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Enhanced recovery after surgery versus conventional approach in peptic perforation- a Randomized Controlled Trial- "ERASE trial"

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Abstract

Background Implementing Enhanced Recovery After Surgery (ERAS) protocol in elective surgeries has improved outcomes. Evidence for a similar role in emergency surgeries must be explored, particularly in patients with peptic perforation. This research aims to study the safety and efficacy of ERAS in patients undergoing surgery for peptic perforation peritonitis.

Material and methods Our study was an open-labeled, randomized, controlled superiority trial conducted on 60 patients of peptic perforation, restricted to first and second category of ASA and distributed equally between the Conventional and ERAS arms. The key interventions in the ERAS arm were intraoperative rectus sheath blockade, encouraging early ambulation, early removal of indwelling catheters and tubes, and early initiation of oral fluid and solid diet.

Results The median length of hospital stay was significantly shorter in the ERAS arm (3 vs 5 days). The patients in the ERAS group were free from all the indwelling catheters within 24 h of the surgery. The time to ambulate (21 h vs 48 h) and initiation of unrestricted clear liquids (after 6 h of surgery) was significantly quicker in the ERAS arm. The surgical site infection (10 vs 5) and pneumonia (5 vs 1) rates were higher in the conventional group. This was clinically significant, even though it failed to attain statistical significance. The comprehensive complication index was significantly higher in the conventional arm. In this study, there was 100% compliance with seven out of eight ERAS interventions.

Conclusion The ERAS protocol helped shorten the time needed to attain the preoperative physiological parameters, including bowel functions and reduced the LOHS in patients operated for peptic perforation.

Keywords Peptic ulcers, Peptic ulcer perforation, Recovery of bowel function, Emergency care, Fluid balance, Length of stay

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Introduction

Traditional methods of perioperative care induce "perioperative surgical stress," a catabolic state, depleting body reserves, suppressing immunity, and increasing the risk of post-operative complications. [1] "Fast track surgery" or "Enhanced Recovery After Surgery (ERAS)," an

evidence-based approach to perioperative care, on the other hand, has been shown to reduce stress and hasten recovery. [2]

The benefits of this new protocol in elective colorectal surgeries [3, 4] garnered enthusiasm among physicians and surgeons of other specialties, including gastrointestinal, hepatobiliary, breast, and gynaecology [5–7]. However, there are few takers of ERAS in the emergency setting (Lohsirwat et al. and Shang et al.) [8, 9], particularly in upper gastrointestinal surgeries. Studies conducted on the effect of ERAS on peptic perforation are a handful, with Gonenc et al. being the pioneers in their series of laparoscopic peptic perforation repairs [10]. This area has been less explored, for which we conducted this Randomised Controlled Trial (RCT) to assess the safety and efficacy of the ERAS protocol in peptic perforation patients.

Study objectives

Primary objective:

To study the effect of enhanced recovery after surgery on the post-operative length of hospital stay.

Secondary objectives:

1. To assess the efficacy of ERAS protocol in terms of recovery of functional parameters
2. To assess the safety of ERAS protocol in terms of morbidity and mortality
3. To evaluate the effect of ERAS on Quality of life using EQ-5D-5L questionnaire.

Methodology

An open-label, randomized controlled, superiority trial with parallel assignment was conducted between February 2020 and December 2021 in the Department of General Surgery of the All-India Institute of Medical Sciences, Bhubaneswar, a tertiary care Institute of eastern India after obtaining ethics approval (IEC number was AIIMS BBSR/PG Thesis/2019–20/65) and registering in the ClinicalTrials.gov (NCT04194060) on 11th December 2019. A computer-generated sequence for simple randomization was obtained, and the allocation was concealed by the serially numbered opaque sealed envelopes technique. The operating room circulating staff nurse, who was not a part of the study team, opened each of these envelopes just after completion of the omental patch repair. All patients aged 18 years or above with American Society of Anaesthesiologists (ASA) score of I or II, intraoperatively diagnosed with peptic perforation (prepyloric or first part of duodenum) and having a perforation size of one centimetre or less, were included in the study.

