Enhanced recovery after surgery (ERAS) protocols is extremely beneficial in liver surgeries – A metaanalysis.

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Abbreviations: Enhanced Recovery After Surgery (ERAS), Weighted Mean Difference (WMD), Confidence Intervals (C.I)

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Dr. Bhavin Vasavada was over all incharge of research and actively contributed in study design, data collection, conduction research, statistics, manuscript written, final approval. Dr. Hardik Patel helped in data collection, conduction research, statistics, manuscript writing.
ABSTRACT:

BACKGROUND: Enhanced recovery after surgery (ERAS) programs aim to improve postoperative outcomes. This metaanalysis aims to evaluate the impact of ERAS programmes on outcomes following liver surgeries.

METHODS: EMBASE, MEDLINE, PubMed and the Cochrane Database were searched for studies comparing outcomes in patients undergoing liver surgery utilizing ERAS principles with those patients receiving conventional care. The primary outcome was occurrence of 30 day morbidity and mortality. Secondary outcomes included length of stay, functional recovery, readmission rates, time to pass flatus, blood loss and hospital costs.

RESULTS: Ten articles were included in the metaanalysis. Overall 30 days mortality rates were 0.65% in ERAS group while 0.97% in standard group (p=0.997). 30 days morbidity rates were not different in ERAS group compared to conventional care patients. (20.2% in ERAS vs. 25% in non ERAS). (p=0.329). Hospital stay, time to pass flatus, time to complete recovery and hospital costs were also significantly reduced due to ERAS protocols. (p value <0.001, 0.005, <0.001, and 0.038 respectively). There was no significant difference in blood loss and readmission rates between the two groups. (p=0.594, and 0.916 respectively)
CONCLUSIONS: The adoption of ERAS protocols significantly reduced morbidity, hospital stay, readmission rates, time to recovery, hospital costs, time to pass flatus. There were no significant differences in 30 day mortality and blood loss.

KEYWORDS: Enhanced recovery after surgery, liver surgery, HPB surgery, morbidity, mortality, liver resection, fast track surgery.

Introduction:

Early recovery after surgery (ERAS) protocol is becoming gold standard in perioperative care with excellent results in colorectal, gastric and HPB surgeries. [1].

ERAS is a evidence based peri-operative protocol which has shown significant improvements in perioperative outcomes.[2]. Despite these overwhelming evidences implementation of these protocols has been very slow and lack wide spread implementation.[3]

ERAS has initially developed for colorectal surgeries [4], However its implementation is being tested in all other field.[4] and it has now spread over other specialities.

ERAS protocols has been applied to liver surgeries also and found to be beneficial.[5]

Primary Aim of this metaanalysis was to study the effect of ERAS protocols on 30 days morbidity and mortality. Secondary aim was to study effect of ERAS protocols
on hospital stay, readmission rates, time to recovery, time to pass flatus, and Hospital costs.

**Material and Methods:**

In this systemic review and metaanalysis we searched EMBASE, MEDLINE, PubMed and the Cochrane Database with key words like “liver surgery”, “Enhanced recovery after surgery”, “ERAS protocols”, “ERAS vs conventional liver surgery”, “morbidity and mortality following liver surgery”, ‘liver resections”. Two independent authors extracted the data (B.V and H.P).

Systemic review and Metaanalysis was done according to MOOSE and PRISMA guidelines. (6,7).

**Statistical analysis**

The meta-analysis was conducted using Open metaanalysis software. Heterogeneity was measured using Q tests and $I^2$, and $p < 0.10$ was determined as significant (8). If there was no or low heterogeneity ($I^2 < 25 \%$), then the fixed-effects model was used. Otherwise, the random-effects model was used. The risk ratio (RR) was calculated for dichotomous data, and weighted mean differences (WMD) were used for continuous variables. Both differences were presented with 95 % CI. For continuous variables, if data were presented with medians and ranges, then we calculated the means and SDs according to Hozo et al. (9). If the study presented the median and inter-quartile range, the median was treated as the mean, and the interquartile ranges were calculated using 1.35 SDs, as described in the Cochrane handbook.
Inclusion criteria:

1. Studies that compared ERAS protocols with that of conventional protocol
2. Minimum 25 numbers of patients
3. Means and standard deviations or medians and range mentioned.
4. Full texts available
5. Prospective, retropectives studies or randomised control trials included.
6. ERAS program should include most of the 17 items included according to ERAS group recommendation. [10].

Exclusion criteria:

1. Studies whose full texts can not be obtained.
2. Studies with no comparable groups [ERAS vs conventional]
3. Duplicate studies.

Assessment of Bias:

Characteristics of the studies are described in table 1. Identified studies were broadly grouped into 1 of 2 types, either randomized trials or cohort studies. Cohort studies were assessed for bias using the Newcastle-Ottawa Scale (10). Randomized trials were assessed based on the Cochrane Handbook. (11) (Table 2 and table 3)

Results:
Search results:

Total 190 studies identified from initial literature search, 157 studies were evaluated after duplicates removed. Only 57 studies included ERAS protocols, 34 studies full text obtained. 13 studies had comparable groups for conventional protocols. Out of it 10 studies included in final analysis as other studies did not include adequate ERAS protocols. [figure 1]. (13-22)

Total 1289 patients’ outcomes were studied from these 10 studies. 618 in ERAS group and 618 in conventional group.

