Impact of Targeted Preoperative Optimization on Clinical Outcome in Emergency Abdominal Surgeries: A Prospective Randomized Trial

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Abstract

Background: Perforation peritonitis continues to be one of the most common surgical emergencies that need a surgical intervention most of the times. Anesthesiologists are invariably involved in managing such cases efficiently in perioperative period. Aims: The assessment and evaluation of Acute Physiology and Chronic Health Evaluation II (APACHE II) score at presentation and 24 h after goal-directed optimization, administration of empirical broad-spectrum antibiotics, and definitive source control postoperatively. Outcome assessment in terms of duration of hospital stay and mortality in with or without optimization was also measured. Settings/Design: It is a prospective, randomized, double-blind controlled study in hospital setting. Materials and Methods: One hundred and one patients aged ≥18 years, of the American Society of Anesthesiologists physical Status I and II (E) with clinical diagnosis of perforation peritonitis posted for surgery were enrolled. Enrolled patients were randomly divided into two groups. Group A is optimized by goal-directed optimization protocol in the preoperative holding room by anesthesiology residents whereas in Group S, managed by surgery residents in the surgical wards without any fixed algorithm. The assessment of APACHE II score was done as a first step on admission and 24 h postoperatively. Duration of hospital stay and mortality in both the groups were also measured and compared. Statistical Analysis: Categorical data are presented as frequency counts (percent) and compared using the Chi-square or Fisher’s exact test. The statistical significance for categorical variables was determined by Chi-square analysis. For continuous variables, a two-sample t-test was applied. Results: The mean APACHE II score on admission in case and control groups was comparable. Significant lowering of serial scores in case group was observed as compared to control group ($P = 0.02$). There was a significant lowering of mean duration of hospital stay seen in case group (9.8 ± 1.7 days) as compared to control group ($P = 0.007$). Furthermore, a significant decline in death rate was noted in case group as compared to control group ($P = 0.03$). Conclusion: Goal-directed optimized patients with perforation peritonitis were discharged early as compared to control group with significantly lesser mortality as compared with randomly optimized patients in the perioperative period.

Keywords: Acute Physiology and Chronic Health Evaluation II, intestinal perforation, outcomes assessment, preoperative period

Introduction

Peritonitis is inflammation of the peritoneum and is most commonly due to a localized or generalized infection. It can be primary, secondary, or tertiary based on the source and nature of microbial contamination. Secondary peritonitis which is due to perforation of the hollow viscus continues to be one of the most common surgical emergencies. Risk factors among the general population include among others, Helicobacter pylori infection, indiscriminate use of steroids and nonsteroidal anti-inflammatory agents, and enteric fever in addition to several other less common causes. This condition most of the times needs an emergency surgical intervention. Since there is lack of data in India regarding its prognostic indicators, morbidity, and mortality patterns,[1] application of a scoring system, is needed to stratify the patients to assess the type and level of care required for a particular patient.

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How to cite this article: Sethi A, Debbarma M, Narang N, Saxena A, Mahobia M, Tomar GS. Impact of targeted preoperative optimization on clinical outcome in emergency abdominal surgeries: A prospective randomized trial. Anesth Essays Res 2018;12:149-54.
The management protocols include mandatory preoperative optimization by intensivist or anesthesiologist to certain extent, surgical intervention, broad-spectrum antimicrobial therapy, and intensive care support. Despite this, management of peritonitis is highly demanding and complex.[2] This group of patients invariably presents with features of sepsis on admission, and thus, the management of sepsis has to be primarily incorporated in the perioperative management protocol. Many anesthesiologists usually may get involve in perioperative period to offer nonpracticing intensive care to such cases in an efficient manner. In recent times, role of anesthesiologist has been evolved as a perioperative physician, and there is definite need to diversify their scope of specialty to critical or intensive care management so as to ensure future leadership position in perioperative medicine. There are various scoring indices such as Acute Physiology and Chronic Health Evaluation (APACHE) score (based on 34 Physiological parameters), the multiorgan failure score,[11-13] and the Mannheim Peritonitis Index,[14,15] for risk stratification in patients of perforation peritonitis. APACHE II was later developed as a simplified and clinically useful system using 12 physiological variables.[16] The score can be translated to a mortality risk level that correlates with observed mortality with reasonable accuracy [Appendix 1].

