

Effectiveness of Management Protocol Created for the Treatment of Advanced Peritonitis Patients - A Prospective Study.

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I. Introduction

Management of advanced peritonitis is a challenging task to deal with high morbidity and mortality. Advanced peritonitis patients present with diffuse purulent peritonitis with sepsis or septic shock. The septic shock and sepsis are the prime reasons for the high morbidity and mortality [11, 19]. Dietmar et al. predicted that the mortality rate in advanced peritonitis was between 34-93% (as per the APACHE II score) in 1990[8]. However, the actual mortality rate in developing countries varies from 45.45 to 58.3% in various series [20, 21].

A suitable management protocol is essential to treat these patients to reduce the mortality rate to $\leq 20\%$, as is done in developed countries [1].

Objectives of the protocol should consist of (1) treatment of aetiological factors and systemic manifestations of advanced peritonitis (2) prevention of complications associated with aggressive resuscitation (3) suggestions regarding relaparotomy and open-abdomen method of treatment.

A management protocol was created which meets the above objectives, and its efficacy tested in the Indian context.

II. Materials and methods:

A prospective study was conducted to ascertain the effectiveness of a management protocol created for the treatment of advanced peritonitis in reducing the mortality rate. This protocol was followed in the management of 25 consecutive patients admitted with advanced peritonitis in a surgical unit in Gandhi hospital Secunderabad between April 2011 and March 2013.

The management protocol incorporated

1. **Early goal-directed therapy** for resuscitation. These are evidence-based guidelines in improving the survival rate in severe sepsis and septic shock [6].
2. **WSACS** (world society of abdominal compartment syndrome) guidelines in the management of intra-abdominal hypertension and abdominal compartment syndrome [28].
3. **WSES** (world society of emergency surgery) guidelines regarding relaparotomy to control persistent infections [2].
4. Suggestions regarding early minimal surgical intervention and post-operative care.

25 Patients with diffuse peritonitis presenting after 48 hours with severe sepsis or septic shock were included in this study. All other patients were excluded.

Eighteen patients presented after 48 hours and seven patients presented after 72 hours after developing symptoms. Seventeen patients were males, and 8 were females. The age of the patients varied from 25 to 65 years. The mean age is 45.1 years.

Table 1 profile of peritonitis

Cause of peritonitis	No of patients
Duodenal or gastric perforation	15
Appendicular perforation	3
Single ileal perforation	2
Multiple ileal perforations	1
Colonic perforation	1
Gangrene of bowel due to a strangulated hernia	1
Gangrene of bowel due to sup mesenteric artery thrombosis	1
Amoebic liver abscess perforation	1

The following practical steps were implemented in all the patients to meet the above objectives of the management protocol.

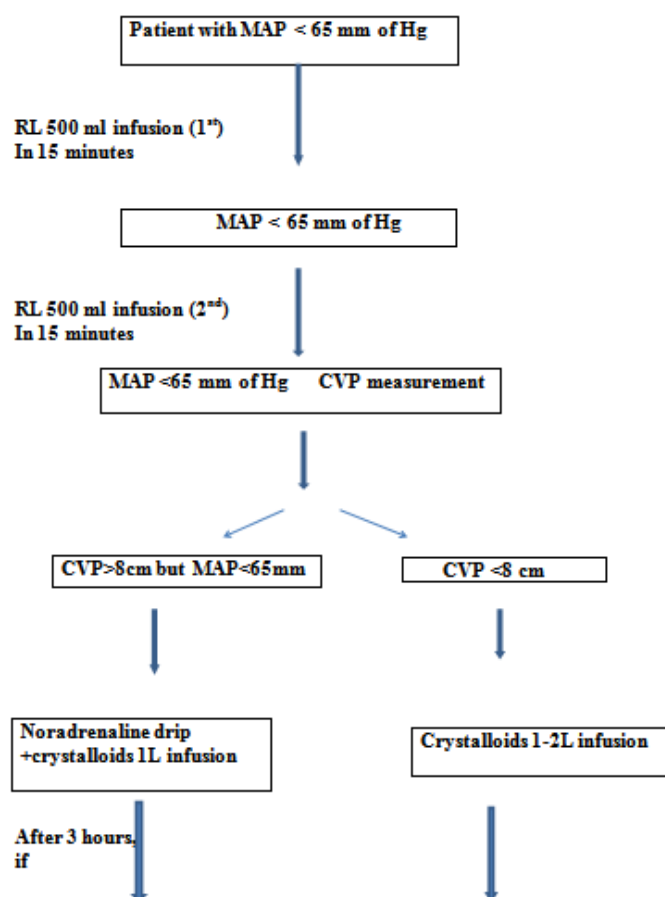
1. The vital data was recorded. Mean arterial pressure (MAP) recordings are a useful guide than the systolic blood pressure recordings in the management.

