Abdelhafez *et al.*
Ain-Shams Journal of Anesthesiology (2022) 14:89
https://doi.org/10.1186/s42077-022-00284-5

Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE Open Access

Transesophageal Doppler corrected flow time versus plethysmography variability index for goal-directed fluid management in cirrhotic patients during liver resection: a randomized controlled trial

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Abstract

Background: Central venous pressure (CVP) readings are affected by several factors. The need to test the technology of noninvasive or minimal invasive monitoring during liver surgery to guide fluids intake is the focus of this trial. Adult hepatic patients undergoing elective open liver resection were randomized into transesophageal Doppler (TED, $n = 20$) or plethysmography variability index (PVI, $n = 20$). PVI blinded to anesthetist in TED group (gp) and vice versa. During dissection, crystalloids were restricted to keep corrected flow time (FTc) parameter of *TED* < 330 msec or *PVI* > 14%, otherwise infused at 6 ml/kg/h. Following resection, colloids infused if *FTc* < 330 msec or *PVI* > 14% despite crystalloids infusion. Primary aim is to compare TED-corrected flow time (FTc, msec) parameter to PVI (%) for guiding intravenous fluids during liver resection. Secondary to study their correlations and each parameter effect on blood loss and consumption, morbidity and intensive care unit (ICU) stay.

Results: It is presented as median [IQ]. Volumes of crystalloids and colloids guided by FTc and PVI were not different ($p = 0.3$, $p = 0.1$, respectively) despite negligible correlations. Normovolemic existed during dissection despite 2 h of fluids restriction. FTc was 327 (320–341) msec, PVI was 11.50 (11.00–14.00) %, and CVP in TED gp 11.00 (10.00–12.00) vs. 9.00 (9.00–11.50) mmHg in PVI gp, $p = 0.2$. Blood loss was 1500 (475–2000) ml in TED vs. 950 (675–1925) in PVI, $p = 0.5$. Patients' % in need for blood transfusion and volumes in TED vs. PVI gps were similar: red blood cells: 30%, 350 (350–350) vs. 40%, 525 (350–700) ml, and $p = 0.2$. Plasma is 20%, 200 (200–300) vs. 40%, and 400 (200–400) ml, $p = 0.3$. There was no difference in nausea, vomiting, or ICU stay, ($p > 0.05$).

Conclusions: Volume of fluids guided by PVI was not different from that by TED, despite lack of correlation. Transfusion-free dissection was possible for a significant number of patients with normovolemia.

Trial registration: PACTR201808140151322 (www.pactr.org)

Keywords: Transesophageal Doppler, Corrected flow time, Pleth variability index, Central venous pressure, Fluid status, Liver surgery

Background

In Egypt, hepatic resection is increasingly been performed for liver malignancy, mainly as a result of hepatitis C, while few are due to metastatic lesions, in contrast to the western countries (Hassan et al., 2001).

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Low central venous pressure (CVP) during liver dissection had been the traditional practice to reduce hepatic congestion and blood loss (Hughes et al., 2015; Li et al., 2014). However, CVP readings are affected by several factors, besides the risk of the invasive approach (Ramsingh et al., 2013). The need to test the technology of noninvasive or minimal invasive monitoring during surgery to guide the fluid intake is the focus of this trial. Two studies by El Sharkawy et al. (2013) and Mahmoud et al. (2016) were able to utilize the transesophageal Doppler (TED) for guiding fluid intake and for hemodynamic monitoring during liver surgery. The primary aim of this trial is to compare the TED-corrected flow time (FTc, msec) parameter to the plethysmography variability index (PVI, %) among hepatic patients during liver resection surgery for guiding intraoperative fluids. Secondary aim is to study their correlations with each other and with the CVP. Finally to study the effect of each parameter on blood loss, blood products consumption, perioperative morbidity and intensive care unit (ICU) stay.

