Prevalence of maternal and fetal complications after general anesthesia for cesarean section in patients with class II HELLP syndrome in Assiut University Hospital

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Background
The low platelet count, associated with HELLP syndrome (HS) has often favored the choice of general anesthesia for the cesarean section (CS); however, general anesthesia in such cases is not a risk-free approach. General anesthesia is associated with increased risk of complications.

Aim of work
To evaluate the safety of general anesthesia in patients with class II HS scheduled for elective CS as regards maternal and fetal complications.

Patients and methods
In this prospective, observational study carried out at the maternal hospital in Assiut University Hospitals. We included all patients with class II HS scheduled for elective CS under general anesthesia who were admitted to the women health hospital during the 1 year. The study collected data about the incidence of neurological complications, incidence of intraoperative hemodynamic instability (hypotension, hypertension, bradycardia, and tachycardia), and effect of general anesthesia on fetal outcome including umbilical blood gas and Apgar score.

Results
The incidence of intraoperative and postoperative complications is higher in HS patients compared with CS in normal parturients as regards intraoperative hypertension, tachycardia, and postoperative neurological complications.

Conclusion
HS patients are at an increased risk of complications during CS under general anesthesia and alternative types of anesthesia like spinal or epidural anesthesia should be considered.

Keywords:
general anesthesia, HELLP syndrome, spinal anesthesia

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Introduction

HELLP syndrome (HS) (hemolysis, elevated liver enzymes, and low platelets) is an obstetric complication with heterogonous presentation and multisystemic involvement. The incidence of HS is between 2 and 12% of all pregnancies, and in 10 and 20% of cases of preeclampsia [1]. It is characterized by microangiopathic hemolytic anemia, elevated liver enzymes caused by intravascular breakdown of fibrin in hepatic sinusoids, and reduction of platelet circulation by its increased consumption. The low platelet count, associated with HS, has often favored the choice of general anesthesia for the cesarean delivery (CD) of these parturient. Spinal and epidural anesthesia have been considered for a long time as a contraindication in HS [2–5]. However, general anesthesia in such cases is not a risk-free approach. General anesthesia is associated with increased risk of difficult airways [6,7], stress response to intubation [8], and aspiration [9]. It is also thought to have an effect on the fetus with the potential placental transfer of inhalational anesthetic prior to delivery [10].

Aim of the study

The current study aimed to evaluate the safety of general anesthesia in patients with class II HS scheduled for elective cesarean section (CS) as regards maternal and fetal complications.

Patients and methods

Type of study

This is a prospective, observational study. The study setting: Assiut University Hospitals, maternal hospital. The protocol of our study was approved by the faculty ethical committee before the beginning of the study, written informed consent was taken from all participants before enrollment.

Study participants

(1) Inclusion criteria:
All patients with class II HS scheduled for elective caesarian section admitted to the women health hospital during the 1 year
Diagnosis of HS was based on the clinical diagnosis of preeclampsia and the following laboratory abnormalities [11]:
   (a) Hemolysis: characteristic peripheral blood smear, serum lactic dehydrogenase of more than or equal to 600 U/l, total bilirubin of more than or equal to 1.2 mg/dl, decreased hemoglobin, and hematocrit
   (b) Elevated liver enzymes: defined as aspartate aminotransferase more than or equal to 70 U/l, alanine aminotransferase more than or equal to 50 U/l, and lactate dehydrogenase more than or equal to 600 U/l
   (c) Low platelet count: class II HS having a platelet nadir between 50 000 and 100 000/μl.

(2) Exclusion criteria:
   (a) Emergency cases
   (b) Placenta previa
   (c) Cardiovascular or cerebrovascular disease
   (d) Morbid obesity with a BMI of more than or equal to 40.

Consent

Written informed consents were obtained from all the study participants before enrollment.

Study tools

The study plans to begin enrollment in March 2017. The enrollment of all participants is projected to be completed in March 2018 with data analysis to follow. The length of participation for each participant began from admission till discharge from the ICU.