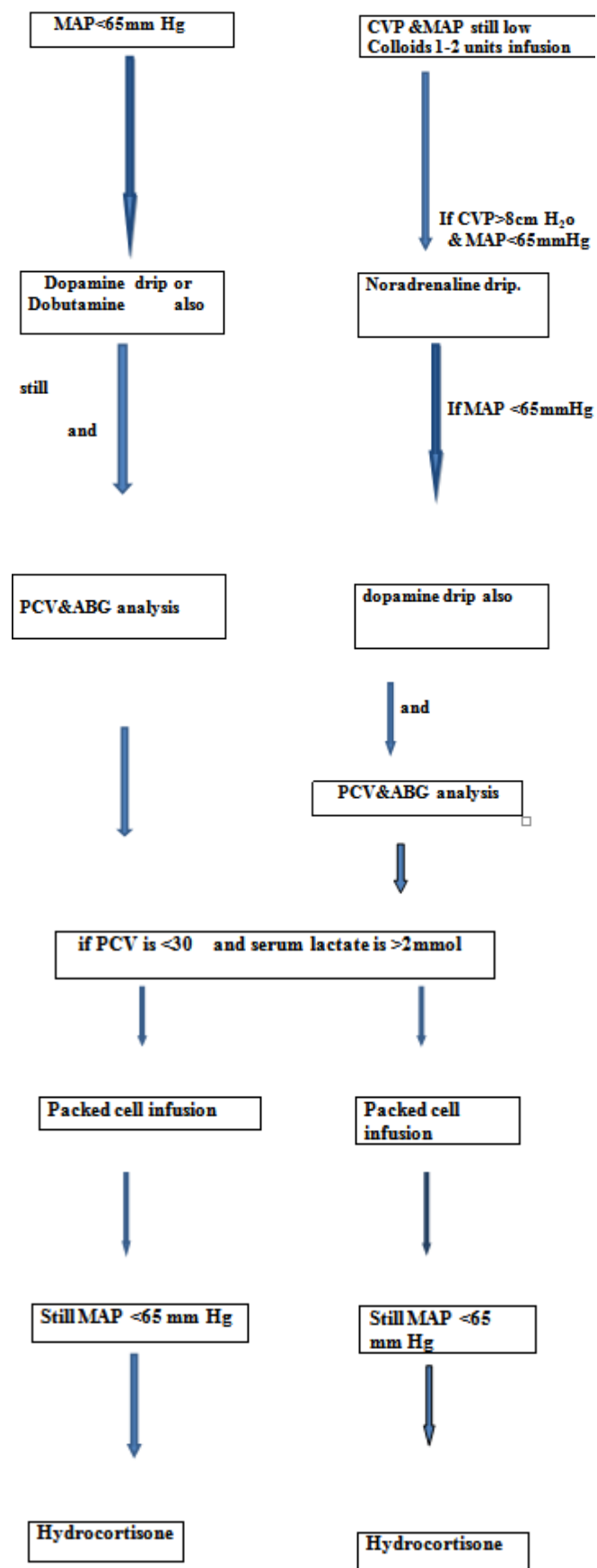
2. Catheterisation was done to measure hourly urinary output.
3. Intra abdominal pressure (IAP) was measured by measuring urinary bladder pressure. **3-way Foley's catheter was** introduced into the urinary bladder. The bladder emptied and 100ml of saline was instilled into the bladder. A water manometer was attached to the Foley's catheter after clamping the drainage channel. The column in the manometer was measured at the level of iliac crest level in the midaxillary line.
4. Two IV cannulas of 18 gauge were introduced. Blood was drawn and sent for the following investigations. The Hb%, PCV, grouping, blood sugar levels, electrolytes and renal function tests were done in all the patients. ABG analysis and serum lactate measurement were also done in patients with septic shock.
5. All the patients received 3rd generation cephalosporin (inj. Cefoperazone 1Gm intravenously twice daily) and inj. Ranitidine at the beginning of the treatment.
6. A nasogastric tube inserted.
7. Early goal-directed therapy guidelines followed during resuscitation with the target of reaching following resuscitation goals. End goals of resuscitation [6] are
 - a. Central venous pressure (CVP) should be 8-12 mmHg
 - b. Mean arterial pressure > 65mmHg
 - c. Urine output > 0.5ml/kg/h
 - d. Central venous oxygen saturation >70%