Metaanalysis:

Primary outcome measures:

30 days mortality:
3 patients died in ERAS out of 458 and 5 patient died in conventional approach out of 511. There was no significant difference between ERAS and conventional group. P=0.792.

30 days morbidity:
30 days morbidity rates were not difference between the two groups. P=0.329. 114/593 patients developed complications in ERAS group vs 171/673 in conventional group.

Secondary outcomes:

We also evaluated hospital stay, time to functional recovery, readmission rates, time to pass flatus, hospital costs and blood loss in ERAS protocols in liver surgery.
As shown in figure 3 hospital stay (p<0.001 WMD -2.191 and time to functional recovery (p<0.001, WMD -2.462) were significantly less in ERAS group however there was no difference in readmission rates.(p=0.916)

There was no difference in blood loss between ERAS and conventional group. (p=0.594). (figure 4). Time to pass flatus and hospital costs were significantly lesser in ERAS group. (p= 0.005 and p= 0.038 respectively with WMD of -0.996 days and – 1803.536 $ respectively).

**Discussion:**

Enhanced recovery after surgery though initially described for colorectal surgery is now becoming standard protocol for all surgeries and it has significantly reduced hospital stay and cost without affecting morbidity and mortality.[1-5]

Started from colorectal surgeries ERAS protocols has now moved to other branches of surgeries. Many authors have tried to study applications of ERAS protocols on liver surgeries. (13-22) and showed ERAS protocol has significant benefit over standard protocols however large number studies and quality metaanalysis are still missing. Purpose of this metaanalysis to compare outcomes between ERAS and conventional group.

After literature review we evaluated 10 studies in this metaanalysis 4 were Randomised control trials (11-14) and 6 were prospective or retrospective cohort studies. (15-20).

We evaluated 30 days mortality and morbidity as primary outcomes and hospital stay,time to complete recovery (time to complete physical independence), readmission rates,time to pass flatus, blood loss and hospital costs as secondary outcomes.
There was no difference in mortality and morbidity between the two groups. (figure 2). Hospital stay, time to functional recovery and time to pass flatus (4 studies) were also significantly different in both the groups. (WMD -2.191, Odds ratio 0.016, and WMD -2.462 respectively).

There was no difference between blood loss and readmission rates between the two group in the metaanalysis. Only 3 studies out of 10 evaluated hospital cost which was significantly lesser in ERAS group. (WMD -1803.536$).

There are some limitations of this metaanalysis as heterogeneity of studies was significantly random effect models were used. Except hospital stay at least one study did not evaluate other factors.

In conclusion ERAS programs in liver surgeries reduce hospital stay, readmission rates, time to recovery, time to pass flatus, hospital cost without affecting 30 days mortality and morbidity.

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### Table 1: Characteristics of studies.

| Study        | Type of study | Number of patients in ERAS group | Number of patients in control group |
|--------------|---------------|----------------------------------|-------------------------------------|
| bobbyv2015   | COHORT        | 91                               | 93                                  |
| vandam2008   | COHORT        | 61                               | 100                                 |
| koea2009     | COHORT        | 50                               | 50                                  |
| lin2011      | COHORT        | 56                               | 61                                  |
| jones2013    | RCT           | 46                               | 45                                  |
| ni2013       | RCT           | 80                               | 80                                  |
| sanchez2012  | COHORT        | 26                               | 17                                  |
| HeF2015      | RCT           | 48                               | 38                                  |
| lu2014       | RCT           | 80                               | 80                                  |
| liang 2016   | RCT           | 80                               | 107                                 |
Table 2: Risk of bias summary of RCT. + denotes low risk of bias, – denotes high risk of bias.

| Study     | Random Sequence generation | Allocation Concealment | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Other |
|-----------|----------------------------|-------------------------|------------------|----------------|----------------|----------------|-------|
| jones2013 | +                         | +                       | -                | +              | +              | +              | ?     |
| ni2013    | +                         | +                       | -                | -              | +              | +              | +     |
| HeF2015   | +                         | +                       | -                | +              | +              | +              | +     |
| lu2014    | ?                         | ?                       | -                | +              | +              | +              | ?     |
| liang2016 | ?                         | ?                       | -                | -              | +              | +              | -     |

Table 3: Assessment of bias in cohort studies. + Denotes low risk of bias, – denotes high risk of bias.