Methods

Study Design: A randomized controlled trial

Ethics approval and consent to participate from the local ethics committee of the Faculty of Medicine at Menoufia University, Egypt (IRB, 0108/2018). Informed written consent was obtained from each patient. The trial registered at the South Africa Pan Cochrane Research Registry (PACTR201808140151322) (www.pactr.org). Consent for publication is "not applicable." The study adheres to CONSORT guidelines. Sources of funding is none. Consecutive adult hepatitis C patients (18–60 years, Child classification A) with cirrhosis confirmed by ultrasonography and scheduled for elective liver resection surgery were included. Exclusion criteria included patients with pulmonary disease, contraindication for esophageal Doppler probe insertion, rupture hepatocellular carcinoma or inoperable, body mass index > 40 kg/m^2, laparoscopic hepatic resection, and/or refusal to participate. Patients were randomized into two groups: TED or PVI groups. Intraoperative primary measurements include the FTc (msec) of TED, PVI (%), CVP (mmHg), and mean invasive blood pressure (IBP) (mmHg). Measurements were recorded at following times: T0, 10-min postanesthesia induction; T1, following abdominal fascia opening; T2, following retractor application; T3, first hour in dissection; T4, 2 h in dissection; T5, following resection completion; and T6, end of surgery. PVI values were blind to the anesthetist in TED group and vice versa. During dissection, the crystalloids were restricted to keep *FTc* < 330 msec in TED group or *PVI* > 14% in PVI group, otherwise infused at 6 ml/kg/h. Following resection, the hydroxyethyl starch (HES, Voluven, Fresenius Kabi, Bad Homberg, Germany) was infused only if *FTc* < 330 msec (maximum 1000 ml) or *PVI* > 14% despite above crystalloids infusion.

TED is a continuous, minimally invasive COP monitor measuring blood flow velocity in the descending aorta by esophageal Doppler technique. Continuous point-to-point measurement of stroke distance is performed by the calculation of stroke volume (mean of five cycles) using aortic diameter from a nomogram based on the patient's age, weight, and height. CO (l.min^{-1}) is calculated as the product of stroke volume and the heart rate. The time needed for blood to flow in a forward direction within the aorta is the systolic flow time. This was corrected for heart rate to give the corrected flow time (FTc). An esophageal Doppler probe (EDM™; Deltex Medical, Chichester, UK) greased with a lubricating gel and passed nasally into the mid-esophagus until aortic blood flow signals was best identified. TED parameters include FTc, normal range: 330–360 ms), stroke volume (SV, normal range: 50–100 cc/beat), cardiac output (COP, normal range: 4–8 l/min), and SVR, normal range: 1900–2400 dynes.sec/cm^5). FTc values for normally hydrated resting healthy individuals are 330–360 msec (Sinclair et al., 1997).

PVI provides a continuous noninvasive measure of the relative variability in the photo plethysmography during respiratory cycles. PVI is used as a dynamic indicator of fluid responsiveness in select populations of mechanically ventilated adult patients. PVI is calculated by the Masimo set pulse oximeter (Masimo Co., Irvine, CA, USA) from the respiratory variations in the perfusion index (PI). The PI is the percentage amplitude difference between the pulsatile-infrared signal and the non-pulsatile infrared signal. The PVI is calculated by measuring changes in the PI during the respiratory cycle: $PVI = [(PImax–PImin)/PImax] \times 100$. Cannesson et al. have demonstrated that the PVI predicts fluid responsiveness in the operating room. They showed that the cutoff value to distinguish responders from nonresponders to intravascular volume expansion (in terms of an increase of cardiac index) was a *PVI* > 14% (Cannesson et al., 2008). PVI was measured with a pulse oximetry probe placed on the finger of the patient. Normal range of PVI (9–13%) (Konur et al., 2016).

