The efficacy of enhanced recovery protocol from anesthesia in diabetic patients undergoing radical cystectomy

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**ABSTRACT**

**Background:** Prevalence of diabetes in surgical patients is 10–40%. They have higher incidence of complications, and longer stay in hospital compared to non-diabetic. Radical cystectomy with urinary diversion is considered one of the high-risk surgeries associated with morbidity and mortality. Enhanced recovery after surgery (ERAS) is an evidence-based multimodal surgical care protocol that improves post-operative outcomes and length of stay (LOS) in patients without diabetes. This study evaluates the evidence on whether diabetic patient(s) would benefit from ERAS pathway.

**The aim of the study:** was to evaluate the efficacy of ERAS protocol from anesthesia in diabetic patients undergoing radical cystectomy.

**Patients and methods:** This study was carried out in Alexandria main University Hospital on fifty-four adult ASA physical status I, II and III participants of either sex. Participants were scheduled for radical cystectomy surgeries under the effect of general anesthesia, following ERAS protocol, divided into two group diabetic and non-diabetic27 participants each. The ICON device was used to measure the stroke volume variation (SVV) to apply goal-directed fluid therapy (GDFT) for all patients.

**Measurements:** Demographic data, hemodynamic parameters (stroke volume, cardiac index), intra-operative fluid requirement, blood loss, postoperative pain intensity, time of first bowel movement, PH, Bicarbonate level, serum lactate level, heamacrit and LOS were measured and recorded.

**Main results:** No statistical significant difference was detected between both groups as regard age, sex, weight, vital signs, serum lactate, first bowel movement and VAS. There was statistical significant difference between both groups as regard fluid requirement, and the days of hospital stay.

**Conclusion:** ERAS is a beneficial protocol to improve postoperative outcome in radical cystectomy surgeries, it can be used in diabetic patients to decrease postoperative morbidity and mortality.

1. **Introduction**

Diabetes is a chronic disease with an estimated prevalence of 7.2–11.4% worldwide [339–536 million], and an expected increase in these numbers over the following decades [1]. People with diabetes are admitted for surgery more than non-diabetics, and prevalence of diabetes in surgical patients is estimated to be 10–15% [2].

Diabetic patients are a high-risk surgical population with longer hospital stays, higher postoperative complications, and greater perioperative morbidity and mortality [3,4].

Bladder tumor is the second common urologic malignancy [5]. Radical cystectomy with pelvic lymph node dissection is the gold standard treatment for muscle-invasive bladder carcinoma [6]. Radical cystectomy demonstrates overall survival rates of 45% [7].

Radical cystectomy with urinary reconstruction is a high-risk surgery with high incidence of morbidity and mortality [8].

Recently, a shift has occurred in the perioperative treatment of patients undergoing cystectomy with referred to Enhanced Recovery After Surgery (ERAS) program [9].

ERAS includes 22 components of pre-, intra- and postoperative care, with all being described as “Strong” recommendations as per the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [10].

Whether diabetic patients should be included in ERAS has been a contentious issue [11], resulting in varying clinical observations and guideline recommendations [12].

There are hypothetical risks to carbohydrate loading (one of the mean elements of ERAS) in individuals with diabetes (like aspiration pneumonia due to...
delayed gastric emptying, and hyperglycemia and its sequels) and it is uncertain whether this may negate any beneficial effects from the other elements of ERAS.

Individuals with diabetes complain of delayed gastric emptying. Chronically hyperglycemia can lead to autonomic neuropathy and intrinsic nervous system dysfunction [13].

Acute hyperglycemia (>11.1 mmol/l) delays gastric emptying, decreases small bowel contractility and stimulates localized pyloric constriction [14]. Another concern with hyperglycemia is its association with postoperative complications. [15] A gap exists in the field of diabetes and postoperative outcomes within ERAS.

We conducted this study to evaluate the efficacy of the use of the ERAS protocol in individuals with diabetes undergoing radical cystectomy surgery.

2. Aim of the work

The present study aims to evaluate the efficacy of protocol for radical cystectomy surgery in diabetic patients.

