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Evaluation of Laparoscopic Splenectomy in Idiopathic Thrombocytopenic Purpura

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ABSTRACT
Background: primary ITP was defined according to the American Society of Hematology 2011 evidence-based practice guideline as a platelet count less than 100 × 10^9/L without other causes or disorders that may be associated with thrombocytopenia. The main first-line therapy for ITP is oral corticosteroids. Splenectomy is generally considered a second-line therapy in patients who are refractory to steroids and in those who relapse after an initial response to medical therapy. **Objective:** the aim of this study was to evaluate the feasibility, safety and efficacy of LS in ITP patients. **Patients and Methods:** this study was carried out on 20 patients diagnose as having ITP and indicated for splenectomy, 60% were females and 40% were males. Their age ranged from 17-33 years with a mean of 24.3± 5.39 years. **Results:** the platelet count raised from (30000 to 140000/L) pre-operative to (90000 to 190000/ L) post-operative. There was statistically significance difference between pre and post-operative platelet count (p <0.001). From the assessment of platelet count according to American Society of Hematology 2011 evidence-based practice guidelines for ITP. Nineteen patients (95%) achieved complete response, while only one patient (5%) achieved partial response. **Conclusion:** it was concluded that LS produces an adequate postoperative rise in platelet count and it is associated with less operating time, post-operative hospital stay, blood loss and postoperative complications.
Keywords: Laparoscopic Splenectomy, ITP

INTRODUCTION
Primary immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura or primary immune thrombocytopenic purpura, is an immune-mediated disease characterized by low platelet counts (< 100 x 10^9/L) as a result of immune mediated destruction of circulating platelets and suppression of platelets production in absence of any obvious initiating and/or underlying cause of thrombocytopenia such as infection, drugs and autoimmune diseases [(1)].

Clinical picture of ITP varies from patient to patient. Nearly one-quarter of patients are asymptomatic and diagnosed as having ITP through incidental routine blood tests [(2)]. Some patients present with mild mucocutanaeous or subcutaneous haemorrhages while others present with major bleeding requiring immediate intervention [(3)]. Severity of bleeding depends upon platelets count as patients with platelet counts less than 10 x 10^9/L are at increased risk of serious or life-threatening internal bleeding (e.g. intracranial haemorrhage, mucocutaneous bleeding, lower gastrointestinal bleeding, other internal bleeding and menorrhagia). Platelet counts between 30-50,000 mm^3 increase the risk of dangerous bleeding from minor trauma, while platelet counts below 10-30,000/mm^3 increase the risk of spontaneous bleeding [(4)].

The spleen plays a critical role in the pathogenesis of ITP. For most patients, the spleen is the primary site of platelet clearance through splenic macrophages which enhance the uptake of antibody-coated platelets resulting in phagocytosis [(5)]. Also, the spleen serves as a critical niche for immune cells that promote anti-platelet antibody formation [(6)]. In addition, the spleen serves as a reservoir for long-lived anti-platelet antibody-producing plasma cells [(7)].

Regarding the treatment of ITP, corticosteroids are considered the first-line therapy for ITP, but only 20%-40% of cases achieve a stable response. Splenectomy is the main therapy for patients failing to respond to corticosteroids for decades, and about two-thirds of patients achieve a long-lasting response. Although some new drugs are developed to treat ITP as second-line therapies in recent years, splenectomy is still the better choice with less cost and more efficiency [(8)].

AIM OF THE WORK
The aim of this study is to evaluate the feasibility, safety and efficacy of LS in ITP patients.

PATIENTS AND METHODS
Patients:
This study was carried out on twenty patients diagnosed as having primary ITP according to the guidelines of the ASH [(9)]. They were referred by the Hematology department to our surgical department in Faculty of Medicine, Al-Azhar University for

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LS. **The study was approved by the Ethics Board of Al-Azhar University.**

Indications for splenectomy in ITP patients:

- Thrombocytopenia with bleeding manifestations as (progressive purpura, ecchymosis, epistaxis).
- Lack of response to conservative treatment (low platelet counts while on massive steroid and/or immunoglobulin therapy).