CVP indicates the circulatory volume and pressures in right atrium but affected by the intrathoracic pressure. CVP normal range varies between 8 and 12 cmH_2O and can increase with mechanical ventilation. Multiple factors affect the CVP readings one of them is the positive end-expiratory pressure (PEEP) and mechanical ventilation, and both increase the intrathoracic pressure and hence the CVP. Yang et al. demonstrated that 0.38

cmH_2O increase in PEEP increases the CVP by 1 cmH_2O (Yang et al., 2012).

Monitoring includes 5-lead electrocardiography and continuous invasive (IBP, mmHg) and CVP (mmHg). The pulse oximetry, nerve stimulator, esophageal temperature, and anesthesia depth monitor (Bispectral index (BIS, Aspect, MA, USA) were also monitored as per anesthesia protocol. The noninvasive hemoglobin (SpHb) concentration (Radical 7, Masimo, Irvin, USA) and laboratory hemoglobin (Lab Hb) was monitored in surgery.

Anesthesia technique is for liver resection as per protocol (Kamel et al., 2012). All patients were on a fixed PEEP of 5 cmH_2O during mechanical ventilation.

General anesthesia was induced with fentanyl 2–4 ug/kg, propofol 2 mg/kg (dose), and rocuronium 0.6 mg/kg dose. Two large-bore peripheral and a right internal jugular central venous catheter was placed. Anesthesia was maintained with a balanced anesthetic technique, consisting of a volatile agent (sevoflurane 0.7–1 MAC) and a mixture of air and oxygen (FiO_2 0.4). For intraoperative analgesia, additional boluses of fentanyl were used. Anesthetic management includes the use of two forced air warming blankets for upper and lower extremities and an infusion blood warmer. The patient's position was carefully checked before draping, and both arms were tucked by the patients' side and well padded to prevent injury of the brachial plexus.

At the end of the procedure, all patients were extubated in the operating theater and admitted to the ICU immediately postoperatively (the intensive care suite is available close to the operating room. An early oral nutrition was encouraged. Standard deep vein thrombosis (DVT) prophylaxis with low-molecular-weight (LMW) heparin was implemented. Other prophylactic measures like intermittent calf compression during surgery and the first 24 h after surgery was always applied to reduce the risk of DVT. Chest physiotherapy and early mobilization is part of the routine immediate postoperative care. Postoperative medications included prophylactic perioperative antibiotic coverage of a third-generation antibiotic, ceftriaxone 1 g every 8 h intravenously as a prophylactic measure together with intravenous metronidazole 500 mg 8 h, and (explain) histamine H_2 receptor antagonist as a prophylaxis for stress ulceration 50 mg intravenously every 8 h.

Intraoperative fluid management

During dissection, crystalloids (Ringer's acetate) were restricted to keep *FTc* < 330 msec and PVI > 14%, but IBP > 60 mmHg and urine output (UOP) >0.5 ml/kg/h were kept at all times. Before and following resection, crystalloids were administered at a rate of 6 ml/kg/h to maintain *FTc* > 330 msec or *PVI* < 13% according to allocated group. Hydroxyethyl starch (HES, Voluven, Fresenius Kabi, Bad Homberg, Germany) was infused (6 ml/kg, max. 1000 ml) if the *FTc* < 350 msec or *PVI* > 14% despite crystalloids infusion. Hemoglobin > 10 g/dl was maintained with packed red blood cell transfusion if required.

Surgical technique

Liver resection was performed with a J-shaped incision and with intraoperative cholangiography to identify bile duct anatomy. The same surgical team performed all the resections. A Cavitron Ultrasonic Surgical Aspirator (CUSA Excel, Valleylab Inc., Boulder, CO, USA) dissection device was used to perform hepatic anterior parenchymal transection with electrocautery and without temporary occlusion of vascular inflow or outflow (Pringle's maneuver).

Demographic data

These are age (y), sex, weight (kg), and body mass index (BMI, kg/m^2).

Operative data

Type of resection, anesthesia duration (minute), total urine output (ml), crystalloids, and colloids (ml) are infused. Blood transfusion requirement (units) and blood loss (ml) were measured by the volume in the suction bottles and by weighing the surgical packs.