APACHE II scoring system has been found to be superior in the prediction of outcome in critically ill patients with perforation peritonitis undergoing emergency laparotomy when used either preoperatively or postoperatively in some studies.[12,13] This system can stratify a wide variety of patients prognostically because of the strong and consistent underlying relationship between acute physiologic derangement and the risk of death during acute illness. APACHE II score has been found to be correlated well to accentuate and measure the various factors needed for better management of underlying pathological condition.[14] Whereas, the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient.[15] In addition, APACHE II is more reliable for the prediction of mortality in secondary peritonitis patients reserved for planned relaparotomy, unlike SOFA.[14] Acute physiological score of APACHE II tends to change in conditions leading to deranged homeostasis. This study has taken into account the APACHE II score and tried to establish a relationship between goal-directed optimization, surgical source control, changes in serial APACHE II scores, and clinical outcome. Objectives of this study were to assess and evaluate APACHE II score at presentation and 24 h after goal-directed optimization, administration of empirical broad-spectrum antibiotics, and definitive source control postoperatively. Outcome in terms of duration of hospital stay and mortality in both the groups were also measured.

**Materials and Methods**

**Patients**

After obtaining clearance from the Institutional Ethics Committee and informed written consent from patients, the study was conducted in accordance with the principles laid out in the Declaration of Helsinki, 2000 from July 2014 to July 2016. Patients with spontaneous bacterial peritonitis, malignancy, patients on anticoagulant therapy, and requiring mechanical ventilation preoperatively were excluded from the study.

**Study design and randomization**

This was a prospective randomized double-blind study. Out of 111 enrolled patients, 101 patients aged 18 years and above of the American Society of Anesthesiologists physical Status I and II (E) with clinical diagnosis of perforation peritonitis were randomly divided into two groups as Group A (Case): 47 patients optimized by goal-directed optimization protocol in the preoperative holding room by anesthesiology residents; whereas in Group S (Control): 54 patients managed by surgery residents also unaware about study in the surgical wards without any fixed algorithm. Randomization was based on a computer-generated random table in accordance with CONSORT guidelines [Figure 1]. The group assignments were based on kept sealed envelopes with allocated group name. The patients, surgeons, and the anesthesiologists involved were unaware of the subjects’ group assignment and study as such.

Patients with abdominal emergencies admitted to general surgery units were prescreened and were included in the study only after a clinical diagnosis of perforation peritonitis was made with reasonable certainty. Assessment of APACHE II score [Appendix 1] was done as a first step and patients were randomly assigned to one of the two groups, case Group (A) and control Group (S). Patients of the case group received standardized, algorithmic management in the preoperative holding room. Central venous cannulation was performed, and goal-directed optimization of these patients was carried out by the anesthesiology resident on call. Those in the control group were managed in the surgery wards by the surgical resident on call. Patients assigned to the case group were optimized till the following targets were achieved central venous pressure (CVP) between 8 and 12 cm H₂O, mean arterial pressure (MAP) of 65 mmHg or above, and urine output equal to or >0.5 ml/kg/h.