All patients were informed about the research aim and methods. An informed written consent was given by all enrolled patients.

Methods:

All patients were subjected to the following:

A) History taking and physical examination.

B) Laboratory investigations:

- Routine laboratory investigations.
- Liver profile.
- Bone marrow biopsy.

C) Abdominal ultrasound:

Spleen size is expressed in terms of the maximum inter-pole length (i.e., the length of the line joining the two organ poles) and is generally classified into three categories: (1) normal spleen size (< 11 cm), (2) moderate splenomegaly (11 to 20 cm), and (3) massive splenomegaly (> 20 cm).

D) Peri-operative considerations:

- All patients received immunization against pneumococcus and H. influenza at least 2 weeks before surgery.
- Patients were shaved from nipples to mid-thigh in night before surgery.
- Ryle tube was placed in all patients and urinary catheter was placed as per surgeon's choice on the day of surgery.
- Antibiotic was given at the time of induction of anaesthesia and were continued for 3-5 days depending on the surgeon's choice.
- Intraoperative/postoperative platelet and blood transfusions were given depending on the individual patient's blood loss intra-operatively.
- Postoperative pain was evaluated by using Visual analogue scale (VAS) during the postoperative period.
- Nature of parenteral analgesic was of surgeon's choice usually opioid congeners/NSAIDs at the standard dose required. Duration of analgesics was depending on the pain experienced by the patient. Oral analgesics were given as and when required after stopping parenteral analgesics.
- Platelet counts were repeated on the following day and subsequently daily till it stabilized.
- Responses to surgery were evaluated a month after the operation based on the American Society of Hematology 2011 evidence-based practice guidelines for ITP[10].

Complete response (CR) was defned as a normal platelet count of >100,000/μL and discontinuation of any medication, with no spontaneous bleeding.

Partial response (PR) was defned as a rise in the platelet count between 30,000 and 100,000/μL, and at least a twofold increase from the baseline platelet count, without spontaneous bleeding and medication.

Non-response (NR) was defined as a platelet count <30,000/μL or an initial rise, but return to a count <30,000/μL. The need to continue or restart medical therapy, such as steroids, to sustain a normal platelet count was also considered as NR, as was spontaneous bleeding within 30 postoperative days.

Relapse in patients with CR and PR was defined as a platelet count <100,000/μL for CR and <30,000/μL for PR, or a less than twofold increase of the platelet count compared to the baseline for a PR. Any occurrence of spontaneous bleeding or the need for medication was also considered as relapse of the ITP.

- Abdominal drain was put in all patients and criteria for drain removal was drain output less than 50 ml for 24 hours.

E) Surgical treatment

Approaches for laparoscopic splenectomy:

The lateral position of the patient uses the weight of the spleen and gravity to gain exposure during various steps of the procedure. In addition, it facilitates dissection of the superior short gastric vessels and superior pole when compared with the traditional anterior approach [11].

Lateral Approach of laproscopic splenectomy (as described by Targarona) [11]

Equipment:

- A standard laparoscopic tray is used for a laparoscopic splenectomy, including laparoscopic scissors and atraumatic graspers.
- Telescopes, including a 0° or 30°, 5- or 10-mm laparoscope, were used, depending on the surgeon's preference and need for visualization.
- Three or four trocars are usually needed; one trocar should be a 12-mm port that can be used for laparoscopic stapler introduction and specimen removal.
- Electrosurgical devices such as an electro-thermal bipolar sealing device, Ligasure (Valley Inc. USA

and Tyco Healthcare Gmbh Austria) and/ or ultrasonic coagulation shears, Harmonic Scalpel (Ethicon Endo-Surgery Inc. Johnson &Johnson Getaway) were used to assist with splenic mobilization and dissection.

- Typically, the splenic hilar vasculature is divided with an endoscopic stapling device with a vascular load stapler.

Positioning:

The patient is positioned in the right lateral decubitus position at an angle of approximately 45-90° (figures 1, 2).

Positioning and stabilization of the patient are facilitated by the use of a beanbag mattress, although various rolls and pads may be used.