500 ml of IV fluids preferably Ringer lactate was infused in 15 minutes. MAP and urine output was recorded. If the MAP was improving and urine output has started, suggest that the patient is responding to treatment and another 500ml of infusion in 15 minutes will improve the condition. If the MAP is 65 mm Hg or more, the patient will receive fluids to a total of 30ml/kg in the following hour simultaneously correcting the electrolyte imbalances if any. The patient is taken up for surgery as soon as he is fit for surgery without delay.

8. With the first 500 ml of infusion in 15 minutes, if the MAP was not improving and urine output was not started another 500ml infused. Even after the 1000ml of infusion in 30 minutes, if the MAP is still below 65mm Hg and urine output has not started, the CVP line was started, and the following algorithm adopted.

The Algorithm of resuscitation in advanced peritonitis.





When the CVP was less than 8cm of H₂O, a further 1-2 litre of Ringer lactate infused till CVP reached 8-10 cm of H₂O. The total amount of fluids infused was restricted to 3 litres.

1-2 units of FFP infused if the CVP and MAP not stabilized with three litres of crystalloids. FFP raises the intravascular oncotic pressure and stabilizes the MAP and CVP.

12 patients were recovered with this treatment in 3-6 hours. Correction of electrolyte imbalance was done and taken up for surgery without delay.

When the CVP was more than 8cm H₂O and MAP is less than 65mm Hg due to septic shock Noradrenalin 0.02' 0.45micro/kg/min (2mg in 500ml 5%D @ 6drops/mnt) drip was started.

6 Patients recovered from the shock and posted for surgery in about 12 hours.

When there was no response, even 3 hours after starting noradrenaline drip, the Dopamine 10micro/kg/min (200mg in 500ml 5% D @ 12drps/mnt) or Dobutamine 2-20micro/kg/min drip also started to increase the cardiac output. Both the drips were continued up to 6 hours.

Seven patients with shock required both vasopressors and inotropes and four recovered from the shock.

PCV, ABG analysis and serum lactate measurement were done in all the 13 patients requiring noradrenaline or noradrenaline+ dopamine during resuscitation.

10 patients had metabolic acidosis, and Sp O₂ was less than 70%.

Table 2 PCV and ABG results

No of Patients	PCV	P _H	Serum lactate
1	28	6.9	3.6mmol
2	30	7.2	2.4mmol
2	32	7.3	2.6mmol
2	30	7.1	3.4mmol
1	32	7.2	3.4mmol
1	30	7.3	3.0 mmol
1	30	7.1	3.1mmol

Patients with serum lactate of >2mmol and PCV of < 35 transfused with fresh blood or packed RBC unit. 10 patients required transfusion.

One patient with PH 6.9 required 50ml. IV sodium bicarbonate also. S_pO₂ has increased after transfusion of blood or packed RBC unit.

Despite the above measures when the shock was not responding, IV hydrocortisone 100mg twice daily was given.

Plain x-ray abdomen was taken in all the patients after recovering from the shock. Contrast CT abdomen was done when the diagnosis was in a dilemma, especially in cases of appendicular, ileal or colonic perforation.

Intra-abdominal pressure (IAP) was monitored soon after catheterisation in all the patients. Intra-abdominal pressure was monitored hourly. All the patients had more than 10 mm Hg of IAP. Twelve patients had 10-25 mm of Hg of IAP. Thirteen patients with septic shock had more than 25 mm of Hg of IAP.

The following conservative measures were adopted to reduce IAP in all the patients during resuscitation.

1. Optimisation of fluid administration: Judicious infusion of crystalloids and colloids (not more than 5 litres during resuscitation) is done to prevent the oedema of the bowel, retroperitoneal tissue and intra-abdominal hypertension.