3. Participants

After approval of the local ethics committee and an informed written consent from each patient, all participants were of American Society of Anesthesiology (ASA) physical status I, II, III. They were admitted to Alexandria Main hospital, 54 participants were scheduled for radical cystectomy surgeries under the effect of general anesthesia, following ERAS protocol, 27 participants in each group. **Group I Diabetic group:** 27 diabetic patients underwent **Group II: Non-Diabetic group:** 27 non diabetic patients.

4. Methods

Both groups received perioperative care to implement ERAS pathway which aimed to give the patient preoperative carbohydrate loading to reduce insulin resistance, insertion of thoracic epidural at T10-T11, intraoperative goal-directed fluid therapy using Stroke volume variation SVV measured by the noninvasive cardiac output measure ICON device, no mechanical bowel preparation, early mobilization postoperative and early oral intake after surgery.

Intraoperative fluid requirements consist of a background maintenance fluid, infusion of a balanced crystalloid solution (Lactated Ringer’s) was delivered with a 2 mL/kg/hour combined with volume therapy (fluid challenges). The stroke volume variation SVV was assessed every 10 minutes using the ICON device. If the stroke volume variation is greater than 12%; a 200 ml bolus of colloid solution (Hydroxyethyl starch 6%) over 5–10 min was given.

If SVV and Stroke volume (SV) were in target range and blood pressure was within 20% of target values then continue to monitor. If SVV was in target range but BP was below 20% of target values then the cardiac index CI was assessed. If Cardiac Index was < 2.5 inotropic agent (Dobutamine: 2.5 µg/kg/min) was considered. If Cardiac Index was > 4 (Norepinephrine: 0.1 µg/kg/min) was considered.

In the diabetic group, blood glucose level was maintained intraoperative between 140 and 180 mg/dl. In patients with type 1 diabetes, the insulin infusion rate began at 1 U/h (50 U short-acting insulin in 50 mL normal saline; 1 U = 1 mL), whereas infusion rates were increased in type 2 diabetics to 2 U/hour. The rate of insulin infusion was adjusted to reach the glycemic goal by checking the blood glucose level every hour.

5. Measurements

The following parameters were measured in both groups:

1. Oxygen saturation, heart rate, mean arterial blood pressure (MABP), core temperature, stroke volume and cardiac index were measured every 30 minutes during surgery and till the end of surgery.
2. Postoperative pain was measured every 2 h for the first 8 postoperative hours using Visual Analogue scale (VAS) score.
3. Total intraoperative fluid requirements (ringer’s, colloid) were calculated.
4. Intraoperative blood loss was recorded.
5. Total intraoperative-packed RBCs and FFPlasma were recorded.
6. PH, Bicarbonate level, Serum lactate level and hematocrit were measured after induction of anesthesia, immediately after recovery, and day 1 postoperative.
7. The total amount of intraoperative insulin units used in group I were measured and the number of patients in group II who needed insulin was recorded.
8. Postoperative first bowel movement was recorded.
9. Postoperative hospital stay days was recorded.

6. Results

The demographic data in both the groups showed great similarities and did not exhibit any statistically significant difference (Table 1).

As regards the hemodynamic parameters, by comparing both groups with each other, there was a statistically significant difference in heart rate recordings at 60, 90, 120 and 150 minutes of measurement, and a statistical significant difference in mean blood pressure at 30, 120, 210 and 240 minutes of measurement.
There was no statistically significant difference was observed between both groups in O2 Saturation values, core temperature and Visual Analogue Scale for postoperative pain.

The comparison of stroke volume values between both groups showed a statistically significant difference at baseline, 120, 150, 240 minutes of measurement. The results also showed a statistically significant difference in cardiac index values at 120 minutes of measurement (Tables 2 and 3).

As regard the laboratory results, the comparison between both groups at different times of measurement showed a statistically significant difference at PH after recovery and PH Day 1 values. Also, there was a statistically significant difference at basal bicarbonate level.

The comparison between both groups at different times of measurement showed significant decrease in hematocrit values in group II at baseline and after recovery measurements (Table 4).

In diabetic group, lactate level showed no statistically significant different at different times of measurement, in non-diabetic group lactate levels showed statistically significant difference at after recovery and Day 1 measurements. But the comparison between both groups at different times of measurement showed no statistically significant difference (Table 5).

As regard the intraoperative blood loss there was no statistically significant difference in the blood loss amount between both groups.