The patient is positioned with the umbilicus at or near the break in the table. This allows more distance between the lower ribs and iliac crest when the table is flexed and the bolster/kidney rest is elevated. All pressure points must be adequately padded.

The surgeon and camera operator stand on the patient's right side, with the video monitors above and lateral to the patient's left shoulder.

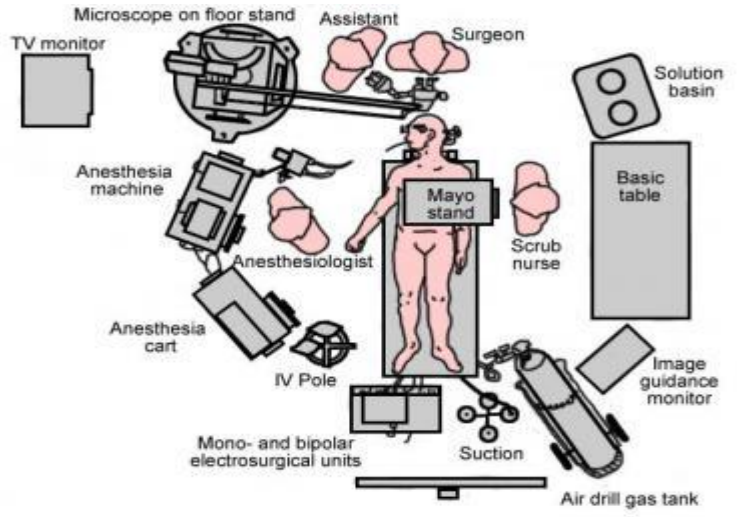

Figure (1): The lateral approach. Patient positioning and operating room setup; three 12-mm trocars are used anteriorly along the left costal margin. A fourth (5-mm or 12-mm) trocar is placed posterior to the iliac crest.

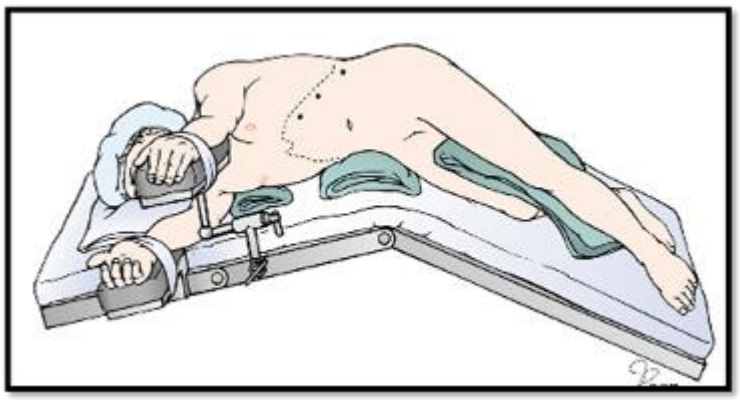

Figure (2): Positioning in LS. Lateral approach.

Trocar Placement and procedure

Intra-abdominal access was obtained; Pneumoperitomium was established either under direct vision (open) or using Verrous needle technique.

A ten mm cannula was placed just above or at superior crease of the umbilicus, used for establishing pneumoperitoneum and inserting the 10-mm 30˚ laparoscope (0 or 30 degree telescope), tow 5 or 10 mm trocars can be placed 3 cm below the left costal margin to form a triangle with the telescope port, the site of these three ports is the exact mirror image of those for laparoscopic cholecystectomy. A fourth 10mm cannula is placed at the epigastrium for a large fan retractor. (figures 3, 4, 5, 6).