Procedure

Preoperative management: all patients were admitted to the obstetric ICU in woman health hospital Assiut University for evaluation and stabilization. All parturients received magnesium sulfate loading dose of 4 g intravenously followed by a maintenance dose of 1 g intravenously per hour for 24 h and oral nifedipine (10 mg tablet, up to five dosages) every 15 min were given until effective blood pressure control (≤150/100 mmHg) is achieved. Blood pressure was measured with automated noninvasive arterial pressure (NIAP) measurement; the blood pressure was measured quarter-hourly for at least 60 min or longer until control blood pressure was achieved. Maintenance of antihypertensive agents was decided by the ICU physician according to the level of blood pressure.

Prophylaxis against acid aspiration efforts are made before operation to reduce the volume and acidity of gastric contents by ranitidine 50 mg intravenously and to increase lower esophageal sphincter by metoclopramide 10 mg intravenously.

Monitoring

On arrival to the operating room, standard monitoring was done with ECG, automated NIAP measurement, and pulse oximetry.

Management of anesthesia

Preoxygenation with oxygen 100% was administrated. Rapid sequence technique induction was achieved by thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg); cricoid pressure applied before consciousness is lost and kept in place until confirmation of tracheal intubation with capnography and inflation of the cuff. Return of spontaneous breathing was observed before using atracurium 0.25 mg/kg. Anesthesia is generally maintained with isoflurane. Five international units of uterotonic oxytocin are administered slowly after the delivery of the baby with reversal of the lateral tilt of the table. An oxytocin infusion of 10 IU/h may be used.

Intraoperative opioid analgesia is generally withheld until clamping of the umbilical cord and then 100 μg fentanyl was given.

Extubation was carried out with the patient maintaining airway reflexes and in the left lateral position. After the operation, the patient was kept in a monitored environment with exactly the same facilities and staffing as a standard recovery unit.

Research outcome measures

(1) Primary outcome:
   (a) The incidence of neurological complications
(2) Secondary outcomes:
   (a) Incidence of intraoperative hemodynamic

instability (hypotension, hypertension, bradycardia, and tachycardia)
(b) Effect of general anesthesia on fetal outcome including umbilical blood gas and Apgar score.

Data collection

(1) Demographic data:
Age, weight, height, parity, gestational age, and comorbid conditions
(2) Preoperative laboratory data:
Complete blood picture, liver function tests, renal function test, coagulation profile, and random blood glucose
(3) Intraoperative data:
Maternal NIAP and heart rate were recorded at baseline and then 3 min after anesthesia, at the time of skin incision, at delivery, and at the end of surgery
(4) Complications related to general anesthesia:
As aspiration, difficulty in the airways, cardiovascular instability with intubation
(5) Fetal monitoring:
Apgar scores at 1 and 5 min after delivery were recorded. Arterial blood gas samples were obtained from the umbilical cord immediately after delivery
(6) Postoperative data:
The same as preoperative investigations for follow-up
(7) Detection of complications related to HS:
A eclampsia, disseminated intravascular coagulation (DIC), renal failure, pulmonary complications, hepatic complications
(8) Postoperative mortality.

Data analysis

Data were analyzed using computer software: Statistical Package for the Social Sciences, version 20 (SPSS statistics for windows, Armonk, NY: IBM corp.).

Statistical tests: data were represented as mean ± SD, median (range), and number (percentage) as appropriate. Paired *t* test was used to compare between values in the same group.

Results

A total number of 55 parturients were enrolled in this observational study. All patients were diagnosed as having HS and scheduled for elective CD.

Patients and surgical data

The mean age of the patients was 27.8 ± 5.2 years, their mean weight was 77.5 ± 8.3 kg, their mean height was 167.3 ± 4.1 cm, their mean parity was 2 (1–4), their mean gestational age was 34 (34–36) weeks, and their mean duration of operation was 47 ± 6.6 h (Table 1).