Patients in refractory septic shock at presentation, with known chronic kidney disease or liver disease, pregnancy, history of chronic steroid abuse, coexistent peptic perforation with a bleeding ulcer, peptic perforation requiring a different procedure than omental patch repair, sealed perforations, malignant perforation, need for post-operative positive pressure ventilator support for more than six hours, urinary catheterization for reasons other than the study, coexistent neurological or psychiatric illness, and patients refusing to provide consent, were excluded from the study.

The sample size was calculated using Open Epi software for a power of the study of 90%. Based on a previous study's data on LOHS, it was found to be 24 (12 per arm). [10] To factor in an expected attrition of 20%, the sample size was re-calculated to 30 (rounded off). However, to study the safety profile in terms of major complications, like a leak or any mortality, the inclusion of a larger sample size was considered, and a convenient sample of at least 60 patients (30 in each group) was planned.

The anaesthesia protocol included a balanced intraoperative fluid administration, the use of short-acting anaesthesia agents (Fentanyl), intraoperative body warmer, and post-operative nausea and vomiting prophylaxis for patients in both arms.

The intraoperative steps included peritoneal lavage with six litres of warm normal saline, open omental patch repair, placement of a sub-hepatic drain, followed by an abdominal closure in layers in all the patients. A bilateral rectus sheath block was administered only to the ERAS group of patients using equal volumes of lignocaine 2% (15 ml) and bupivacaine 0.5% (15 ml) solution on either side of the abdominal wound. The conventional arm received routine post-operative analgesics. The omental patch repair was performed using 2–0 round body polyglactin sutures by plugging the defect with the omental pedicle. The fluid balance was calculated at the end of the procedure [Total intravenous fluid administered minus (Intraoperative urine output + Intraoperative peritoneal contamination + Approximate blood loss)].

The post-operative interventions are outlined in Table 1.

The Boey's score [11], PULP score [12], Comprehensive complication index (CCI-which represents a logarithmic score of all the Clavein-Dindo complication score) [13] and intraoperative fluid balance were calculated for all the patients.

The pre-defined criteria for discharge of patients in either group included normal body temperature, tolerating at least a semisolid oral diet, complete absence of pain or well-controlled with oral analgesics, and ability

Table 1 Postoperative interventions

Intervention	Conventional group	ERAS group
Mobilization	As per patients' comfort	Encouraged to mobilize off the bed after effect of general anaesthesia has weaned off
Oral intake	Initiated after passage of first flatus	Unrestricted clear liquids after 6 h of surgery Unrestricted liquid diet allowed at 24 h of surgery and if the patient tolerates, then solid diet was allowed in the next meal
Intravenous nutrition after surgery	Intravenous (IV) infusion of glucose saline on the day of surgery and continued till complete oral intake (at least liquids) is reinstated	
Removal of Nasogastric tube	Output < 300 ml/day with resolution of ileus	Immediately after surgery (on the OR table) after aspirating the gastric content through nasogastric tube
Removal of urinary catheter	Patient sits on bed side/ambulate	After recovering from the effect of General anaesthesia
Removal of sub-hepatic drain	When patient tolerates unrestricted amount of liquid diet and drain output is less than 200 ml/day	Anytime within 24 h Drain was not removed when effluent fluid was bilious or purulent
Post-operative analgesia	**IV analgesics till 96 h** IV Acetaminophen 1gm every 6 h IV Tramadol 50 mg every 12 h **After 96 h** Oral Acetaminophen 1000 mg SOS	Bilateral rectus sheath block before closure of rectus sheath **First 48 h post op:** IV Acetaminophen 1gm every 6 h & IV Diclofenac 75 mg every 12 h **48 to 96 h**: Oral Acetaminophen 1000 mg 6 hourly **> 96 h** Oral Acetaminophen 1000 mg SOS
Post-operative antibiotics	IV Cefuroxime 1.5gm 12 hourly for three days Clarithromycin based triple therapy (H. pylori kit) 3 tablets 12 hourly for 14 days, was started as soon as oral feeding was resumed	
Post-operative prokinetics	None	IV Metoclopramide 10 mg every 8 hourly × 3 days
Chest physiotherapy	Actively done in both the arms	
Proton pump inhibitors	Initiated preoperatively (injection Pantoprazole 40 mg) and continued postoperatively	