Intraoperative hemodynamic parameters include heart rate (HR) (bpm), mean IBP (mmHg), CVP (mmHg), and PVI (%) and TED data: FTc (msec), and SVR (dyn.sec.cm^{-5} and COP (l/min).

Sample size calculation

The minimal sample size was calculated based on a study. The study aims to assess the accuracy of PVI to predict preload responsiveness in perioperative and critically ill patients (Yin & Ho, 2012). A total sample size of 40 patients (sample size per group = 20) is the enough required sample for the condition of all individual, but one pair agrees with each other ($k \geq 1$), as statistically significant with 80% power and a significance level of 95%. Sample size does not need to increase to control for attrition bias.

Method of randomization

The allocation sequence was generated using randomized (random number generator with sealed opaque envelopes). Allocation sequence/code concealed from the

person allocating the participants to the intervention arms using sealed opaque envelopes.

Statistical methodology

Data are collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (ver 21) as numerical or categorical, as appropriate. Kolmogorov-Smirnov test of normality revealed significance in the distribution of most of the variables, so nonparametric statistics is adopted. Data were described using median and interquartile range (IQR). Categorical variables were described using frequency and percentage. Comparisons were carried out using Mann-Whitney *U*-test. Comparisons were carried out among related samples by Friedman's test. Pairwise comparison when Friedman's test was significant was carried out using Dunn-Sidak method. Nonparametric Kendall's tau correlation (τ) was used. Rule of thumb for interpreting the size of a correlation coefficient. Chi-square test was used to test association between qualitative variables. Box and Whiskers plot were used accordingly. An alpha level was set to 5% with a significance level of 95%, and a beta error is accepted up to 20% with a power of study of 80%.