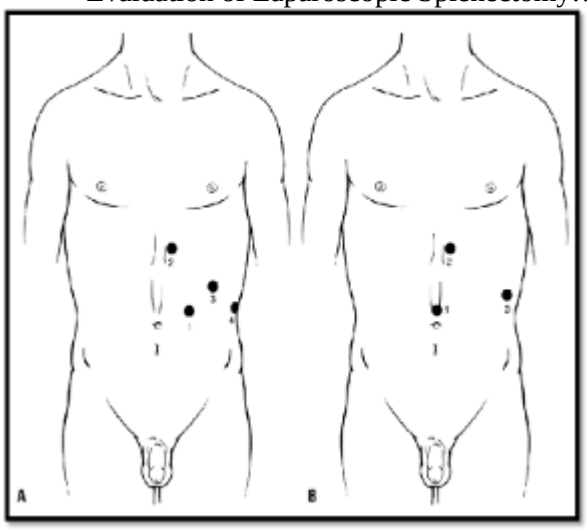

Figure (3): Trocar placement for laparoscopic splenectomy. **A.** Recommended trocar placement. Port 1 is 12 mm, whereas the remainders are 5-mm ports. Port 4 is omitted for the three-port technique. **B.** Alternative for trocar placement.

Figure (4): Trocar placement laparoscopic splenectomy: lateral approach.

Figure (5): Laparoscopic splenectomy: lateral approach. Shown are alternative trocar placements. In some patients a 12 mm trocar may be placed in the umbilicus to gain a cosmetic advantage, and most of the other trocars may be downsized to 5 mm.

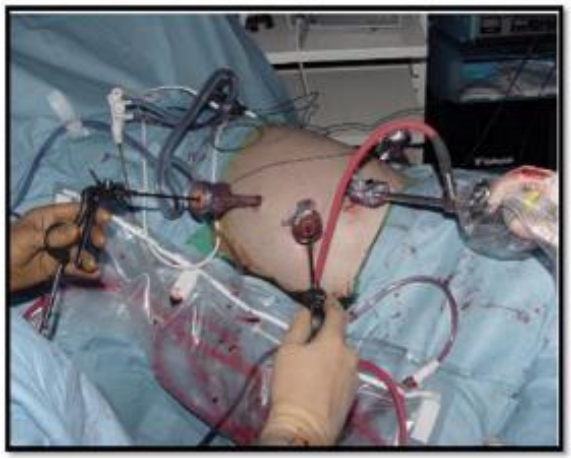

Figure (6): Laparoscopic port placement for the lateral approach.

Intra-operative data:

- The feasibility of the procedure.
- The duration of the procedure.
- Intra-operative blood loss.
- Intra-operative blood and platelet transfusion.
- Conversion to open splenectomy and its causes.
- Presence or absence of accessory spleen.

Post-operative course and complications:

- Time to return of peristalsis and resumption of oral feeding.
- Early postoperative complications e.g. bleeding.
- Late postoperative complications e.g. wound sepsis, sub-phrenic collection … etc.
- Duration of hospital stay.

Follow-up:

The patients were followed up at the end of the first postoperative month by platelet count, physical examination and abdominal ultrasonography.

Statistical analysis:

After collection of data, it was coded and transformed into a specially designed format to be suitable for computer feeding. All entered data were verified for error. Data were analyzed using the Statistical Package for Social Sciences (SPSS ver.20 Chicago, IL, USA). Qualitative data were described using number and percent while quantitative data were described using mean, standard deviation, median and range. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, normally distributed data were tested using parametric tests while not normally distributed data were tested using nonparametric tests. Comparing quantitative variables between 2 groups was conducted using Independent sample *t*-test. In all statistical tests, level of significance below which the results were considered to be statistically significant was 0.05.

RESULTS

I- Demographic data of the studied patients

This study was carried out on twenty patients diagnosed as having primary ITP according to the guidelines of the IWG.

Their age ranged from 17-33 years with a mean of 24.3± 5.39 years. They were 12 females (60%) and 8 males (40%). Data regarding age and sex of the studied patients is illustrated in table 1.

Table (1): Age and sex distribution of the studied patients

Demographic data	Patients (n = 20)	
	No.	%
Age (years)		
Min. – Max.	17.0 – 33.0	
Mean ± SD	24.3 ± 5.39	
Median	24.5	
Sex		
Male	8	40.0
Female	12	60.0

II- History taking

Most of the studied patients (75%) were complaining of purpura and ecchymosis while the other manifestations of bleeding as gum bleeding, epistaxis, menorrhagia and fatigue were present in variable percent (ranging from 40% to 15%) in the studied patients. Regarding the associated comorbidities, only one patient (5%) has bronchial asthma, while the other patients (95%) were free from any chronic illness. Regarding the surgical

history, only two patients (10%) have a history of appendectomy (table 2).