to carry out normal daily activities independently. The 30-day morbidity in terms of post-operative complications, readmissions, and mortality was recorded. The Quality-of-Life score (EQ-5D-5L questionnaire) was estimated at discharge and 1-month follow-up. An intention-to-treatment analysis was performed using SPSS software (version 23). Qualitative variables were compared using the chi-square test, while the quantitative variables were compared using the student t-test (normally distributed dataset) and Mann Whitney test (skewed dataset). A p-value < 0.05 was considered significant. The post study power and effect size were estimated using the software G*Power 3.1. The work has been reported in line with Consolidated Standards of Reporting Trials (CONSORT) Guidelines. [14]

Results

The baseline preoperative characteristics of all the 60 patients included in the study were similar in both arms. (Table 2).

The median LOHS in the ERAS arm was 3 (IQR 1), while it was 5 (IQR 2) in the conventional arm, which was statistically significant. The minimum length of stay was as little as two days in a couple of cases, which was observed in the ERAS group. On the contrary, two patients in the conventional group were discharged after 20 days; one patient suffered a burst abdomen, and the other developed abdominal sepsis in the post-operative period. Due to the presence of these outliers, the median was adopted as the measure of central tendency for comparing the average length of stay. The return of functional parameters, which included time to ambulation, detection of first bowel sound, the passage of first flatus, and first stool, was significantly quicker in the ERAS arm than in the conventional arm. The time to withdraw the indwelling catheters (nasogastric tube, urinary catheter, and subhepatic drain) was also significantly shorter in the ERAS arm. The patients in the ERAS arm enjoyed a quicker return to intake of fluid and solid diet along with the omission of intravenous fluids, which were statistically significant. (Tables 3 and 4).

The rate of surgical site infection in the conventional arm was twice that in the ERAS arm; however, it did not reach statistical significance (p-value -0.17). Two of the patients in the conventional arm who had developed surgical site infection went on to develop a burst abdomen. One of them needed hospitalization for 22 days, while the other needed readmission for

Table 2 Baseline characteristics: ASA(American Society of Anaesthesiologists), TLC (Total leucocyte count)

Characteristics	Conventional (n = 30)	ERAS (n = 30)	*p*-value
Age (years)	43.7 ± 2.78	44.37 ± 2.72	0.878
Sex(M/F)	30/0	28/2	0.15
ASA1	7	10	0.39
ASA2	23	20	
Boey's score			
0	7	10	0.82
1	15	19	
2	2	1	
PULP score			
0	4	2	0.47
1	6	17	
2	18	11	
3	1	0	
More than 7	1	0	
Haemoglobin (gm/dl)	14.14 ± 0.28	13.55 ± 0.41	0.241
Albumin (mg/dl)	3.35 ± 0.10	3.45 ± 0.11	0.552
TLC (per mm^3)	11.46 ± 1.06	11.49 ± 0.86	0.983
Operative duration(hours)	1.93 ± 0.43	1.93 ± 0.06	0.987
Intraoperative IV fluids (ml)	1397.5 ± 105.5	1242.33 ± 62.08	0.210
Blood loss(ml)	109.33 ± 10.869	103.33 ± 12.2	0.63
Urine output/hour(ml)	77.67 ± 6.96	96.32 ± 6.95	0.06
Fluid balance(ml)	295 ± 186.8	614.44 ± 76.12	0.12

enterocutaneous fistula, which spontaneously healed with conservative management. Baring this the only other patient needing readmission in the conventional arm had developed left lung consolidation with pleural effusion. Three patients needed readmission in the ERAS arm, one for adhesive intestinal obstruction and the other two for post-operative pneumonia and burst abdomen. There were two mortalities in this study, both in the conventional arm, one for refractory hyperkalaemia and another for persistent abdominal sepsis. (Table 5) The CCI was significantly higher in the conventional arm, with a mean score of 12.47 ± 3.8 compared to the mean score of 3.4 ± 1.3 in the ERAS arm.