2. NG tube aspiration

3. Colonic decompression

4. Analgesia

12 patients responded to conservative measures and IAP was decreased to <15mm of Hg.

Despite the above measures, the IAP was found to be more than 15mm Hg in 13 patients. CRD flank drains were inserted under local anaesthesia in these patients during resuscitation. 1-2 litres of fluid was drained reducing the IAP to <15 mm of Hg.

Patients were carefully monitored after insertion of flank drains as the sudden development of hypotension or worsening the hypotension is common after drainage. It was treated with an infusion of one to two units of FFP and fluids, to maintain 8-10 cm of H₂O of CVP and above 65mm Hg of MAP.

Patient's SpO₂ was continuously monitored with a pulse oximeter. SpO₂ was maintained above 85% with oxygenation through oxygen face mask delivering 6-8LPM.

All the patients were resuscitated to reach the goals set for parameters.

Resuscitation of 12 patients with sepsis was completed in 6 hours. It took 12-20 hours in 12 patients with septic shock and IAP of more than 25 mm of Hg. It took about 24 hours in one patient with septic shock. All the patients were shifted to the operation theatre without delay after resuscitation.

Table 3 details of operative procedures

Aetiology of peritonitis	Operative procedure	no
Duodenal & gastric perforation	Closure with omental patch	15
Appendicular perforation	appendicectomy	3
Single ileal perforation	Closure of perforation	2
Multiple ileal perforations	Resection and ileostomy	1
Intestinal strangulation	Resection of small bowel and anastomosis	2
Gangrene small bowel due to superior mesenteric artery thrombosis	Resection and anastomosis	1
Liver abscess perforation	Peritoneal Lavage	1

Abdominal cavity thoroughly explored and lavage was done with warm saline until clear fluid returns. Iodine or any chemical agents have not been used to lavage the peritoneal cavity. In amoebic liver abscess, the cavity lavage was done with inj. metronidazole.

The abdomen closed in a single layer reinforced with tension sutures in all the patients. Open-abdomen method of treatment was not required in our series as the IAP was brought to less than 15mm of Hg in all the patients.

Post-operative recovery was turbulent and needed ventilator support in eight patients. These patients were managed in ICU for 3-5 days. Four of these patients recovered. The ventilator support was weaned off 24-72 hours after surgery in these patients.

Three patients expired in 24-48 hours. One patient expired after 72 hours.

Remaining patients were managed in HD units until they were stabilised.

Continuous monitoring of IAP, CVP, SPO2 and MAP was done in all the patients in the post-operative period till they are shifted to post-operative ward.

Relaparotomy was done in three patients.

Table 4 details of relaparotomy patients.

Aetiology	Cause of relaparotomy	No of patients	results
Superior mesenteric artery thrombosis	Extension of gangrene of the bowel	1	died
Duodenal ulcer perforation	P.O. Duodenal leak after closure with omental patch	1	died
Ileal perforation	Faecal fistula	1	survived

Mortality rate: four (4/25) patients died. One patient treated for superior mesenteric artery thrombosis and three patients for duodenal ulcer perforation.

III. Observations

Eighteen patients presented forty-eight hours after developing symptoms. Seven patients presented after seventy-two hours.

12 patients were in sepsis, resuscitated with IV fluids. Thirteen patients were in septic shock required vasopressors, inotropes and hydrocortisone during resuscitation.

Patients with septic shock had raised serum lactate levels and were treated with dopamine drip and packed cell transfusion. Only one patient required IV sodium bicarbonate.

IAP was between 10-25 mm of Hg in 12 patients and reduced to < 15 mm of Hg with conservative management.

IAP was more than 25mm of Hg in 13 patients and required decompression with CRD drains. Conservative measures are not effective to reduce the IAP to less than 15 mm Hg in these patients. Sudden development of hypotension or worsening of hypotension noticed in all the patients' after drainage.

None of the patients required Open abdomen method of treatment. The abdomen was closed in all the patients.

Eight patients required postoperative ventilator support. Seven of them presented after 72 hours.

Relaparotomy was done in 3 patients.

4 patients expired. All the expired patients presented after 72 hours.

IV. Discussion

Advanced peritonitis patients present with diffuse peritonitis with severe sepsis or septic shock. These patients require immediate treatment to prevent further morbidity and mortality.