Table (2): History taking regarding bleeding manifestations, associated comorbidities and previous surgical history of the studied patients

History taking	Patients (n = 20)	
	No.	%
Bleeding manifestations		
Purpura and ecchymosis	15	75.0
Gum bleeding	8	40.0
Epistaxis	6	30.0
Fatigue	8	40.0
Menorrhagia	3	15.0
Associated comorbidities		
Bronchial asthma	1	5.0
Previous abdominal surgery		
Appendectomy	2	10.0

III- Investigation

In the studied group, the pre-operative platelet count was ranged from 30000 to 140000/L with a mean of 100500/L (SD = 29179.12), while the spleen size by ultrasonic measurement was ranged from 11-18 cm (mean ± SD = 14.3±1.86 cm) (table 3)

Table (3): Pre-operative investigations of the studied patients

Pre-operative investigations	Patients (n = 20)
Platelet count (/L)	
Min. – Max.	30000 – 140000
Mean ± SD.	100500 ± 29179.12
Median	105000
Spleen size (cm)	
Min. – Max.	11 – 18
Mean ± SD.	14.3 ± 1.86
Median	14

IV- **Intra-operative data**

1- **Duration of the operation:** In the studied patients, the operative time ranged from 70 -150 minutes with a mean of 97.4 ±17.04 minutes (table 4).

2- **Intra-operative blood loss:** The intra-operative blood loss ranged from 80-700 ml with a mean of 175.5 ±135.23 ml (table 4).

3- **Intra-operative blood and platelets transfusion:** Regarding the intra-operative blood and platelet transfusion, two patients (10%) received blood transfusion while three patients (15%) received platelet transfusion (table 4).

4- **Detection of accessory spleen:** Accessory spleen was detected only in one case (5%) in splenocolic ligament (table 4).

5- **Conversion to open splenectomy:** In this study, conversion of laparoscopic to OS was required only in one patient (5%) due to inability to control bleeding in this patient (table 4).

Table (4): Intra-operative complications in the studied patients

Intra-operative complications	Patients (n = 20)	
	No.	%
Operation time (minutes)		
Min. – Max.	70 – 150	
Mean ± SD	97.4 ±17.04	
Median	96.5	
Intra-operative blood loss (milliliters)		
Min. – Max.	80-700	
Mean ± SD	175.5 ± 135.23	
Median	145	
Other intra-operative complications		
Intra-operative platelet transfusion	3	15
Intra-operative blood transfusion	2	10
Detection of accessory spleen	1	5
Conversion to open splenectomy	1	5

V- Post-operative complications and follow up

1- **Recovery of gastrointestinal function:** In the studied patients, the recovery of gastrointestinal function (ability to tolerate solid food) was ranged from 8-24 hours with a mean of 9.75±3.53 hours (table 5).

2- **Length of hospital stay :** Regarding the length of hospital stay, it was ranged from 1-4 days with a mean of 1.3± 0.73 days (table 5).

3- **Pain assessment by visual analogue scale (VAS):** Regarding pain assessment, it was assessed by VAS at 12 hours following the surgery. It was ranged from 3-6 with a mean of 4.4±1.09 (table 5).

4- **Post- operative platelet count:** During the first month of follow up, the platelet count raised to a range of 90000 to 190000/ L with a mean of 147750 ± 23646.24/L (Table 5). Thus, there is statistically significance difference between pre and post-operative platelet count (p <0.001) (table 6). From the assessment of platelet count according to American Society of Hematology 2011 evidence-based practice guidelines for ITP. Nineteen patients (95%) achieved complete response, while only one patient (5%) achieved partial response (platelet count of this patient = 90000/ L) (table 5).

5- **Other post-operative complications:** No other complications were observed in the studied patients such as bleeding, wound sepsis or gaping, chest infection and left sub- phrenic collection.