The mean health score of the patients, calculated using the EQ-5D-5L questionnaire at the time of discharge in the conventional arm, was 73.21 ± 2.7, while it was 65.83 ± 2.9 in the ERAS arm, which was statistically significant. However, this value was not adjusted as per the shorter postoperative stay witnessed in the ERAS group of patients.

According to the EQ-5D-5L questionnaire, at the time of discharge, the proportion of patients having either no or slight restriction in mobility, self-care, performing usual activities, and no or slight anxiety/depression were equal in each arm (p value = 0.4,0.4,0.58 and 0.6 respectively). (Tables 6, 7).

At the one month follow up, the mean health score was equal in either arm. (p value = 0.28) The proportion of patients with no or slight pain rose to 88%, with equal occurrences in either group.

Compliance with the ERAS-specific parameters was 100% in all except the intraoperative fluid balance, which could be achieved only in 10% of cases. Out of 30 patients in the ERAS arm, 27 were compliant with seven ERAS-specific parameters (out of 8), while the

Table 3 Assessment of the outcome (functional and perioperative measures) parameters based on Effect size and Confidence interval (CI) of the effect size; l: lower, u: upper. *: Mann Whitney test. #: days

Parameters(hours)	Conventional (n = 29)	ERAS (n = 30)	*p* value	Effect size	C I of effect size(l)	C I of effect size (u)
Length of stay#	5 (IQR 2)	3 (IQR 1)	0.001*	1.10	0.55	1.64
Time to ambulation	48.39 ± 3.77	21.26 ± 1.73	0.00	9.18	7.45	10.91
Tube management						
Time to remove nasogastric tube	50 (IQR 31)	0 (IQR 0)	0.00*	16.21	13.24	19.18
Time to remove subhepatic drain	84.04 ± 4.7	21.47 ± 2.09	0.00	17.07	13.95	20.19
Time to remove urinary catheter	39.43 ± 3.74	16.33 ± 1.44	0.00	8.09	6.55	9.64
Functional recovery						
Reappearance of bowel sound	44.24 ± 3.98	26.93 ± 2.20	0.003	5.34	4.25	6.43
Resumption of flatus	51.03 ± 2.50	34.27 ± 2.50	0.002	3.06	2.31	3.81
Resumption of stool	81.03 ± 5.13	61.03 ± 15.62	0.001	1.67	1.07	2.26
First fluid diet	70.86 ± 5.11	37.13 ± 2.41	0.00	8.40	6.8	9.99
First solid diet	89 (IQR 32)	55 (IQR 21)	0.00*	8.55	6.93	10.18
Time to stop IV fluids	81.36 ± 5.96	46.33 ± 2.92	0.00	7.404	5.974	8.834

Table 4 Assessment of the outcome measures based on Median, Mean, 95% confidence interval, skewness coefficient