The departmental fixed protocol for goal-directed optimization was as follows: boluses of 0.9% saline 20–30 ml/kg of body weight were given every 30 min to achieve the first goal (CVP 8–12 cm H₂O). If MAP was <65 mmHg after reaching the first goal, vasopressor (norepinephrine infusion) was given to achieve and maintain the second goal (MAP >65 mmHg). Our third goal was to ensure a urine output of >0.5 ml/kg/h. Every admitted patient included in this study underwent Foley’s urine catheterization as a part of hospital protocol, and urine output was monitored with the aid of urometer on hourly basis. For achieving set target of urine output ≥0.5 ml/kg/h, every patients in case group were adequately resuscitated with rapid administration of crystalloid (ringer lactate, 0.9% normal saline). In some patients’ volume up to 30–40 ml/kg were also administered. However, colloids (hydroxyethyl starches) and diuretics were avoided completely to achieve this goal.
perioperatively. In contrast, the patients in control group were managed according to the clinical judgment without any fixed algorithm. Empirical broad-spectrum antibiotic cover was given to all such patients suspecting sepsis in both the groups as a part of institutional protocol. Patients in the case group were taken up for surgery after objectively achieving all three goals (end points of resuscitation) while those in the control group were taken up for surgery after subjective hemodynamic stabilization.

**General anesthesia**
All patients in each group received standard general endotracheal anesthesia. General anesthesia was induced by administering intravenous (IV) fentanyl (2 µg/kg), propofol (1–2 mg/kg), and tracheal intubation was facilitated with IV rocuronium (0.9 mg/kg) and appropriate sized endotracheal tube. Mechanically controlled ventilation was adjusted to maintain a tidal volume of 8 mL/kg, and rate of ventilation was adjusted to maintain end-tidal carbon dioxide (EtCO₂) at 30–35 mm Hg. Maintenance of anesthesia was carried out using isoflurane at 1 minimum alveolar concentration in a total gas flow of 2 L/min of an air and oxygen mixture delivered from a closed circle absorber breathing circuit with intermittent IV boluses of atracurium. Intraoperatively, electrocardiogram, heart rate, oxygen saturation, noninvasive blood pressure, EtCO₂, and urine output were monitored. Decision to extubate the patients or to continue ventilation was based on the patient’s clinical condition and immediate postoperative arterial blood gas parameters. Intraoperatively, each patient of both groups subjected to similar anesthetic strategy and management as per preplanned strategy informed to the involved anesthesiologist unaware about the study. Patients were intensively observed in Intensive Care Unit (ICU) for first 24 h after surgery as a part of institutional protocol. In postoperative period (during first 24 h) also each patient from both groups receive similar ICU care unprejudiced. Thereafter, patients were closely monitored in postoperative recovery room for the next 72 h.

**The studied variables**
The primary end point was to measure APACHE II score 24 h postoperatively in each patient. Patients were shifted to postoperative ward after 72 h and followed up till discharge from hospital. In hospital, duration of stay and mortality were taken as the secondary end points parameters to assess.

**Statistical analysis**
All cases data forms were checked for completeness and inappropriate or illogical responses. The forms were entered using Microsoft 2013 Excel worksheet. The databases were validated, and all inconsistencies and differences were resolved. Statistical analyses were performed using STATA 12 for Windows (Stata Corp E.P., Texas, USA). A sample size of approximated 50 including 10% dropouts in each group with an α error of 5% and a β error of 20% was based on the previous study[7] to powered the study to approximately 80%. Categorical data are presented as frequency counts (percent) and compared using the Chi-square or Fisher’s exact statistics as appropriate. The statistical significance for categorical variables was determined by Chi-square analysis. For continuous variables, a two-sample t-test was applied. Results were expressed as mean ± standard deviation with confidence intervals. \( P < 0.05 \) was considered statistically significant.
RESULTS