As regards comorbid conditions, preeclampsia was diagnosed in 34 (61.8%) parturients; eclampsia was diagnosed in six (10.9%) parturients, concealed hemorrhage was diagnosed in only two patients and represents about 3.6%

Laboratory data

As regard blood picture; hemoglobin level and hematocrit was significantly decreased in postoperative period, anemia was detected in 18 parturients in postoperative period compared to only 11 parturients in preoperative period. WBCs and platelets significantly increased. No changes was observed in

Table 1 Patients and surgical data

Parameters	
Age	27.8±5.2
Weight	77.5±8.3
Height	167.3±4.1
Parity	2 (1-4)
Gestational age	34 (34-36)
Duration of operation	47.4±6.6
Comorbid conditions	
No	13 (23.6)
Preeclampsia	34 (61.8)
Eclampsia	6 (10.9)
Concealed hemorrhage	2 (3.6)

Data were expressed as mean±SD, median (range), and *n* (%).

Table 2 Blood picture

	Preoperative	Postoperative	*P*
Hemoglobin level (g/dl)	10.4±2.1	9.7±1.4	0.027
Hematocrit (%)	32.6±5.9	30.7±4.4	0.038
Anemia	11 (20)	18 (32.7)	0.000
WBCs (l/µl)	12 893.3±4120.4	15 560.2±4791.1	0.000
Platelet count×(10^3/µl)	75 585.5±14 734.8	144 028.7±42 762.7	0.000

Data were expressed as mean±SD and *n* (%). WBC, white blood cell.

Table 3 Liver function tests and coagulation profile

	Preoperative	Postoperative	
Prothrombin time (s)	12.5±1.3	12.1±0.2	0.006
Partial thromboplastin time (s)	35.9±8.9	29.8±4.8	0.000
AST (IU/l)	253.2±287.4	47.7±21.9	0.000
ALT (IU/l)	158.7±149.2	56.8±30.5	0.000
LDH	786±197.6	287.1±116.2	0.000
Bilirubin (µmol/l)	41.1±61	10.5±14.4	0.000
Total protein (g/dl)	53.9±9.4	57.3±9.8	0.034
Albumin (mg/dl)	27.2±3.9	28.6±3.7	0.153

Data were expressed as median (range) and mean±SD.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactic dehydrogenase. *P* value more than 0.05 is nonsignificant.

kidney function, random blood sugar and proteinurea significantly lower in post-operative period copared to preoperative period. Prothrombin time and partial thromboplastin time increased significantly, liver enzymes and bilirubin decreased significantly, while total protein and albumin significantly increased [Table 2].

Complete blood picture

Postoperative hemoglobin level, hematocrit, and platelets decreased significantly from preoperative values; white blood cells increased after operation; anemia was diagnosed in 11 patients preoperatively and 18 patients postoperatively.

Liver function and coagulation profile

All postoperative parameters of liver function decreased significantly from preoperative values (Table 3).

Kidney function random blood sugar

There are no significant differences between preoperative and postoperative blood urea and serum creatinine (Table 4). Random blood sugar decreased significantly from 6.6 ± 2.2 to 5.7 ± 1.2 mmol/l. Proteinuria decreased significantly from 3 (0–3) to 1 (0–1).

Hemodynamics

Arterial blood pressure changes

Compared with the baseline, systolic, diastolic, and mean arterial blood pressure values increased significantly at the time of skin incision, while there were nonsignificant differences at 3 min after induction, at the time of delivery, and at the end of surgery (Tables 5–7).

Heart rate

Compared with the baseline the mean heart rate showed statistically significant increase at 3 min after induction, skin incision, delivery time, and at the end of surgery (Table 8).

Intraoperative complications

Intraoperative hypotension occurred in six out of 55 patients which represent 6.7% of cases (Table 9).

Intraoperative hypertension was observed in 10 (18%) patients.

Intraoperative bradycardia was observed in three (5.5%) patients.

Table 4 Kidney function and random blood sugar

	Preoperative	Postoperative	
Urea (mmol/l)	7.1±3	7.8±5.3	0.310
Creatinine (μmol/l)	98.7±76.3	88.9±79.1	0.099
RBS (mmol/l)	6.6±2.2	5.7±1.2	0.003
Protein urea	3 (0-3)	1 (0-1)	0.000

Data were expressed as mean±SD and median (range).RBS, random blood sugar. *P* value more than 0.05 is nonsignificant.