Parameters (hours)	Conventional (n = 29)			ERAS (n = 30)			*p* value
	Median (IQR)	Mean ± SD	Confidence interval, skewness	Median (IQR)	Mean ± SD	Confidence interval, skewness	
Length of stay#	5 (2)	6.29 ± 0.7	4.79–7.78, **3.18**	3 (1)	3.47 ± 0.15	3.16–3.77, 0.92	0.001*
Time to ambulation	47(13.5)	47.69 ± 3.84	39.81–55.58, 0.987	20(11.3)	21.26 ± 1.73	17.72–24.81, 0.732	0.00
Time to remove nasogastric tube	50(31)	56.21 ± 4.88	45.44–66.13, **1.22**	0	0.0 ± 0.0	0,0	0.00*
Tube management							
Time to remove subhepatic drain	85(29)	84.04 ± 4.7	74.39–93.68, 0.14	22(16)	21.47 ± 2.09	17.18–25.75, 0.66	0.00
Time to remove urinary catheter	38(34)	39.43 ± 3.74	32.30–47.94, 0.42	16.5(14.3)	16.33 ± 1.44	13.37–19.29, 0.26	0.00
Functional recovery							
Return of bowel sound	36(38)	43.39 ± 4.03	35.12–51.67,0.59	24(18)	26.93 ± 2.20	22.42–31.45, 0.73	0.003
Resumption of flatus	48(36)	51.03 ± 2.50	41.03–59.83, 0.82	31(22)	34.27 ± 2.50	29.15–39.38, 0.19	0.002
Resumption of stool	81(31)	81.03 ± 5.13	69.19–90.38,0.24	60(23)	61.03 ± 15.62	55.2–66.87, 0.74	0.001
First fluid diet	72(31)	70.86 ± 5.11	60.36–81.35, 0.26	36(22)	37.13 ± 2.41	32.20–42.07, -0.50	0.00
First solid diet	89(32)	97.07 ± 6.1	84.4–109.7, **1.8**	55(21)	56.87 ± 2.52	51.69–62.04, -0.19	0.00*
Time to stop IV fluids	78(40)	81.36 ± 5.96	69.12–93.60	46(19)	46.33 ± 2.92	40.36–52.31, 0.21	0.00

Skewness coefficient between 1 to -1 are accepted for normality. *: Mann Whittney test. #: days

Table 5 Complications and post operative adverse events : Absolute numbers(percentages)

Parameters	Conventional (n = 30)	ERAS (n = 30)	p-value
Surgical site infection	10 (33.33)	5 (16.66)	0.17
Pneumonia	5 (66.66)	1 (3.33)	0.12
Abdominal wall dehiscence	3 (10)	1 (3.33)	0.33
Post-operative ileus	4 (13.33)	2 (6.66)	0.39
Abdominal sepsis	**2 (6.66)**	**0 (0)**	0.22
Nasogastric tube reinsertion	1 (3.33)	2 (6.66)	0.51
Urinary catheter reinsertion	2 (6.66)	2 (6.66)	0.60
Readmission	2 (6.66)	3 (10)	0.54
Reoperation	1 (3.33)	0 (0)	0.35
Mortality	2 (6.66)	0 (0)	0.15

remaining three were compliant with all the ERAS-specific parameters.

The comparison of various ERAS arm parameters in the study by various authors has been summarized in Table 8.

Post-study power analysis

The effect size of various functional parameters is outlined in Table 3. The effect size of all the studied parameters is exceptionally high. This suggests a beneficial effect of ERAS intervention in recovery of the gastrointestinal functional parameters, removal of indwelling catheters and the overall length of stay.

The study employed a two-tailed t-test to compare the means of two independent groups. An effect size (d) of

Table 6 Quality of life assessment at discharge in ERAS arm(n = 30)

Severity	Restriction in Mobility	Restriction in Self-care	Restriction in Usual activity	Pain	Anxiety/Depression
None	19 (63.33%)	18 (60%)	16 (53.33%)	5 (16.16%)	24 (81.2%)
Slight	10 (33.33%)	10 (33.33%)	11 (36.33%)	16(53.33%)	6 (19.81%)
Moderate	1 (3.33%)	2 (6.66%)	2 (6.66%)	8 (26.66%)	0 (0%)
Severe	0 (0%)	0 (0%)	1 (3.33%)	1 (3.33%)	0 (0%)
Extreme	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7 Quality of life assessment at discharge in conventional arm. (n = 28)

Severity	Restriction in Mobility	Restriction in Self-care	Restriction in Usual activity	Pain	Anxiety/Depression
None	12(42%)	15(52.5%)	14(50%)	4(14%)	20(70%)
Slight	10(35%)	9(31.5%)	8(28%)	18(63%)	5(17.5%)
Moderate	4(14%)	3(10.5%)	5(17.5%)	5(17.5%)	3(10.5%)
Severe	1(3.5%)	0 (0%)	1(3.5%)	1(3.5%)	0 (0%)
Extreme	1(3.5%)	1(3.5%)	0 (0%)	0 (0%)	0 (0%)

Table 8 Comparison of various parameters between RCTs: Gonenc et al., Mohsina et al., ERASE trial