As per 2013 world society of emergency surgery (WSES) guidelines (recommendation 1A) “the septic shock and severe sepsis of abdominal origin require early hemodynamic support, source control and antimicrobial therapy.” [2]

Delay in treatment leads to increased morbidity and mortality [24]. Jain NK et al. claimed that there is an increased mortality rate due to delay in the surgical intervention [22].

RanjuSingh et al. reported that 80% of non-survivors of their series were operated upon, 24 hours after admission. The mortality rate is 57.7%, in delay in the intervention of more than 24 hours. Even among the late presenters when the intervention was done within 24 hours, the mortality rate was dropped to 25% [21].

Late presentation depends on several demographic factors which are beyond the control of treating surgeon but with proper management protocol delay in treatment can be avoided in the majority of patients.

So a management protocol created based on the evidence based guidelines to treat the advanced peritonitis patients.

25 critically ill patients with advanced peritonitis were selected in this study and the above-said management protocol followed.

All our 25 patients received third-generation Cephalosporin and metronidazole intravenously at the beginning of resuscitation. It is reported that each hour delay in the administration of antimicrobials increases the mortality rate [29].

Mean arterial pressure monitored in these patients gave a more accurate picture of perfusion of organs than the systolic blood pressure monitoring. As per the surviving sepsis guidelines, mean arterial blood pressure should be > 65 mm Hg [4]. The hypovolemia in these patients was corrected using crystalloids first, preferably Ringer lactate. Among the crystalloids, Ringer lactate preferred over normal saline. Balanced salt solutions such as Ringer lactate and Plasma-Lyte do not cause a non-gap metabolic acidosis and may reduce the need for renal replacement therapy. Normal saline is associated with hyperchloremic metabolic acidosis, acute kidney injury and the need for renal replacement therapy [25]. In the study conducted by Matthew W. Semler et al. concluded that intravenous administration of balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction [24].

Surviving sepsis guidelines [26] advocates rapid infusion of fluids.

In thirty minutes 1000ml of Ringer lactate was infused as a challenging dose. Even after fluid challenge if the hypovolemia persists, CVP measurement was done hourly to assess the body fluid volume. If CVP was less than 8mm hg one to two litres of crystalloids were given in an hour in incremental challenging doses of 500 ml every 15 minutes as long as parameters are improving. One to two units of FFP infused if the CVP is not improving with the incremental challenging doses of IV fluids. The crystalloids seep through the dilated capillaries of these patients with sepsis resulting in persistent hypotension.

Colloids are necessary for sustained maintenance of the CVP & MAP in normal limits for a more extended period with limited amounts of fluids. Colloid solutions contain particles that exert the oncotic pressure, remain in the intravascular space until the reticulo endothelial system removes these particles. As they remain in intravascular space for about 6 to 24 hours, smaller volumes required for resuscitation [30].

Colloids (albumin) infusion advised when the large amounts (more than 30ml/kg) of crystalloids infusion required during resuscitation [26]. FFP infused in place of albumin which is costly and economically not feasible.

Large amounts of crystalloids infusion lead to interstitial oedema. It will lead to increased IAP and (ACS) Abdominal compartment syndrome (caused by retroperitoneal oedema and oedema of the bowel) resulting in difficulty in the closure of the abdomen.

More than 3 litres of fluid infusion is one of the causes of abdominal compartment syndrome [33]. Prevention and early treatment of potential cause may prevent progression of Intra-abdominal hypertension (IAH) to ACS [28]. So Optimizing the fluid infusion either with hypertonic solutions or with colloids is advised (Grade 1 C) and thereby avoiding excess fluid infusion (Grade 2D) [28]. Hence crystalloids infusion was restricted to 3 litres, and one to two units of FFP infused.

Twelve patients were resuscitated with the treatment mentioned above, reached resuscitation goals in 3-6 hours and taken up for surgery. The IAP was reduced to less than 15 mm Hg. Thus the ACS and its complications were prevented and abdomen was closed in a single layer with tension sutures. Postoperative period was uneventful, and no mortality noticed in this group.

The challenging 1-1.5 litre of IV fluids infusion corrected the CVP but did not correct the MAP in 13 patients. It is due to peripheral vasodilatation, and for correction, vasopressors are required. As per the guidelines of surviving sepsis campaign 2012, noradrenaline is the first choice vasopressor (grade 1B) [26]. Six patients recovered from the shock in three hours with noradrenaline drip.

