorded in all readings in the first 5 days. IAH was defined as consistently increased IAP ≥12 mm Hg recorded by 2 readings during at least 8 hours. IAP measurements were continued as long as

| Table 1. Modified Marshall Scoring System for Organ Dysfunction Score |
|---------------------------------------------------------------|
| Organ system | 0 | 1 | 2 | 3 | 4 |
| Respiratory (PaO2/FiO2) | >400 | 301-400 | 201-300 | 101-200 | ≤101 |
| Renal* (serum creatinine, mmol/L) | ≤134 | 134-169 | 170-310 | 311-439 | >439 |
| Renal* (serum creatinine, mg/dL) | <1.4 | 1.4-1.8 | 1.9-3.6 | 3.6-4.9 | >4.9 |
| Cardiovascular (systolic blood pressure, mm Hg)† | >90 | <90 and fluid responsive | <90 and not fluid responsive | <90, pH<7.3 | <90, pH<7.2 |

For nonventilated patients, the FiO2 can be estimated from below:

| Supplemental oxygen, L/min | FiO2 (%) |
|----------------------------|----------|
| Room air                   | 21       |
| 2                          | 25       |
| 4                          | 30       |
| 6-8                        | 40       |
| 9-10                       | 50       |

A score of 2 or more in any system defines the presence of organ failure.

*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 µmol/L or ≥1.4 mg/dL; † Off inotropic support.
patient manifested any sign of acute organ dysfunction and were discontinued only when IAP values had been below 10 mm Hg for 48 hours (in absence of any acute organ dysfunction). In case of any recurrent organ dysfunction IAP measurements were reconsidered. IAP was thus successfully measured in all patients with mild pancreatitis for at least 2 days or more in case of need as assessed by above said criteria (minimum 12 recordings every 4 hourly).

IAP was measured in all patients with severe pancreatitis for at least 3 days or more in case of need as assessed by above said criteria (minimum 18 recordings every 4 hourly were successfully obtained in patients with severe pancreatitis but no IAH, minimum 30 recordings every 4 hourly were successfully obtained in all patients with severe pancreatitis and presence of IAH, even more frequent recordings were obtained in patients with ACS).

ACS was defined as sustained IAP >20 mm Hg (measured by two readings at least 4 hours apart) that was associated with organ dysfunction-failure. Organ dysfunction-failure for a particular organ system was defined as modified Marshall score ≥2 for that particular organ system (Table 1). Modified Marshall score was calculated daily (using the worst values of physiological variables for the day for a particular organ system) and was used to follow-up response of patient to therapy and was used to individualize day to day hospital management of the patient (organ failure as defined by Atlanta Symposium was used only to determine severity of acute pancreatitis). Furthermore modified Marshall score 2 has similar cut offs of values for shock, disseminated intravascular coagulation (DIC), renal failure and respiratory failure as Atlanta Symposium definitions for organ failure. This is in accordance with WSACS guidelines which recommend using Sepsis Related Organ Failure Assessment score ≥3 or an equivalent score to determine organ failure while deciding presence or absence of ACS.5,12

3. Patient management protocol

Patients were treated by our standard management of pancreatitis protocol and practice guidelines in acute pancreatitis.5 All patients with the diagnosis of SAP underwent a CECT scan by the seventh day (preferably on fifth day) or earlier as deemed necessary (repeat computed tomography [CT] scan decision was individualised if a prior CT scan was available) and the morphologic characteristics on the CECT scan were evaluated by a senior radiologist with calculation of CT severity index.13

Infected necrosis was deduced by presence of gas in retro peritoneum on CECT scan and supported by a positive blood culture or/and confirmed by fine needle aspiration cytology of necroma under ultrasound or CT guidance. Operative management for infected necrosis was done by necrosectomy and closed continuous postoperative lavage apart from antibiotics. Established hospital protocol did not consider IAP measurements while management of acute pancreatitis but individual decisions regarding management of IAH and ACS were made in discussion with critical care team and patient and relatives based on best available evidence.