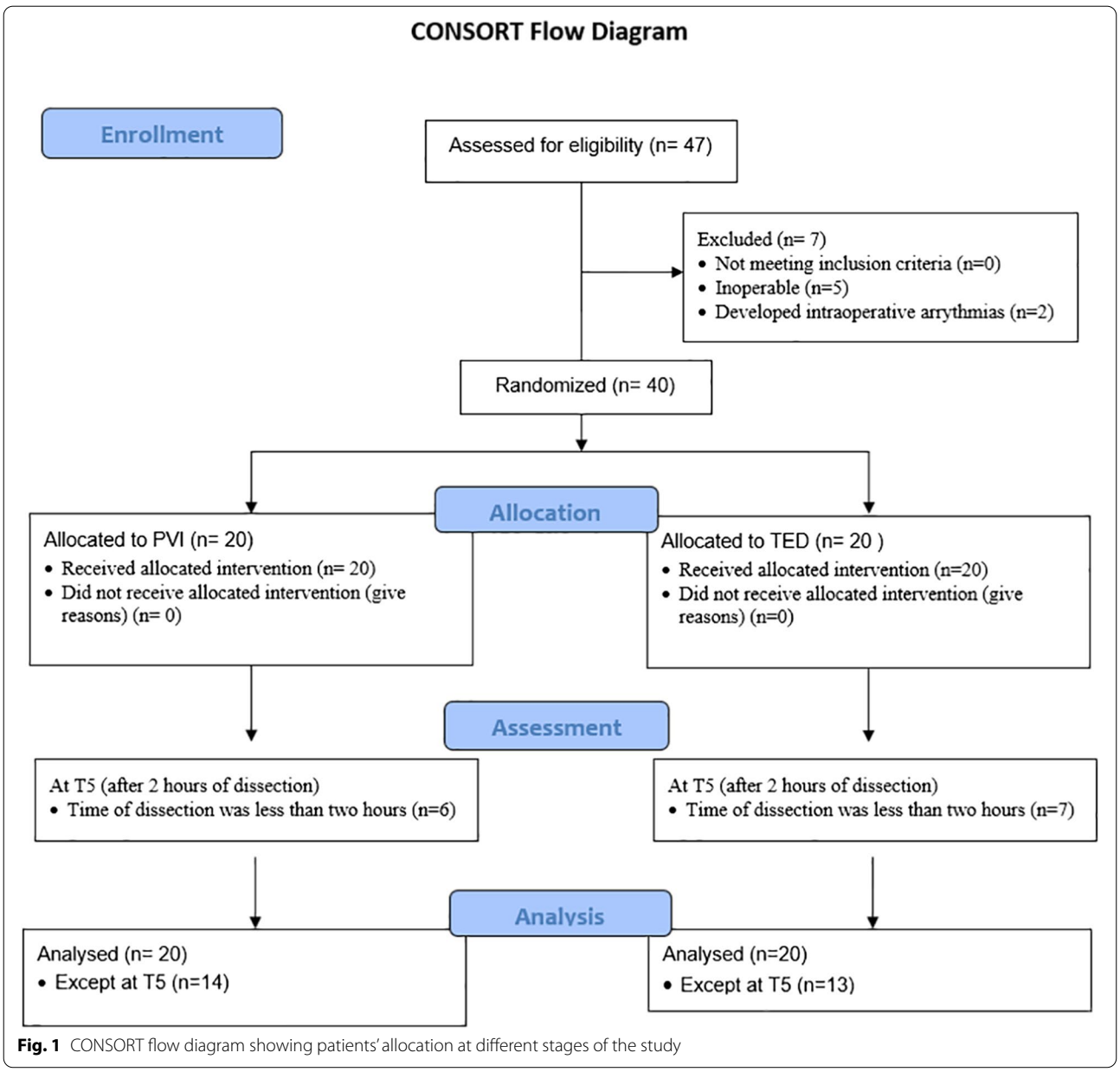

Fig. 1 CONSORT flow diagram showing patients' allocation at different stages of the study

Results

Forty-seven patients were enrolled in the trial (7 excluded) after August 2018–September 2020. Only 40 were randomized into two groups as in CONSORT flow chart (Fig. 1). Data are presented as median (IQR). Patients' demographics and clinical and operative characteristics for TED group vs. PVI group were comparable (Table 1). Diabetes mellitus was present in 10 vs. 9, and hypertension was only present in 5 vs. 4 patients among the TED vs. PVI groups, respectively. None of

Table 1 Patients' clinical and operative characteristics of transesophageal Doppler (TED) compared to plethysmography variability index (PVI)