Out of 101 allocated patients in both groups, 7 were excluded from final data analysis because of disagreement with preset study protocol criteria [Figure 1]. Demographic parameters such as age, sex, and gender were comparable among each group [Table 1]. The mean APACHE II score on admission in case group is 6.8 ± 3.7 and in the control group is 7.1 ± 2.6. There was no significant difference between the two study groups [Table 2]. There is a significant lowering of serial APACHE II scores in case group as compared to control group \( P = 0.02 \); Table 2. Serum lactate levels at the time of admission in control and case group were 3.45 and 3.38 mmol/L respectively [Table 2]. Majority of operative procedure were omentopexy of prepyloric perforation and primary repair of ileal perforation with proximal ileostomy [Table 3]. Postoperatively after 24 h, serum lactates values were 3.14 and 2.02 mmol/L in control and cases, respectively, that were found to be highly significant on analysis \( P < 0.001 \). Most commonly encountered complication in immediate postoperative period was atelectasis or ventilator-associated pneumonia and wound infection [Table 4]. However, the incidence of overall complications was seen higher in control group but on comparison no statistical significance was found. On follow-up examination, no significant difference was noticed except for the mortality. There was significant lowering of mean duration of hospital stay seen in case group (9.8 ± 1.7 days) as compared to control group (11.26 ± 3.2 days) \( P = 0.007 \); Table 2. The number of deaths in case group was 4.3% while that in the control group was 18.7%. There was significant decline in death rate in case group as compared to control group \( P = 0.03 \); Table 2.

DISCUSSION

Majority of the perforation peritonitis patients present late with sepsis which further increases morbidity and mortality. Both sepsis and third space loss of fluid due to perforation leads to imbalance between oxygen demand and delivery resulting in tissue hypoxia and subsequent multiple organ failure. Several studies support the concept that persistent shock have an adverse impact on survival in a time-dependent manner and therapeutic strategies involving early recognition and rapid reversal of shock improves survival. Perforation peritonitis is a frequently encountered surgical emergency in tropical countries like India. It affects mostly the young population.\(^1\)\(^2\) Despite advances in management protocols, it poses a formidable challenge for perioperative physicians.\(^3\)

Majority of cases present late with features of sepsis and septic shock.\(^10\) Therefore, for such a setting, there is enough justification in favor of goal-directed optimization which has evidence-based role in improving outcomes in sepsis and septic shock as established after the landmark study by Rivers et al.\(^{17}\)

In this study, we found that the majority of patients had upper gastrointestinal tract perforation, i.e., 54% suffered from prepyloric perforation and the rest had ileal perforation [Table 3]. This concurs with earlier studies of Jhobta et al.\(^{16} \) and Ramachandra et al.\(^{18} \) which showed greater percentage of perforation cases involving upper gastrointestinal tract in India. APACHE II is a severity of disease classification system,\(^{11}\) among one of the several ICU scoring systems. It is applied within 24 h of admission in an ICU, an integer score from 0 to 71 computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. We observed that the majority of the patients in case group showed features of sepsis; notably, tachycardia (pulse rate >90/min), tachypnea (respiratory rate >20), hypotension (systolic blood pressure <90 mmHg), and temperature >38°C. Such patients underwent a goal-directed optimization as per our study protocol. Boluses of 0.9% saline (20–30 ml/kg body weight) were given every 30 min to achieve the first goal (CVP 8–12 cm H\(_2\)O). If MAP was <65 mmHg after reaching the first goal, vasopressor (norepinephrine infusion) was instituted to achieve and maintain the second goal (MAP >65 mmHg). Our third goal was to ensure a urine output of >0.5 ml/kg/h. The initial APACHE II score and serum lactate levels taken at admission were comparable in both case and control groups (6.8 ± 3.7 vs. 7.1 ± 2.6); (3.38 ± 1.56 vs. 3.45 ± 1.2), respectively, whereas there was a highly significant reduction in APACHE II score 24 h postoperatively in both the groups (2.2 vs. 4.5). The surgeries performed in majority of patients were primary

### Table 1: Patient’s demographic characteristics

| Variables                  | Group S* | Group A* | \( P \) (two-sided) |
|----------------------------|----------|----------|---------------------|
| Age (year)                 | 49.2±7.2 | 47.9±8.8 | 0.43                |
| Sex (male/female)          | 38/12    | 37/13    | -                   |
| Weight (kg)                | 64.3±5.4 | 65.4±4.8 | 0.30                |
| Height (cm)                | 160.5±4.1| 161.46±6.4| 0.40               |
| Duration of surgery (min)  | 118.42±15.48| 120.4±14.34| 0.52               |