Data was also collected about body mass index (BMI), length of hospital stay, development of persistent systemic inflammatory response syndrome (SIRS; persistent defined as lasting more than 24 hours; diagnosed if two or more of the standard four criteria detected), multiorgan failure (two or more organs showing modified Marshall score ≥2), and presence of septic complications, intra-abdominal collections needing aspiration, and/or percutaneous drainage apart from standard demographic and clinical data.14

4. Follow-up

All patients were followed up for at least 30 days from initial episode of acute pancreatitis (less in case of mortality before this interval). Weekly visits were scheduled in the Out Patient Department in case patient was discharged earlier.

5. Statistical methods

All continuous variables; are presented as the median (interquartile range) or as mean±SD and the proportions are expressed as numbers (%). The independent sample t-test, Mann-Whitney U test and Fisher exact F test with appropriate corrections were used for data analysis with level of significance decided beforehand at p<0.05 with two tailed distribution.15 Friedman test was used to compare multiple measurements obtained for the same patient over different time intervals. Kruskall-Walls test was used to evaluate covariance among independent samples for nonparametric data. Confidence intervals (CIs) are reported with 95% confidence limits with appropriate corrections.

RESULTS

A total of 40 patients were included in the prospective study with Table 2 summarizing the distribution of patients across mild (n=24, 60%) and severe (n=16, 40%) study groups with similar distribution of age, gender, and aetiology of acute pancreatitis. Interestingly, higher BMI is significantly associated with development of severe disease. Patients presented with mean 1.7 (0.3) days of symptoms. Peak IAP was noted on a median 2 days (interquartile range, 1 to 3 days) from the onset of symptomatology. Not a single case of IAH was noted in the patients with mild pancreatitis (median IAP 8, [4.5 to 8 mm Hg]) and thus no further analyses of this subgroup of study population was felt necessary. No deaths were noted in patients with mild pancreatitis. IAH was thus noted to be a phenomenon almost exclusively associated with severe disease (95% CI, 0.7% to 20%, Binomial Wilson).

Among patients with SAP three scenarios were noted either they did not develop IAH (n=8, 50%) or they developed IAH but
not ACS (n=5, 31.2%), or they developed ACS (n=3, 18.7%) (Fig. 1). Mortality was not noted among patients without IAH (Table 3) and was significantly higher in patients with ACS than in patients with severe disease but without ACS (Table 4). Median duration of hospital stay was noted to be significantly higher in patients with severe pancreatitis and IAH (median 14 days [12 to 24 days]; excluding patients with early mortality within 5 days) than those without IAH but with severe disease (median 8 days [7 to 8 days]; p=0.0054; Mann-Whitney U statistic 0.5). Multiple organ failure and extent of pancreatic necrosis >50% were seen exclusively among patients with ACS. Infected pancreatic necrosis was also found exclusively in patients with IAH with two cases of ACS developing evidence of infection of pancreatic necrosis late in the course of disease while one patient with ACS dying within 3 days of admission. Among patients with severe disease and IAH but without ACS only one patient developed infection of pancreatic necrosis while no infection of pancreatic necrosis were noted in patients with severe disease without IAH. Thus patients with severe disease and IAH had higher incidence of infection in pancreatic necrosis than patients with severe disease but no IAH (p=0.076). Interestingly, the admission values of IAP did not differ significantly from Maximum IAP values over the next 2 to 5 days and effect of pain control on measured IAP values appeared negligible (Fig. 2) with all awake patients achieving scores ≤4 on VAS scale (median 2 [1 to 2]). All three of APACHE II score ≥8, IAP >8 mm Hg, and persistent SIRS were found to compare favourably in identifying patients with acute pancreatitis going to develop severe disease on receiver operating characteristic analyses (Fig. 3). Moreover APACHE II score ≥8 and persistent SIRS were found 100% sensitive in identifying patients with severe disease that were going to develop ACS (Table 5). IAP shared a strong significant positive relationship (Pearson r=0.8064) with APACHE II score (Fig. 4) and as another affirming measure the three ordinal subgroups of patients with severe disease based on