Seven patients not recovered from hypo perfusion with noradrenalin drip alone. The mean arterial pressure was fluctuating between 55-65mm Hg, spo2 was less than 70, and serum lactate rose. Dobutamine drip also started along with noradrenaline.

If the features of hypo perfusion are persistent even after attaining adequate circulating blood volume and noradrenaline drip, the Dobutamine drip advised. (Grade 1C) [26]. Four patients recovered after Dobutamine drip.

Metabolic Acidosis observed in 10 patients with septic shock.

Ten patients had a metabolic acidosis due to lactic acidosis with pH varying from 6.9 to 7.3. Only one patient had 6.9 others had from 7.1 to 7.3.

In metabolic acidosis, less than 35 of PCV and less than 70% of Spo2 suggest inadequate oxygen delivery to tissues with increased oxygen extraction from blood and anaerobic metabolism. Whole blood or packed RBC transfused to increase oxygen delivery and adequate tissue perfusion. Effective therapy of lactic acidosis due to shock is to reverse the cause [30].

Surviving Sepsis guidelines recommend against the use of bicarbonate for lactic acidosis for pH of more than 7.00 [31].

Routine use of bicarbonate for the treatment of severe acidemia and lactic acidosis due to sepsis is subject of controversy and, the current opinion does not favor routine use of bicarbonates [32].

In our series, the metabolic acidosis was corrected in nine patients by blood transfusion and Dobutamine drip when the pH is above 7.00 and PCV is <35.

50 ml of sodium bicarbonate infused in one patient when the pH was less than 7.00.

When the shock was not responding to the above measures, IV hydrocortisone 100mg twice daily was given for five days to three patients. It proved beneficial in these patients in recovering from septic shock. The use of corticosteroids in septic shock is associated with an increased risk of secondary infection and is controversial. However, as per the studies [1, 2, 30], 200-300mg intravenous hydrocortisone for 100 hours should be considered in refractory shock [2].

Sepsis And Septic Shock- Intra-Abdominal Pressure:

Sepsis and septic shock due to peritonitis are the risk factors of development of IAH. Evidence of new organ failure associated with IAH defined as ACS. Incidence of organ failure is most significant with IAP of >25 mm Hg [33]. So monitoring of IAP and treatment of IAH is very much essential to include in the management protocol of patients with advanced peritonitis.

As per the guidelines of world society of abdominal compartment syndrome, [28]

1. Intra-abdominal pressure measured in sepsis and septic shock.
2. Trans-bladder technique of measuring IAP advised.
3. IAP should be continuously measured or at least every 4-6 hours (Grade 1 C)
4. IAP should be maintained ≤ 15 mmHg by conservative measures first (Grade 1C)
5. If IAP is >25mm Hg and is refractory to conservative measures, surgical decompression is advised (Grade 1D).

The IAP was reduced to <15mm Hg either by conservative management or by decompression with percutaneous drainage in all our patients.

All patients had undergone surgery when the IAP was <15mm Hg and abdomen could be closed without any problem. Post-operatively IAP was measured every fourth hourly, and the optimum fluid infusion was done with crystalloids and colloids to maintain the IAP to <15mm Hg.

Surgical procedures:

“The goals of surgical treatment are eliminating the cause of the contamination, reducing the bacterial inoculum and preventing persistent or recurrent sepsis” [1]. During the surgical procedures “Keep it simple” principle was followed limiting to the above-said goals. It restricts the prolonged surgical and anaesthesia time preventing the insults to the already compromised immune system.

Surgical procedures followed in our series are simple and completed in a minimum possible time. During index operation itself, in one case, relaparotomy was planned for a second look. Planned relaparotomy was done after 48 hours in a case of superior mesenteric artery thrombosis to know the status of intestines.

On-demand relaparotomy performed in postoperative duodenal leak after the closure of DU perforation, and in P.O.fecal fistula after the closure of enteric perforation. The first one is an emergency and the second one is a semi-emergency.