There was a statistically significant difference in the lactated ringer’s amount consumed between both groups. The mean amount of lactated ringer’s consumed in diabetic group was (1022.22) and (794.44 ± 197.25) in non-diabetic group (p = 0.003).

There was a statistically significant difference in the colloid amount consumed between both groups. The mean amount of hydroxyethyl starch consumed in diabetic group was (1325.92 ± 320.56) and (1133.33 ± 277.35) in non-diabetic group (p = 0.010).

There was no statistically significant difference in the total amount of packed RBCs consumed between both groups intra-operatively, but there was a statistically significant difference in the total amount of fresh frozen plasma consumed between both groups. The mean amount of FFP consumed in diabetic group was (2.18 ± 0.68) and (1.81 ± 0.92) in non-diabetic group (p = 0.044).

The mean amount of intraoperative insulin units used in group I was 7.85 ± 1.06 and only 3 patients in group II needed intraoperative insulin to control blood glucose level.

By comparing the first bowel movement (days) in each group there was no statistically significant difference in the first bowel movement in the diabetic group (1.92 ± 0.67) and (1.77 ± 0.64) in the non-diabetic group (p = 0.416).

There was a statistically significant difference in the length of hospital stay (days) between both groups when the comparison was established between them. The mean of hospital stay was (7.74 ± 0.92) day in the diabetic group and (6.48 ± 0.89) day in the non-diabetic group (P < 0.001) (Table 6).

By analyzing the results of the study, there was found that 44.1% of change in the length of the hospital stay can be explained by significant factors like the amount of Fresh Frozen Plasma, the lactated Ringer’s solution and Packed RBCs consumed by the patients (Table 7).
7. Discussion

ERAS is an evidence-based perioperative care protocol, it was proven that it had a major impact on lowering the recovery time and improving postoperative outcomes. [16]

Individuals with diabetes are a high-risk surgical population, and despite advances in perioperative care with the introduction of the ERAS program, it is unknown whether postoperative outcomes are altered by enrollment in an ERAS program compared to conventional care. [17]

Therefore, our aim in the study was to apply the ERAS program in diabetic patients undergoing radical cystectomy and shortening the length of hospital stay and first bowel motion.

In the present study, the results showed that the applied protocol of intraoperative GDF (goal-directed fluid therapy) used in ERAS, reduced the total volume of crystalloids consumed by patients significantly despite of increased amount colloids consumed by diabetic patients.

Junliu et al. [18] conducted a randomized controlled study on 76 elderly patients scheduled for radical resection of bladder cancer. They were divided into two groups. 38 patients received routine fluid management (control group) and 38 patients received GDF (study group). The results showed that crystalloid consumption and total volume of fluid consumption were significantly less in the study group than the control group while, colloidal infusion was obviously higher in the study group when compared with those in control group.

In our study, the Stroke Volume Variation SVV was assessed using the noninvasive cardiac output monitoring device.

Waldron et al. [19] conducted a study on 100 adult patients undergoing elective colorectal surgery. The intraoperative GDF was guided by the esophageal Doppler monitor EDM and the noninvasive cardiac output monitor NICOM. The EDM had significantly more missing data than the NICOM. The NICOM works similarly to the EDM in assessing GDF, with no clinically significant differences in results, and offers more easy practice as well as fewer missing data points.

Table 6. Comparison between the two studied groups according to blood loss, Lactated Ringer’s, colloid (Hydroxyethyl starch), packed RBCs, Fresh Frozen Plasma, first bowel movement and length of hospital stay.