Table 5 Systolic blood pressure changes

Systolic blood pressure (mmHg)		*P*
Baseline (mmHg)	150.7±15.6	
3 min after induction (mmHg)	154.4±18.5	0.194
At skin incision (mmHg)	160.7±28.9	0.021
At delivery (mmHg)	150.8±27.9	0.976
At the end (mmHg)	153.9±30.2	0.468

Data were expressed as mean±SD. *P* value less than 0.05 is significant compared with the baseline value.

Table 6 Diastolic blood pressure changes

Diastolic blood pressure		*P*
Baseline (mmHg)	99.9±10.7	
3 min after induction (mmHg)	101.3±11.3	0.443
At skin incision (mmHg)	106.7±17.7	0.011
At delivery (mmHg)	94.8±19.5	0.072
At the end (mmHg)	99.8±19.5	0.969

Data were expressed as mean±SD. *P* value less than 0.05 is significant compared with baseline value.

Table 7 Mean arterial blood pressure changes

Mean arterial pressure (mmHg)		*P*
Baseline (mmHg)	116.8±12.2	
3 min after induction (mmHg)	119±13.3	0.305
At skin incision (mmHg)	124.7±21.3	0.014
At delivery (mmHg)	113.4±22.1	0.298
At the end of surgery (mmHg)	117.8±23	0.759

Data were expressed as mean±SD. *P* value less than 0.05 is significant compared with baseline value.

Table 8 Heart rate changes

Heart rate (beats/min)		*P*
Baseline (beats/min)	89.7±12.7	
3 min after induction (beats/min)	100.4±16	0.000
At skin incision (beats/min)	95.5±16.6	0.002
At delivery (beats/min)	95.2±13.8	0.000
At the end (beats/min)	103.6±16.5	0.000

Data were expressed as mean±SD. *P* value less than 0.05 is significant compared with the baseline value.

Table 9 Intraoperative complications

Hypotension	6 (10.9)
Hypertension	10 (18.2)
Bradycardia	3 (5.5)
Tachycardia	10 (18.2)
Arrhythmia	1 (1.8)
Difficult airway	4 (7.3)
Aspiration	0 (0)

Data were expressed as *n* (%).

Intraoperative hypertension: 10 (18.8%) patients suffered from intraoperative tachycardia.

Arrhythmia: arrhythmia was observed in one (1.8%) patient.

Postoperative complications

Table 10.

Neurological complications

Occurred in six (10.9%) cases. They presented with convulsions, focal neurological deficits, and deterioration of consciousness level. Urgent computed tomography brain showed two cases of cerebral hemorrhage, three cases of brain edema, and two cases of reversible cerebral encephalopathy. The two cases with cerebral hemorrhage were mechanically ventilated, and the other five cases received oxygen through a simple face mask. Six cases improved and discharged home while in one with cerebral hemorrhage was massive and was declared as brain dead who died after 1 week.

Acute kidney injury

Acute kidney injury (AKI) defined as a creatinine level more than or equal to 1.2 mg/dl or 106.08 μmml/l and/or oliguria less than 400 ml/24 h. Acute renal failure is diagnosed as persistent oliguria and increase in serum creatinine for 3 days [12]. AKI occurred in 12 (21.8%) parturients, who were oliguric with slight increase in serum creatinine 1.2–2 mg/dl or 106.08–176.8 μmml/l; three cases showed a moderate increase in serum creatinine 2–4 mg/dl and oliguria; and three cases showed marked increase in serum creatinine of more than 4 mg/dl (353.6 μmml/l). Dialysis was needed in three cases. Six cases were completely recovered and serum creatinine returned to normal values, while the remaining two cases passed into chronic course on the follow-up (they were chronic hypertensive).

Thromboembolic events

Deep venous thrombosis (DVT) occurred in two (3.6%) parturients pulmonary embolism.

DIC

Occurred in six (10.9%) cases.

Pulmonary edema

Was reported in two (3.6%) cases.

Reoperation

Occurred in only one parturient.