On-demand relaparotomy was advised in patients deteriorating or not improving clinically [34] with persistent infection or recurrent infections. These patients benefit from re-operations to control the MODS triggered by these infections [2]. However, relaparotomy in patients with APACHE 2 score of more than 26 does not influence survival rate [1]. So it is challenging to decide whether the relaparotomy benefit a patient or not. Postoperatively patient requires ventilator support and intensive care. The mortality rate was 43% with the above care [36]. In many situations, the Interventional radiologist is helpful to drain the pus collection under US guidance or CT guidance. Relaparotomy not advised, and percutaneous drainage indicated if the infection is localized and are no signs of generalized peritonitis (Recommendation 2C) [2]. So relaparotomy is to be considered when all other possibilities of controlling infection are exhausted. The postoperative intraabdominal abscess was noted in four patients in our series and managed to drain under ultrasound guidance successfully.

Patients with a persistent infection requiring on-demand relaparotomy are less in number in India when compared to west due to variance in etiological factors. Upper gastrointestinal tract perforations are the leading cause of peritonitis in India whereas lower GIT perforations are more common in the west.

In India, duodenum and stomach perforations constitute 45-65% cases of peritonitis whereas in the west 10-12% [11, 12, 13, 14, and 15]. In the west, colonic perforations constitute 33-40% cases of peritonitis [1] whereas in India it is between 3 to 5 % [11, 12]. Feculent peritonitis in colonic perforations is challenging to control with the first laparotomy. On-demand relaparotomy is required to control persistent infection. In gastric and duodenal perforations, persistent infection is uncommon. In our series, gastroduodenal perforations constitute 60% and no colonic perforations. Hence on-demand relaparotomy for clearing persistent infection was not needed in our series.

Relaparotomy either on-demand or planned does not have a difference in mortality rate. Relaparotomy can be decided based on contextual criteria and determined on a case-by-case basis [35].

Abdomen closed in a single layer with tension sutures in all the patients in our series. The maintenance of IAP to ≤ 15 mmHg with the judicious use of fluids and decompression of the abdomen is the prime reason in preventing oedema of the abdominal wall and retroperitoneum facilitated the closure of the abdomen. So none of our patients required the open-abdomen method of treatment. WSACS suggested not routinely use the open abdomen for septic cases versus trauma cases. (Recommendation 2C). The discrepancy in risk and benefits along with economic considerations was the primary reason [36].

Postoperative management of critically ill patients requires ventilator support, ICU care and multidisciplinary approach. In the west where colonic perforations are common, post-operative ICU care for about fifteen days, and the ventilator support for about ten days is required [1]. 33% of our patients required ICU care and ventilator assistance for 3-4 days. At the time of admission, these patients were in septic shock. Post operatively continuous monitoring of MAP, IAP and Spo₂ was done apart from other routine vital signs. The IAP was maintained below 15 mm Hg by conservative measures and optimizing the fluid administration. Spo₂ was maintained above 95% with nasal oxygenation and, the Hb% kept above 10 gm.

Four patients (16%) expired in our series. One patient with superior mesenteric artery thrombosis and three are with duodenal ulcer perforation. In this series, the mortality rate in du perforation is 20%. Different series gives a different mortality rate in D.U. perforation ranging from 6-28% [15, 20, 21 and 23]. The mortality rate given by these series is the overall mortality rate of critically ill and non-critically ill patients. So the mortality rate calculated for all the patients treated for peritonitis is not high. However, the mortality rate calculated only for critically ill patients is found to be high.

Delayed presentation patients are associated with diffuse peritonitis with varying degrees of septicemia [21] and critically ill. A.I.Ugochukwu et al. reported a 58.3% the mortality rate in patients presented after 48 hours [20]. Ranju Singh et al. reported 45.45% mortality in patients presented after 72 hours. In our series, all patients presented after 48 hours -the mortality in advanced peritonitis due to D.U. perforation could be reduced to 20% and the overall mortality in advanced peritonitis is reduced to 16% with our management protocol. Efficient usage of crystalloids, colloids, vasopressors and inotropes during resuscitation preventing fluid overload and ACS, early recognition and treatment of IAH and metabolic acidosis, simple initial surgery, newer broad-spectrum antibiotics, advances in anaesthesia and postoperative care are the essential factors in our protocol kept the mortality rate to below 20% in advanced peritonitis.

Conclusions: advanced peritonitis carries a high mortality. A suitable management protocol based on the proper understanding of pathophysiology can have an impact in reducing the mortality rate to <20% in these patients.

Ethical approval: “All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

Informed consent: “Informed consent was obtained from all individual participants included in the study”

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