| Study     | Representat ive of exposed cohort | Selecti on of non expose d cohort | Ascertainment of Exposure | Demonstrat ion that outcome was not present at start of study | Comparability of cohorts | Assess m ent of outcomes | Adequa te time for follow up | Comple te Follow up of cohort | Total score |
|-----------|-----------------------------------|-----------------------------------|---------------------------|---------------------------------------------------------------|--------------------------|---------------------------|-------------------------------|-------------------------------|-------------|
| bobbyv2015 | +                                 | +                                 | +                         | +                                                             | -                        | +                        | -                             | +                             | 7           |
| vandam2008 | +                                 | +                                 | +                         | +                                                             | -                        | -                        | +                             | +                             | 6           |
| koea2009  | +                                 | -                                 | -                         | +                                                             | -                        | -                        | +                             | +                             | 4           |
| lin2011   | +                                 | +                                 | +                         | +                                                             | -                        | +                        | +                             | +                             | 7           |
Figure 1. Search strategy according to PRISMA guidelines.

| Studies     | Estimate (95% C.I.) | Ev/Trt | Ev/Ctrl |
|-------------|---------------------|--------|---------|
| bobby v 2015| 0.397 (0.109, 1.278)| 30/91  | 32/93   |
| vandsem 2008| 1.546 (0.796, 2.990)| 25/61  | 21/100  |
| he 2015     | 0.911 (0.279, 2.976)| 7/48   | 6/38    |
| jones 2013  | 0.640 (0.173, 1.254)| 8/46   | 14/45   |
| sanchez 2012| 0.578 (0.146, 2.266)| 3/26   | 3/17    |
| korea 2009  | 0.675 (0.246, 1.966)| 8/50   | 11/50   |
| lin 2011    | 0.937 (0.509, 2.278)| 34/60  | 16/61   |
| lu 2014     | 0.684 (0.261, 1.985)| 7/135  | 12/142  |
| liang 2016  | 0.432 (0.228, 0.830)| 18/80  | 47/117  |
| Overall (I²:1263 %, P=0.329) | 0.792 (0.584, 1.073) | 120/593 | 171/683 |
Metaanalysis of 30 days mortality. There was no significant difference between mortality between ERAS vs conventional approach. (p=0.999)

| Studies          | Estimate (95% C.I.) | Ev/Tt | Ev/Ctrl |
|------------------|---------------------|-------|---------|
| bobby v 2015     | 0.937 (0.599, 1.728)| 30/91 | 32/93   |
| vandem 2008      | 1.546 (0.796, 3.000)| 25/41 | 21/100  |
| he 2015          | 0.312 (0.279, 0.976)| 7/84  | 6/185   |
| jones 2013       | 0.444 (0.173, 1.254)| 8/44  | 14/45   |
| sanchez 2012     | 0.978 (0.146, 6.565)| 3/23  | 2/17    |
| hees 2009        | 0.676 (0.244, 1.854)| 8/50  | 11/60   |
| lin 2011         | 0.977 (0.406, 2.352)| 14/56 | 16/61   |
| lu 2014          | 0.484 (0.261, 1.794)| 7/115 | 12/162  |
| liang 2016       | 0.433 (0.224, 0.823)| 18/40 | 47/117  |
| Overall (I²=1263 %, P=0.329) | 0.792 (0.594, 1.073)  | 120/592 | 171/683 |

30 days Morbidity rates were significantly lesser in ERAS group p<0.001 odds ratio 0.329

Figure 2 metaanalysis of 30 days mortality and morbidity rates between ERAS vs conventional approach.

| Studies          | Estimate (95% C.I.) |
|------------------|---------------------|
| bobby v 2015     | 0.000 (-0.941, 0.941) |
| oas 2008         | -2.000 (-8.394, 4.394) |
| n 2011           | -4.000 (-7.197, -0.803) |
| n 2013           | -3.000 (-4.175, -1.825) |
| sanchez 2012     | -1.200 (-1.820, -0.580) |
| lu 2015          | -3.700 (-4.955, -2.445) |

Overall (I²=8022 %, P<0.001) weighted mean difference -2.191 (95% confidence interval 3.039- 1.343)
Readmission rates were same in both the groups. (p=0.916)

_times to functional recovery was also significantly lesser in ERAS group. P<0.001. weighted mean difference -2.462 (-3.826, -1.104)

Figure 3 metaanalysis of hospital stay, readmission rates and time to functional recovery.

Forest plot for blood loss. P=0.594.
| Studies  | Estimate (95% C.I.) |
|---------|-------------------|
| koea 2009 | 0.670 (-1.825, 3.165) |
| ni 2013  | -0.900 (-1.483, -0.317) |
| He F 2015 | -1.000 (-1.213, -0.787) |
| lu 2014  | -12.000 (-18.482, -5.518) |
| Overall (I^2=76.71 %, P=0.005) | -0.996 (-1.925, -0.068) |

Forest plot for time to pass flatus p=0.005. WMD= -0.996 (95% CI -1.925 - 0.068)

| Studies  | Estimate (95% C.I.) |
|---------|-------------------|
| lin 2011 | -14.000 (-1184.398, 1143.602) |
| He F 2015 | -1728.000 (-2323.811, -1132.189) |
| liang 2016 | -1077.000 (-1966.085, -187.915) |
| Overall (I^2=69.33 %, P=0.038) | -1187.750 (-1803.536, -569.964) |

Forest plot for hospital cost p=0.038 WMD (-1803.536 -- -569.964)

Figure 4. Metaanalysis for blood loss, time to pass flatus and hospital cost