*Values expressed in mean±SD. SD=Standard deviation

### Table 2: Acute Physiology and Chronic Health Evaluation II score on admission, 24 h postoperatively, and final outcome comparison in between groups

| Groups          | APACHE II | Duration of stay (days) | Serum lactate | Final outcome |
|-----------------|-----------|-------------------------|---------------|--------------|
|                 | Admission*| Postoperative*           | Admission*    | Postoperative*| Discharge (%) | Death (%) |
| Control (S)     | 7.1±2.6 (6.34-7.85)| 4.5±3.2 (3.57-5.43) | 11.26±3.2 (10.33-12.18) | 3.45±1.2 (3.11-3.79) | 3.14±1.08 (2.83-3.45) | 39 (81.25) | 9 (18.75) |
| Case (A)        | 6.8±3.7 (5.7-7.89) | 3.2±2.2 (2.54-3.85) | 9.8±1.7 (9.29-10.30) | 3.38±1.56 (2.93-3.83) | 2.02±0.45 (1.89-2.15) | 44 (95.65) | 1 (4.35) |
| \( P \)         | 0.65      | 0.02                    | 0.007         | 0.80 <0.001   | 0.03          | 0.03       |

*Values expressed in mean±SD (95% CI). CI=Confidence interval, SD=Standard deviation, APACHE=Acute Physiology and Chronic Health Evaluation II
Table 3: Types of surgery performed in each group

| Operation done                                         | Control (S) (%) | Case (A) (%) | P (two-sided) |
|--------------------------------------------------------|-----------------|--------------|---------------|
| Primary repair of ileal perforation with proximal ileostomy | 16 (33.33)      | 18 (39.13)   | 0.71          |
| Omentopexy of prepyloric perforation                   | 27 (56.25)      | 26 (56.52)   | 0.85          |
| Primary repair of ileal perforation                    | 5 (10.41)       | 2 (4.34)     | 0.46          |
| Total                                                  | 48              | 46           |               |

Table 4: Incidence of postoperative complications in both groups

| Postoperative complications | Control (S) (%) | Case (A) (%) | Student t-test (P) |
|-----------------------------|-----------------|--------------|--------------------|
| Paralytic ileus             | 4 (8.3)         | 2 (4.3)      | 0.35               |
| Intra-abdominal collection or abscess | 2 (4.1) | 1 (2.1) | 0.48               |
| Wound infections            | 6 (12.5)        | 2 (4.3)      | 0.14               |
| Abdominal wall dehiscence   | 1 (2)           | 0            | 0.47               |
| Pulmonary atelectasis or VAP | 12 (25)      | 5 (10.87)    | 0.06               |
| Enterocutaneous fistula*    | 0               | 0            | -                  |
| Adhesive intestinal obstruction | 2 (4.3)         | 1 (2.1)      | 0.49               |
| Incisional hernia*          | 0               | 0            | -                  |

*Complication observed on follow-up. VAP=Ventilator associated pneumonia

repair of prepyloric perforation with omentopexy (case and control 54% each). This study is in agreement with the study of Ramachandra et al. in reference to type of surgical procedure performed. However, 24 h later, postoperatively serum lactate values were found highly significant in case group only.