| Blood loss (ml) | Group | Test of significance | P value |
|-----------------|-------|----------------------|---------|
| Diabetics       |       |                      |         |
| Median          | 2333.33 ± 521.83 |                      |         |
| Min.            | 2200.0 |                      |         |
| Max.            | 3700.0 |                      |         |
| Non diabetics   |       |                      |         |
| Median          | 2094.44 ± 400.56 | Mann Whitney         | p = 0.115 |
| Min.            | 2000.0 | U = 454.0            |         |
| Max.            | 3000.0 |                      |         |
| Lactated Ringer’s(ml) |       |                      |         |
| Mean ±SD       | 1022.22 |                      |         |
| Median          | 1000.0 |                      |         |
| Min.            | 700.0  |                      |         |
| Max.            | 1800.0 |                      |         |
| Colloid (Hydroxyethyl starch) (ml) |       |                      |         |
| Mean ±SD       | 1325.92 ± 320.56 | Mann Whitney         | p = 0.010* |
| Median          | 1300.0 | U = 508.0            |         |
| Min.            | 800.0  |                      |         |
| Max.            | 2000.0 |                      |         |
| Packed RBCs(units) |       |                      |         |
| Mean ±SD       | 2.74 ± 0.71 | Mann Whitney         | P = 0.817 |
| Median          | 3.0    | U = 376.5            |         |
| Min.            | 2.0    |                      |         |
| Max.            | 4.0    |                      |         |
| Fresh Frozen Plasma (units) |       |                      |         |
| Mean ±SD       | 2.18 ± 0.68 | Mann Whitney         | P = 0.044* |
| Median          | 2.0    | U = 473.5            |         |
| Min.            | 1.0    |                      |         |
| Max.            | 4.0    |                      |         |
| First Bowel movement (days) |       |                      |         |
| Mean ±SD       | 1.92 ± 0.67 | Mann Whitney         | P = 0.416 |
| Median          | 2.0    | U = 406.5            |         |
| Min.            | 1.0    |                      |         |
| Max.            | 4.0    |                      |         |
| Length of hospital stay (days) |       |                      |         |
| Mean ±SD       | 7.74 ± 0.92 | Mann Whitney         | P < 0.001* |
| Median          | 8.0    | U = 600.5            |         |
| Min.            | 6.0    |                      |         |
| Max.            | 9.0    |                      |         |

Table 7. Multiple linear regression analysis of factors affecting length of hospital stay.

| Significant factors in the model | Unstandardized B | T test significance | ANOVA | R square |
|----------------------------------|------------------|---------------------|-------|----------|
| Fresh Frozen Plasma             | 0.743            | t = 5.057 p < 0.001*| F = 3.139P < 0.001* | 0.441     |
| Lactated Ringer’s solution       | 0.002            | t = 3.629 p = 0.001* |       |         |
| Packed RBCs                      | -0.443           | t = 2.412p = 0.020* |       |         |
In our study, the target blood glucose level for the perioperative period was 80–180 mg/dl and was controlled by the basal–bolus insulin regimens which are recommended over sliding scale regimens. Similarly, did Albalawi et al. [17] in their study about the effect of ERAS in individuals with diabetes.

As regard first bowel movement, there was no statistically significant difference in the first bowel movement in the diabetic and the non-diabetic groups. Contrary, Frees et al. [20] prospectively randomized 27 patients undergoing radical cystectomy, 12 patients followed an ERAS protocol and 15 patients followed a standard protocol. The results showed that the time to first bowel movement was 2 days shorter in ERAS group.

There was a statistically significant increase in the length of hospital stay (days) in the diabetic group when compared to the nondiabetic group. Similarly, Luther et al. [21] Consecutive patients undergoing elective major colorectal procedures had data regarding length of stay, comorbidities, and major complications prospectively collected. The study included 143 patients. The median length of stay of the non-diabetic patients was 5 days (Interquartile range 4–7.5, n = 125) while in the diabetic group the median length of stay was significantly longer at 7 days (5–15.5, n = 18, P = .041 Mann–Whitney). Diabetic patients who have elective colorectal surgeries have a significantly longer length of stay in hospital than patients without diabetes despite being managed with an ERAS protocol.

7.1. Conclusion

ERAS is a beneficial protocol to improve postoperative outcome in radical cystectomy surgeries. It reduces the length of hospital stay and decreases time to bowel activity. ERAS can be used in diabetic patients to decrease postoperative morbidity and mortality. Stroke Volume Variation SVV measured by ICON device is an effective noninvasive method for GDFT.

7.2. Strength of the study

Randomization, participants undergoing radical cystectomy surgeries under ERAS protocol in our urology department, the noninvasive method of measuring the SVV and cardiac index.

7.3. Limitations of the study

Better outcomes in laparoscopic or robotic cystectomy surgeries, the use of electrical cautery interferes with the ICON device signals.

Disclosure statement

No potential conflict of interest was reported by the authors.

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