Table 10 Postoperative complications

Complication	
Neurological complications	6 (10.9)
Kidney involvement	12 (21.8)
AKI with dialysis	5 (9.1)
AKI passed into CRF	1 (1.8)
Pulmonary edema	2 (3.6)
Eclamptic fit	4 (7.3)
Thromboembolic	2 (3.6)
DIC	6 (10.9)
Reoperation	1 (1.8)
Death	1 (1.8)

Data were expressed as *n* (%).AKI, acute kidney injury.

Table 11 Fetal outcome

	GA group (*n*=30)
Fetal blood gas	
pH	7.3±0.4
HCO_3 (mEq/l)	20.8±3.7
PO_2 (mmHg)	20.4±7.3
Base deficit	−5.8±3.5
$PaCO_2$ (mmHg)	39.3±7.7
Apgar score at 1 min	9 (6-10)
Apgar score at 5 min	10 (9-10)

Data were expressed as mean±SD.GA, general anesthesia.

Mortality

One (1.8%) patient died on the seventh postoperative day due to multiorgan failure and cerebral hemorrhage.

Fetal outcome

For fetal pH the mean values were 7.3 ± 0.4; the bicarbonate level was 21.05 ± 3.81 mEq/l; $PaCO_2$ was 39.3 ± 7.7; base deficit was −5.8 ± 3.5 (Table 11).

Apgar score measured at 1 min showed 9 (6–10). After 5 min the Apgar score was 10 (9–10).

Discussion

Anesthesia for CD in patients with HS is a challenge. The low platelet count, associated with HS, has often favored the choice of general anesthesia for the CS of these parturients. However, general anesthesia in such cases is not a risk-free approach. General anesthesia is associated with increased risk of difficult airways [6,7], stress response to intubation [8], and aspiration [9]. It is also thought to have an effect on the fetus with the potential placental transfer of inhalational anesthetics prior to delivery [10].

The current study investigated the postoperative outcomes in patients with class II HS, the platelet count was between 50 000 and 100 000/μl with a mean platelet count of 75.55 ± 15.63 × 10^3/μl under general anesthesia in 55 parturients.

Regarding the effects of general anesthesia on hemodynamics incidence of intraoperative hypertension occurred in 10 (18.8%) patients and tachycardia occurred in 10 (18.8%) patients, while hypotension occurred in six (10.9%) cases and bradycardia in three (5.5%) cases, so the hemodynamic effects is unpredictable.

The exaggerated hypertensive response to airway manipulations during general anesthesia carries a risk of cerebral hemorrhage, which is the primary cause of death in patients with preeclampsia [10,13,14]. This was evident in this study which showed a marked significant increase in the arterial blood pressure and heart rate at the time of intubation or skin incision and tissue retraction from baseline in our patients.

There is a known risk of maternal death associated with general anesthesia This may be attributed to the risk of difficult airways. There are several reasons for this: pregnancy may induce an edema in airways and severe bleeding; limited movement of the cervical spine; and breast enlargement because of obesity in pregnancy, which can hinder laryngoscopies and intubation [15,16]. These factors may raise Mallampati category 3 to category 4 [7]. In fact, a fault in endotracheal intubation after inducing general anesthesia is eight-fold higher in a delivering woman that in the general population, and is one of the causes that leads to maternal morbidity and mortality [17]. In severe pulmonary embolism (PE) and HS, there is more increased airway edema and easy bruising that can obscure the laryngoscopic view during intubation. This was evident in this study where two cases explicit difficult intubation and showed a marked increase in arterial blood pressure. The triennium report from the Center for Maternal and Child Enquiries reported two cases of direct anesthetic deaths on administration of general anesthesia to a parturient due to failure to ventilate the lungs and aspiration of gastric contents in the postoperative period [18]; however, in our study no complication occurred due to aspiration. This could be explained by exclusion of emergent cases from the study and due to the relatively small sample size.

There are risks related to pulmonary ventilation or gastric aspiration as these patients are considered to have a full stomach, even though they have been fasting, because their stomach takes longer to empty [9].

In our study neurological complications occurred in six (10.9%) cases. Two cases had cerebral hemorrhage, three cases had brain edema, and two cases had posterior reversible cerebral encephalopathy syndrome. The high incidence of neurological complications was associated with an increase in arterial blood pressure that occurred with general anesthesia.