There was unanimity in mean duration of hospital stay in this study as seen in the past studies. Postoperative complications (immediate and on follow-up) were compared between groups [Table 4]. However, overall incidence is found higher among control group, but they failed to reach statistical significance for either abdominal or pulmonary complications. Rivers et al. showed that there was a significant reduction in the duration of hospital stay among those who were treated by goal-directed optimization. In accordance, we found that optimized patients in case group were discharged early (9.8 ± 1.7 days) as compared to control group (11.26 ± 3.2 days). The study of Han et al. observed that early shock reversal by adequate fluid resuscitation was associated with improved outcome and each hour of delay in resuscitation was associated with 50% increased odds of mortality. Another study of Whalen et al. showed that aggressive fluid resuscitation early in the treatment course led to a decreased occurrence of persistent shock and subsequently improved survival of patients with septic shock. In this study, we observed a lower mortality rate in the case group (4%) compared to the control group (16%). Moreover, the morbidity and mortality rates do not merely depend on the surgical method deployed, but rather on the general condition of the patient, severity of infection, and the duration of pathological state before definite management. It is, therefore, of paramount important to provide attentive goal-directed preoperative optimization, including aggressive resuscitation by means of IV fluids and adequate antibiotic coverage.

This study is inspired by and broadly follows the principles established in the study by Rivers et al. with variations and modifications such as exclusion of central venous oxygen saturation measurement largely due to resource limitations and feasibility considerations prevalent in the day-to-day practice in a rural medical college hospital setting.

**Conclusion**

Goal-directed optimized patients with perforation peritonitis were discharged early with significantly lesser mortality as compared with randomly or inadequately optimized patients in perioperative period.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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Appendix 1: Acute Physiology and Chronic Health Evaluation II scoring system

| Physiologic variable             | High abnormal range | Low abnormal range |
|----------------------------------|---------------------|--------------------|
|                                  | +4                  | +3                 | +2                  | +1                  | 0        | +1            | +2            | +3            | +4 Points |
| Temperature-rectal (°C)          | ≥41                 | 39-40.9            | 38.5-38.9           | 36.8-36.4           | 34-35.9  | 32-33.9       | 30-31.9       | ≤29.9        |
| Mean arterial pressure (mmHg)    | ≥160                | 130-159            | 110-129             | 70-109              | 50-69    | 55-69         | 40-54         | ≤5           |
| Heart rate (ventricular response)| ≥180                | 140-179            | 110-139             | 70-109              | 12-24    | 11-10         | 6-9           | ≤5           |
| Respiratory rate (nonventilated  | ≥50                 | 35-49              | 25-34               | ≤20                 | 20-29.9  | 20-55         | 20-55         | ≤20          |
| Oxygenation: A-aDO₂ or PaO₂ (mmHg)| ≥500                | 350-499            | 200-349             | ≤200                | ≤200     | ≤200          | ≤200          | ≤200         |
| a. FIO₂≥0.5 record A-aDO₂        | ≥7.7                | 7.6-7.69           | 7.5-7.59            | 7.4-7.49            | 7.25-7.32 | 7.15-7.24     | ≤7.15         | ≤<7.15       |
| b. FIO₂<0.5 record PaO₂          | ≥180                | 160-169            | 155-159             | 150-154             | 120-129  | 111-119       | ≤110          | ≤<110        |
| Arterial pH (preferred)          | ≥7                  | 6-6.9              | 5.5-5.9             | 5.5-5.4             | 2.5-2.9  | 2.5-2.9       | ≤2.5          | ≤<2.5        |
| Serum sodium (mEq/L)             | ≥7                  | 6-6.9              | 5.5-5.9             | 5.5-5.4             | 2.5-2.9  | 2.5-2.9       | ≤2.5          | ≤<2.5        |
| Serum creatinine (mg/dL)         | ≥6.5                | 5.5-6.9            | 4.5-5.4             | 4.5-5.4             | 2.5-2.9  | 2.5-2.9       | ≤2.5          | ≤<2.5        |
| Hematocrit (%)                   | ≥30                 | 20-39.9            | 15-19.9             | 15-19.9             | 1-2.9    | 1-2.9         | ≤1            | ≤<1          |

A. Total acute physiology score (sum of 12 above points)
B. Age points (years) <44=0, 45-54=2, 55-64=3, 65-74=5, ≥75=6
C. Chronic health points
Total APACHE II score

APACHE=Acute Physiology and Chronic Health Evaluation II, GCS=Glasgow Coma Score