Table (5): Post-operative complications in the studied patients

	Post-operative complications	Patients (n = 20)	
		No.	%
Recovery of gastrointestinal function (hours)	Min. – Max.	8 – 24	
	Mean ± SD	9.75 ± 3.53	
	Median.	9	
Length of hospital stay (days)	Min. – Max.	1-4	
	Mean ± SD	1.3 ± 0.73	
	Median	1	
Pain assessment (VAS)	Min. – Max.	3-6	
	Mean ± SD	4.4 ± 1.09	
	Median	4	
Post-operative platelets count (/L)	Min. – Max.	90000 – 190000	
	Mean ± SD	147750 ± 23646.24	
	Median	150000	
Post-operative response	Complete response	19	95
	Partial response	1	5

Table (6): Comparison between pre and post-operative platelet count in the studied patients

Platelets count	Pre-operative	Post-operative	*t*	*p*
Min. – Max.	30000 – 140000	90000 – 190000		
Mean ± SD.	100500 ± 29179.12	147750 ± 23646.24	5.626 *	<0.001*
	105000	150000		

t: Student t-test, * $p \leq 0.05$ (significant).

DISCUSSION

Primary ITP was defined according to the American Society of Hematology 2011 evidence-based practice guideline as a platelet count less than 100×10^9/L without other causes or disorders that may be associated with thrombocytopenia [(10)].

The main first-line therapy for ITP is oral corticosteroids. Splenectomy is generally considered a second-line therapy in patients who are refractory to steroids and in those who relapse after an initial response to medical therapy [(12)].

Since the first LS was reported by **Delaitre *et al*.** [(13)] in 1991, this technique has gradually replaced traditional OS as the technique of choice because of decreased postoperative pain, shorter hospitalization, faster recovery and decreased cost [(8)].

So, this work was carried out to evaluate the feasibility, safety and efficacy of LS in ITP patients.

Twenty patients were included in this study, 60% were females and 40 % were males. Their age ranged from 17-33 years with a mean of 24.3± 5.39 years. These findings were in agreement with the results of **Supe *et al.*** [(14)] and **Gupta *et al.*** [(15)] According to prevalence estimates of adult chronic ITP in the United States done by **Feudjo-Tepie *et al.*** [(16)], it was found that females had higher prevalence than males (28.1 versus 18.8 per 100,000). In addition, prevalence increased with age (from 17.0 in the age group 18–49 to 36.2 in the age group 65 and older).

Regarding the clinical manifestations of the studied patients, the most common manifestations were purpura and ecchymosis which were present in (75%) of the studied patients. These findings were in agreement with **Ravikiran *et al.*** [(17)]. Also fatigue was common in 40% of the studied patients which is similar to the results achieved by **Newton *et al.*** [(18)] who concluded that fatigue is a common symptom among patients with ITP regardless their platelets count.

As regards the preoperative investigations in the studied group, the ultrasonic measurement of the spleen was ranged from 11-18 cm with a mean ± SD = 14.3±1.86 cm. This assessment was very important to assess the liability of laparoscopic intervention in the studied patient. As very massive splenomegaly (≥ 25 cm cranio-caudal length) remains a relative contraindication to laparoscopic approach as the technical difficulties in exposure and manipulation of these organs becomes increasingly difficult, and the advantages of the laparoscopic approach becomes less clear because conversion to open, reoperation for bleeding and other complications are more frequent [(19)].

Also **Feldman *et al.*** [(20)] concluded that LS offered benefits for most patients with spleen size between 15 and 25 cm, as it is associated with faster time to oral intake and shorter hospital stay.

The intra-operative blood loss ranged from 80-700 ml with a mean of 175.5 ±135.23ml. Only two patients (10%) received blood transfusion while three patients (15%) received platelets transfusion. The minimal amount of blood loss and reduced the need for blood and platelets transfusion in laparoscopic approach of ITP was confirmed and explained by **Vecchio *et al.*** [(21)].