In literatures which studied maternal mortality in HS, it was noticed that the most frequent cause of maternal mortality of HS is cerebral hemorrhage [19].

Vigil-de Gracia and colleagues reported one case death in severe PE of 120 cases, five deaths out of 120 cases in eclampsia with HS, and nine deaths of 119 cases of eclampsia with HS. Complications were higher in eclampsia with the HS group: 63 versus 21 in the eclampsia group. Cerebral hemorrhage was the main cause of death [20].

In a study by Helguer *et al*. [21] on 102 cases of HS, 20 deaths were reported. Cerebral hemorrhage was the main cause (70%).

The previous two studies support the dangers of high systolic or diastolic blood pressure in combination with HS or thrombocytopenia and seizures (known as the 'dangerous triad') [22].

Miguil and Chekairi [23] reported 23 deaths out of 342 cases with eclampsia; 61% of deaths had cerebral hemorrhage or ischemia.

Martin and colleagues studied 28 cases of stroke retrospectively in preeclampsia/eclampsia, of which 18 had HS, systolic pressure was 160 mmHg or greater in 23 (95.8%) and more than 155 mmHg in 100%. Fifteen patients died following a stroke (53.6%). They concluded that a more significant risk factor for complications is high systolic blood pressure [24].

A UK study reported 18 deaths caused by preeclampsia/eclampsia: 44.4% had HS and 33.3% presented with eclampsia. The recommendations on the clinical practice include treating all women with a systolic blood pressure greater than 160 mmHg [25].

Vigil-De Gracia studied 102 women with eclampsia; blood pressure was elevated beyond 160/110 mmHg in 39 (38%) patients; and 25% had less than 140/90 during the seizures. Twenty-six patients had HS. There were seven (6.8%) maternal deaths in the entire cohort of patients, six of them who died had HS; cerebral hemorrhage was the cause of death in two women, multiple organ failure in two, disseminated intravascular coagulation in two, and sepsis in one.

Osmanagaoglu *et al.* [26] studied maternal outcome in 37 cases of HS; there were 11 maternal deaths, four (36%) of them were due to cerebral hemorrhage.

Bateman *et al.* [27] found that the presence of hypertension and coagulopathy are independent risk

factors for pregnancy-related intracranial hemorrhage (ICH). This vasoconstrictive phenomenon might be related to increased concentrations of oxyhemoglobin derived from hemolysis [28,29]. HS increases such risk dramatically [30].

Regarding DIC this is consistent with the findings of Osmanagaoglu *et al.* [26] 5%, Haddad *et al.* [31] 8%, Cavkaytar *et al*. [32], 8%.

Regarding renal complications, the present study showed that AKI occurred in 12 (21.8%) parturients. Dialysis was needed in five (9.1%) cases. Eleven cases were completely recovered and serum creatinine returned to normal values, while the remaining one case passed into chronic course on the follow-up (they were chronic hypertensive).

In a study by Celik *et al*., [33] acute renal failure (ARF) is diagnosed in 13 cases (36%), six of the 13 patients who had ARF were subjected to hemodialysis. Two patients died because of the development of ARF, DIC, and acute respiratory distress syndrome (ARDS).

Also, Cavkaytar *et al*. [32] studied 61 parturients with HS developed antenatally, 15% of the cases developed acute renal failure.

In a retrospective study by Dasgupta and colleagues involving 116 preeclamptic parturients undergoing CS, they found that a higher rate of neonatal asphyxia was noticed when general anesthesia was administered for CS delivery when compared with RA (P = 0.0006) [34]. Similarly, the neonatal base deficit was significantly higher in severe preeclamptic parturients who had general anesthesia for CS delivery when compared with parturients who had spinal anesthesia [35]. The lower rate of neonatal asphyxia in both groups which was observed in our study may be explained by the high gestational age compared with the Dasgupta and colleagues study.

Conclusion

HS patients are at an increased risk of complications during CS under general anesthesia and alternative types of anesthesia such as spinal or epidural anesthesia should be considered.

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Conflicts of interest

There are no conflicts of interest.

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