RCT/Parameters	Gonenc et al	Mohsina et al	ERASE trial
Open/Laparoscopic repair	Laparoscopy	Open	Open
Intraoperative nerve block	None	Epidural analgesia	Bilateral rectus sheath block
Immediate removal of nasogastric tube	✓	✖	✓
LOHS	3.8 ± 1.9 days	5.36 ± 1.8 days	3 days, IQR 1 day
Time to oral intake	1.55 ± 1.27 days (liquid or solid: not mentioned)	1.52 ± 0.76 days (liquid diet) 2.64 ± 1.08 (solid diet)	1.54 ± 0.1 days (liquid diet) 2.36 ± 0.1 days (solid diet)
Time to removal of subhepatic drain	✖	1.38 days	0.9 days
Time to ambulation	✖	✖	0.88 ± 0.07 days
Surgical site infection	1/21	5/50	5/30
Pulmonary complication	1/21	2/50	1/30
CCI estimation	✖	✖	✓
Quality of life assessment	✖	✖	✓
Compliance to ERAS elements estimation	✖	✖	✓

✖: not mentioned/ not analysed

✓: mentioned/ analysed

4.95 was observed (Table 3) with a significance level of 0.05. The non-centrality parameter was calculated to be 19.01, with a critical t value of 2.002 and 57 degrees of freedom, resulting in an achieved power of approximately 99.9%, surpassing the commonly accepted threshold of 80%.

The high effect size and the achieved power indicate that the study can detect meaningful differences between the groups at the given sample size and achieve an authentic effect if one exists.

Discussion

There was a statistically significant reduction in the average LOHS, the primary outcome of our study, was two days shorter in the ERAS arm (3, IQR 1 day) as compared to the conventional arm (5, IQR 2 days). In an RCT conducted by Gonenc et al. in 49 patients undergoing laparoscopic perforation repair, the median length of hospital stay was 3.8 days in the ERAS arm and 6.9 days in the conventional arm. [10] On the contrary, Mohsina et al., in their series of 100 patients where open repair of the perforation was done, had a much longer hospital stay with a mean LOHS of 5.36 days in the ERAS arm and 9.78 days in the conventional arm. [15] Their study, being the second such in the world after Gonenc et al., got a longer LOHS, which could have been due to some lag in shifting from the conventional protocol to the ERAS or suboptimal compliance to the ERAS protocol [10]. Although the patients in our study were operated on by the open method, it is noteworthy that the length of hospital stay was marginally better than the previous studies, including that of Gonenc et al. where the surgeries were performed laparoscopically [10]. This might have broader applicability in various populations, more importantly in low- and middle-income countries (LMICs), as by far, most peptic perforation closures are done using the open method in such areas. Thus, open surgery may not necessarily delay recovery if the other ERAS criteria are meticulously followed. Moreover, protocolized

discharge criteria, as our study followed, could help patients' timely discharge without prejudice.

The average time of initiating oral intake in the ERAS group in our study was 38 h (1.58 days), comparable to the previous studies by Gonenc et al. (1.55 days) and Mohsina et al**.** [10, 15]. These results were worse by no more than 12 h when compared with colorectal emergencies, where the initiation of diet could be successfully done within 24 h. [9, 16]

The age-old notion of delayed removal of nasogastric (NG) tube after abdominal surgeries supposedly has been practiced to decrease the chances of post-operative vomiting, pneumonia, and anastomotic leak. This dogma has been challenged of late [17, 18]. With the concept of ERAS coming up, early removal of NG tubes was successfully demonstrated in emergency colorectal surgeries [9, 16] as well as in peptic perforation cases [10, 15]. In our study, the nasogastric tube could be removed immediately after the extubation in the ERAS group, as was also done by Gonenc et al. [10], without any major concerns, thus questioning its blanket use in emergency abdominal surgeries.