Also, it is very important to mention that platelet transfusion was given to the studied patients after ligation of the splenic artery. As in patients with ITP, about one-third of transfused platelets are sequestered in the splenic pool where they are destroyed and their measured survival time is shortened, ranging from 2 to 3 days to a matter of minutes [(22)]. The immunological destruction of platelets in the spleen limits the value of platelet transfusion in the presence of functioning spleen.

Moreover, platelets are a scarce resource and transfusion is associated with risks of alloimmunization, transmission of infection, allergic reactions, thromboembolic complications and transfusion-related acute lung injury. There was one case (5%) in which conversion to open splenectomy became necessary due to excessive blood loss and inability to control bleeding during dissection of splenic hilum and mobilization of spleen. This was in agreement with many authors [(23)]. **Qu *et al.*** [(24)] also reported conversion of LS to OS in 4 patients, two of them had extensive tense vascular adhesion tissue around the splenic hilar, and the other two patients had uncontrollable operative bleeding.

As regards the postoperative course, the recovery of gastrointestinal function (ability to tolerate solid food) was ranged from 8-24 hours with a mean of 9.75±3.53 hours. This mean was lower than the mean reported by **Qu *et al.*** [24] (36±6 hours) and **Tada *et al.*** [25] (1.8 ± 1.3 days) and more than the mean reported by **Ravikiran *et al.*** [17] (7.5±4.79 hours). The longest time for recovery was referred to the patient whose laparoscopic operation was converted to open.

Regarding the length of hospital stay, it was ranged from 1-4 days with a mean of 1.3± 0.73 days in the studied patients. It was close to the duration reported by **Gupta *et al.*** [15] (2-4 days). While, it was less than the duration reported by **Arham *et al.*** [23] (9±3 days) and by **Keidar *et al.*** [26] which ranged from 1 to 17 days due to occurrence of some complications such as wound infection (8 days), sub-phrenic abscess (15 days) and retroperitoneal hematoma (17 days).

Regarding pain assessment, it was assessed by VAS at 12 hours following the surgery. It was ranged from 3-6 with a mean of 4.4±1.09. Because of the small incision and rapid convalescence, LS had less major morbidity, less need for postoperative analgesia and required a shorter postoperative hospital stay than OS [124-127]. Thus, LS was more cost effective. **Watson *et al.*** [27] demonstrated that the reduction in the postoperative stay after LS led to a 47% cost savings.

Moreover, no other complications were detected in the studied patients such as bleeding, wound sepsis or gaping, chest infection and left sub-phrenic collection. A meta-analysis of 51 published series with a total of 2940 patients reported that LS was associated with significantly reduced procedure-related morbidity and shorter hospital stay than OS [28].

Regarding the platelet count, the platelet count raised from (30000 to 140000/L) pre-operative to (90000 to 190000/ L) post-operative. Thus, there is statistically significance difference between pre and post-operative platelet count (p <0.001). These results were in agreement with many authors [14, 15, 17, 26] as they reported significant increase of platelet count in most of their patients post-splenectomy.

Nineteen patients (95%) showed complete response (platelet count of >100, 000/μL and discontinuation of any medication, with no spontaneous bleeding), while one patient (5%) showed partial response (a rise in the platelet count between 30,000 and 100,000/μL, and at least a two fold increase from the baseline platelet count, without spontaneous bleeding and medication).

Also, the most consistent predictor of success or failure after splenectomy for ITP is platelet count response to splenectomy, especially during the immediate postoperative period [29]. However, many reports on the topic failed to mention the effect of platelet transfusion, which can significantly affect platelet count. **Supe *et al.*** [14] reported that platelet count increased from 23,142 ± 12,680 preoperatively to 170,000 ± 66,000 1 day after splenectomy after 2.80 ± 0.80 bags of platelet transfusion, but did not compare the effects of transfusion in patients that did or did not receive transfusion. **Fabris *et al.*** [30] had also believed that immediate post splenectomy thrombocytosis could be an indicator of long term remission.

CONCLUSION

It was concluded that LS produces an adequate postoperative rise in platelet count and it is associated with less operating time, postoperative hospital stay, blood loss and postoperative complications.

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