	TED $n = 20$	**PVI** $n = 20$	***P***
Age (y)			
• Min-max	32.00–66.00	34.00–64.00	
• Mean ± std. deviation	57.00 ± 7.49	55.60 ± 0.46	$Z_{(MW)} = 0.367$ $p = 0.714$ NS
• 95% CI for mean	53.50–60.50	51.65–59.56	
• Median (IQR)	59.50 (55.00–61.50)	57.50 (54.50–61.50)	
• KS test of normality	$D = 0.205$, $p = 0.027$*	$D = 0.229$, $p = 0.007$*	
Surgical time (min)			
• Min-max	120.00–240.00	120.00–250.00	$Z_{(MW)} = 1.021$ $p = 0.307$ NS
• Mean ± std. deviation	204.00 ± 35.19	192.00 ± 37.18	
• 95% CI for mean	187.5–220.47	174.5–209.40	
• Median (IQR)	210.00 (180.00–240.00	185.00 (160.00–225.00)	
• KS test of normality	$D = 0.153$, $p = 0.200$ NS	$D = 0.127$, $p = 0.200$ NS	
Anesthesia time (min)			
• Min-max	165.00–285.00	150.00–280.00	$Z_{(MW)} = 1.512$ $p = 0.131$ NS
• Mean ± std. deviation	243.75 ± 35.76	227.00 ± 37.29	
• 95% CI for mean	227.0148	209.5479	
• Median (IQR)	260.4852	244.4521	
• KS test of normality	240.00((225.00–277.50) $D = 0.169$, $p = 0.139$ NS	230.00 (190.00–260.00) $D = 0.139$, $p = 0.200$ NS	
MELD score			
• Min-max	6.43–9.85	6.43–11.90	
• Mean ± std. deviation	8.36 ± 0.98	8.40 ± 1.73	
• 95% CI for mean	7.90–8.82	7.59–9.20	$Z_{(MW)} = 1.393$ $p = 0.694$ NS
• Median (IQR)	8.52 (7.65–9.13)	7.94 (7.13–9.65)	
• KS test of normality	$D = 0.157$, $p = 0.200$ NS	$D = 0.157$, $p = 0.200$ NS	
BMI (kg/m^2)			
• Min-max	60.00–100.00	52.00–90.00	
• Mean ± std. deviation	80.65 ± 9.72	74.30 ± 11.37	
• 95% CI for mean	77.09–86.20	68.99–79.61	$Z_{(MW)} = 1.888$ $p = 0.059$ NS
• Median (IQR)	80.00 (76.50–89.00)	75.00 (65.00–85.00)	
• KS test of normality	$D = 0.117$, $p = 0.200$ NS	$D = 0.128$, $p = 0.200$ NS	
Type of liver resection			
Caudate lobe	1 (5.0%)	2 (10.0%)	$Z = 0.600$ $p = 0.5485$ NS
Right formal	1 (5.0%)	4 (20.0%)	$Z = 1.4343$ $p = 0.1527$ NS
Left formal	3 (15.0%)	0 (0.0%)	$Z = 1.800$ $p = 0.0718$ NS
Left lateral	5 (25.0%)	3 (15.0%)	$Z = 0.790$ $p = 0.4295$ NS
Non anatomical	10 (50.0%)	11 (55.0%)	$Z = 0.3166$ $p = 0.7489$ NS

Abbreviations: *n*, number of patients; *min-max*, minimum-maximum; *CI*, confidence interval; *IQR*, interquartile range; *KS*, Kolmogorov-Smirnov; *MW*, Mann-Whitney *U*-test ; *statistically significant ($p < 0.05$); *NS*, statistically not significant ($p \geq 0.05$); *MELD*, model of end-stage liver disease; *BMI*, body mass index

Table 2 Corrected flow time (FTc), plethysmography variability index (PVI), and central venous pressure (CVP) at different times during liver resection