In previous studies, the average time to remove the subhepatic drain in the ERAS group ranged from 1.38 to 2.9 days. The ERAS group of patients in our study were free of all tubes in our study within 24 h including the sub hepatic drain (0.9 days) and the urinary catheter (0.66 days). This enabled them for early ambulation contrary to the conventional arm patients, who were reluctant to move around with the drain bags, catheters and intravenous line, despite active motivation. The bilateral rectus sheath block employed in our study minimised the post operative pain and surgical stress. This could also avoid the use of an epidural catheter, which could hinder ambulation due to the presence of an additional catheter. This was reflected in our series where the average time to initiate ambulation, was 21 h. The time to ambulation was not objectively assessed in the previous studies [10, 15].

In our study, the surgical site infection rate was more than twice in the conventional arm (33.33%) than the ERAS arm (14.81%). Although the difference did not achieve statistical significance, it showed a definite trend towards meaningful results. The SSI rates in other studies ranged from 10%-15% in the ERAS arm versus up to 30% in the conventional arm [19]. However, in stark contrast, the study by Gonenc et al. reported only one subject of SSI, which would be the standout advocate of minimal access surgery in the management of peptic perforation. [15, 19–21] We hypothesize that the lesser surgical stress led to better healing and clinically significant lesser SSI in the ERAS arm.

The pulmonary complication rate was the second most witnessed complication after SSI in our study, as has been seen in other similar studies, irrespective of whether it was done by open or laparoscopic method [10, 15, 19]. Five patients in the conventional arm of our study experienced pneumonia in comparison to just one patient in the ERAS arm. The use of a bilateral rectus sheath could have contributed to low pneumonia rates in the ERAS arm due to better pain relief, lowering the chances of basal atelectasis.

We specifically looked at the complication of abdominal wall dehiscence (deep surgical infection), which was not assessed in any previous studies. Two patients in the conventional group had this complication, leading to prolonged hospital stays and mortality in one of them. [10, 15, 19]

CCI is a quantitative score of various post-operative complications, earlier reported in elective radical gastric surgeries and emergency left colonic surgeries [13]. Our study was the first to use the index in peptic perforation which was found to be significantly more in the conventional group indicating a wider set of complication in a given patient.

Quality of life

The effect of ERAS on the QOL had not been studied in any of the four studies undertaken on peptic perforation. We included this dimension in our study using the EQ-5D-5L questionnaire to assess various health related parameters based on patient's perception.

The proportion of patients attaining their pre-illness level of mobility, self-care, usual activity, pain perception, and mental state were equal in both study groups.

We did not separately assess the pain scores in our study, instead perception of pain was recorded as a part of the EQ-5D-5L QOL assessment at the time of discharge and one month follow up. The majority of the patients (42 out of 60), irrespective of the group, in this study had either no pain or mild pain at discharge, the proportion being similar across both arms. The health score component of the EQ-5D-5L was also statistically better in the conventional arm (73.21 ± 2.7) than in the ERAS arm (65.83 ± 2.9) at discharge time. These findings could be explained by the fact that patients in the ERAS arm were discharged nearly two days earlier than the conventional arm when the pain was perceived, and the health scores could still be worse. Despite being discharged early, patients in the ERAS arm did not have higher pain perception, thus allowing them to perform their daily activities. (Tables 6 and 7). Moreover, none of these patients had difficulty at home, and no patient returned for pain in the early post-operative period.

Thus, we found that discharging patients with oral analgesics for pain, is feasible without causing much inconvenience to the patients.

Compliance to ERAS elements

The study of compliance is essential to assess the overall implementation of the protocol and to individualize the contribution from each of its elements. Since our randomization started intraoperatively, we analysed the eight ERAS elements as would be applicable to an intraoperative and post-operative emergency surgery setting. The compliance was 100% in seven out of the eight elements studied. However, the intraoperative fluid balance compliance was markedly low at 10 percent. This can be ascribed to the over-administration of intravenous fluids by the anaesthetists in fear of hemodynamical instability. However, good communication and coordination between the surgeon and the anaesthetist regarding pertinent intraoperative events can better the adherence to ERAS protocol. A study by Vinas et al. demonstrated an overall compliance rate of 62 percent with the least contribution from the intraoperative elements [16]. Gustafson et al. in their study have demonstrated improved clinical outcomes when the compliance rate was 70 percent or more and, no benefit was observed if the compliance was less than 50 [22].