### Table 2. Demographic and Clinical Variables for Patients with Mild and Severe Acute Pancreatitis

| Variable                              | Mild pancreatitis (n=24) | Severe pancreatitis (n=16) | p-value |
|---------------------------------------|--------------------------|-----------------------------|---------|
| Age, yr                               | 49.5 (40.5-57)           | 43.5 (37-49.5)              | NS*     |
| Male sex                              | 14 (58.3)                | 10 (62.5)                   | NS*     |
| Body mass index                       | 23.7 (1.1)               | 26.2 (2.4)                  | <0.001* |
| Aetiology                             |                          |                             |         |
| Biliary                               | 10 (41.6)                | 8 (50)                      | NS†     |
| Idiopathic                            | 7 (29.1)                 | 3 (18.7)                    |         |
| Alcoholic                             | 5 (20.8)                 | 5 (31.2)                    |         |
| Hyperlipidemia                        | 1 (4.1)                  |                             |         |
| Others                                | 1 (4.1)                  |                             |         |
| APACHE II score in first 24 hours of admission | 4 (3-6)                  | 9 (6-11.5)                  | 0.0008* |
| CT severity index                     | 2 (1-2)                  | 6 (4-8)                     | <0.0001*|
| Maximum IAP, mm Hg                    | 8 (4.5-8)                | 12 (8-16)                   | <0.0017*|
| Persistent SIRS                       | 3 (12.5)                 | 12 (75)                     | <0.01 (RR, 6; CI, 2-17.9) |
| Deaths                                | 0                        | 4 (25.1)                    | 0.02†   |
| Duration of stay, day                 | 5 (4-6)                  | 11 (9-23)                   | <0.0001*|

Data are presented as median (interquartile range) or number (%). NS, not significant; APACHE, Acute Physiology and Chronic Health Evaluation; CT, computed tomography; IAP, intra-abdominal pressure; SIRS, systemic inflammatory response syndrome; RR, relative ratio; CI, confidence interval.

*Unpaired t-test, Welch corrected, normality tested by Kolmogorov and Smirnov method; †Fisher exact test, with a confidence interval calculated using the approximation of Katz; ‡Mann-Whitney U test (if one or both datasets failed the normality test).
DISCUSSION

Our study confirms the findings of many previous observers that acute pancreatitis is a risk factor for developing IAH and ACS. A summary of epidemiology of IAH and ACS in patients with SAP is given in Table 3. Absence of IAH and ACS in patients with mild disease and incidence of IAH in 50% patients with severe disease and ACS in 18.7% patients with severe disease is in agreement with the data in more recent series and is the lowest reported so far. Effort has been made to strictly follow the prescribed protocol in measurement of IAP with consideration given to confounding factor of pain as well as timing of initial measurement which has not been explicitly detailed so far in previous literature. IAH is noted to be an early phenom-
enon and is amenable to intervention and thus it makes sense to recommend its surveillance. Increasingly data is accumulating that early surgical decompression may help reduce mortality in patients with SAP and ACS. There has been scepticism in past if IAP monitoring helped survival but recent evidence shows improvement in survival with evolving management of IAH and ACS. Although not yet specifically proven in patients with SAP; findings of significantly increased extent of pancreatic necrosis in patients with ACS along with increased incidence of infection in presence of IAH in view of the known fact of infection of pancreatic necrosis being one of the main determinants of mortality in patients with SAP offers provoking evidence. Moreover our study hints at possible subcategories among spectrum of patients with severe disease discriminated by IAP and thus patients with severe disease may not be a homogenous group. This inhomogeneity has been considered in a recently suggested update for classification of acute pancreatitis who have also recommended modified Marshall score for assessment of organ failure.

Routine transvesical pressure measurements in all patients with acute pancreatitis may be cumbersome and not without risks and our study identified that all patients with manifest organ failure or persistent SIRS or APACHE II score ≥8 should be offered IAP monitoring and present guidelines by WSACS may be followed. Presence of IAH and ACS remain as valid marker for severe disease with its presence in mild disease being rare.

In conclusion, presence of IAH in the setting of acute pancreatitis is associated with severe disease, increased development
of infected pancreatic necrosis (p=0.076) and a significantly longer hospital stay (p=0.0054) with ACS being associated with increased extent of pancreatic necrosis, multiple organ failure and mortality among patients with severe disease (all p-values <0.01). Routine transvesical pressure measurements in all patients with acute pancreatitis may not be necessary and patients with manifest organ failure or persistent SIRS or APACHE II score ≥8 should be offered IAP surveillance.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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