A strict checklist-based implementation of the ERAS parameters by investigating resident and the strict monitoring of the progress by the principal investigator ensured an overall compliance rate of ERAS parameters to touch 88.75%.

Validity of the study

The participants were enrolled after computer-generated randomization sequence and allocation concealment with SNOSE techniques. In each patient selected in the study, the interventions were made as per the study arm (ERAS or conventional), and discharge was planned later based on pre-defined and objective criteria. Moreover, compliance with ERAS-specific interventions was nearly a cent percent, except for one parameter (intraoperative fluid balance), thus minimizing any performance bias. Thus, the internal validity of the study was high.

External validity

We anticipated a higher incidence of post-randomisation attrition in patients of ASA III and IV due to higher likelihood of ventilatory support or prolonged requirement of a urinary catheter. This would have hampered the patients' objective assessment of the ERAS parameters. Hence, the study was conducted on all ASA I and II patients without any sociodemographic restrictions or restrictions for any form of addiction or substance abuse. Hence, the study has high external validity in all ASA I and II patients irrespective of the time, clinical setting, and regional variation (population, ecological, and temporal validity).

Future studies could explore the efficacy and safety of ERAS in patients with higher ASA grades to evaluate its applicability across a wider range of surgical populations.

Strength and weakness of the study

The study objectives were well defined, and the methodology, including the randomization, allocation, and outcome assessment, was described in detail, enhancing the transparency and reproducibility of the study. It was a well-designed randomized controlled trial with 90% power. It was adequately powered as a convenient sample of twice the calculated sample size was taken to assess the safety profile of ERAS in the study population. The functional parameters were recorded in hours to have a more accurate comparative analysis. The use of Comprehensive complication index made the assessment of the complication rates more objective. This is the only study that compares the quality of life of this study population. The compliance to ERAS parameters in peptic perforation was measured, which is the first study of ERAS in emergency surgeries. Assessment of the pain scores with the VAS score could have helped us with a more objective assessment of pain perception. We excluded the ASA III and IV groups of patients. Including the ASA III and IV group of patients could have helped us analyse this high-risk subset. The study was open label because of which there could have been chances of biases. A study with double or triple blinding could have eliminated some of them. Lastly, a better co-ordination between the surgical team and anaesthetists can prevent excessive fluid administration and achieve an optimum fluid balance.

Conclusion

Implementation of the ERAS protocol in the peptic perforation patients in our study improved functional outcomes and led to an earlier discharge of patients, without any significant addition to the morbidity or mortality, verifying its safety and efficacy. Open surgery for peptic perforation does not necessarily delay recovery if the other ERAS criteria are meticulously followed. Optimal compliance with the ERAS parameter is feasible in the emergency setting, with a collective effort from both the surgical and anesthesia teams. Further research in similar lines on ASA III and IV patients will be required to investigate any potential benefits in these critically ill patients. Moreover, studies involving larger populations can

further strengthen the position of ERAS in Emergency (ERAS-E) and improve the outcomes in these patients.

Abbreviations

ERASE	Enhanced recovery after surgery in emergency
ERAS	Enhanced recovery after surgery
LOHS	Length of hospital stay
OR	Operative room
ASA	American society of anaesthesiologists
PULP	Peptic ulcer perforation
IQR	Interquartile range
NG	Nasogastric
CCI	Comprehensive complication index

Author contributions

SSM, TSM, SK, MKS, UH and PK designed the protocol, consent form, and data entry form. MKS, SSM., TSM, PKSi and PKSa: data collection, analysis of results. PKSa and UH reviewed the literature. SSM, TSM, MKS: Manuscript preparation. TSM, SSM, PKSa, PKSi, SK, MKS, UH and PK reviewed and revised and drafted the final manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

The study was approved by the Institutional Ethics Committee, AIIMS Bhubaneswar, Odisha, India.

Informed consent

A written informed consent was taken from all the participants.

Conflict of interest

The authors declare no competing interests.

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