	After induction	After abdominal fascia opening	After retractor application	1 h after opening of fascia	Every 2 h of dissection	After resection	At end of surgery	Test of significance
Corrected flow time (FTc) (msec) TED-guided fluid								
n	20	19	20	20	13	20	20	
Min-max	200.00–371.00	205.00–400.00	115.00–387.00	119.00–415.00	180.00–540.00	288.00–390.00	235.00–390.00	$\chi^{2(df=6)} = 5.595$ $p = 0.470$ NS
Median	324.50	319.00	319.50	332.00	327.00	330.00	352.00	
IQR	(275.00–335.50)	(255.00–350.00)	(304.00–342.00)	(294.00–355.50)	(300.00–341.00)	(311.50–350.00)	(322.00–360.50)	
PVI-guided fluid								
n	20	20	20	20	14	20	20	
Min-max	205.00–450.00	230.00–389.00	246.00–400.00	249.00–405.00	209.00–400.00	220.00–453.00	241.00–424.00	$\chi^2_{(df=6)} = 3.138$ $p = 0.791$ NS
Median	310.00	324.50	334.50	344.00	320.50(260.00–	342.00	354.50	
IQR	(251.50–342.00)	(284.00–355.00)	(304.00–370.00)	(301.00–356.50)	372.00)	271.00–388.00	313.50–399.00	
Test of significance	$Z_{(MW)} = 0.014$ $p = 0.989$ NS	$Z_{(MW)} = 0.913$ $p = 0.361$ NS	$Z_{(MW)} = 0.961$ $p = 0.337$ NS	$Z_{(MW)} = 0.365$ $p = 0.715$ NS	$Z_{(MW)} = 0.194$ $p = 0.846$ NS	$Z_{(MW)} = 0.230$ $p = 0.818$ NS	$Z_{(MW)} = 0.758$ $p = 0.449$ NS	
Plethysmography variability index (PVI) (%) TED-guided fluid								
N	20	20	20	20	14	20	20	
Min-max	5.00–32.00	4.00–26.00	7.00–30.00	6.00–30.00	9.00–24.00	5.00–18.00	7.00–17.00	$\chi^2_{(df=6)} = 4.921$ $p = 0.554$ NS
Median	11.00	12.00	13.00	12.00	13.50	10.50	12.00	
IQR	9.00–14.00	9.50–14.50	9.50–16.50	9.50–15.50	10.00–14.00	8.50–13.50	8.50–13.50	
PVI-guided fluid								
N	20	20	20	20	14	20	20	
Min-max	7.00–27.00	8.00–16.00	8.00–20.00	7.00–17.00	9.00–17.00	7.00–20.00	6.00–17.00	$\chi^2 \chi_{df=6)} = 9.671$ $p = 0.139$ NS
Median	13.00	11.50	12.50	13.50	11.50	15.00	14.00	
IQR	11.00–15.00	10.00–14.00	11.00–14.50	10.50–15.00	11.00–14.00	12.00–15.50	11.00–15.50	
Test of significance	$Z_{(MW)} = 1.591$ $p = 0.112$ NS	$Z_{(MW)} = 0.014$ $p = 0.989$ NS	$Z_{(MW)} = 0.381$ $p = 0.704$ NS	$Z_{(MW)} = 0.340$ $p = 0.734$ NS	$Z_{(MW)} = 0.023$ $p = 0.981$ NS	$Z_{(MW)} = 2.506$ $p = 0.012$*	$Z_{(MW)} = 0.758$ $p = 0.449$ NS	
Central venous pressure (CVP) (mmHg) TED-guided fluid								
n	20	20	20	20	13	20	20	
Min-max	6.50–15.00	6.50–15.00	5.00–16.00	5.00–17.00	2.00–15.00	4.60–15.00	6.00–15.00	$\chi^{2(df=6)} = 2.723$ $p = 0.843$ NS
Median	9.50	9.00	9.50	10.70	11.00	10.35	10.00	
IQR	7.70–11.50	7.65–11.50	7.30–12.50	9.10–12.00	10.00–12.00	8.05–12.50	8.75–11.25	
PVI-guided fluid								
n	20	20	20	0	14	20	20	
Min-max	5.00–14.00	5.00–15.00	1.00–14.00	7.00–14.00	0.00–14.00	4.60–14.60	3.80–15.00	$\chi^{2(df=6)} = 4.329$ $p = 0.632$ NS
Median	9.00	10.00	9.75	10.00	9.00	10.00	10.00	
IQR	6.95–11.50	8.00–11.75	8.00–12.00	8.00–12.00	9.00–11.50	8.50–10.75	(8.00–12.00)	
Test of significance	$Z_{(MW)} = 0.827$ $p = 0.408$ NS	$Z_{(MW)} = 0.258$ $p = 0.797$ NS	$Z_{(MW)} = 0.054$ $p = 0.957$ NS	$Z_{(MW)} = 0.448$ $p = 0.654$ NS	$Z_{(MW)} = 1.055$ $p = 0.292$ NS	$Z_{(MW)} = 0.571$ $p = 0.568$ NS	$Z_{(MW)} = 0.314$ $p = 0.754$ NS	

n number of patients. *Min-max*, minimum-maximum. *CI* confidence interval. *IQR* interquartile range. *KS* Kolmogorov-Smirnov. *Statistically significant ($p < 0.05$). *NS* statistically not significant ($p \geq 0.05$)

the included patients suffered from ischemic heart disease or chronic pulmonary disease. FTc, PVI, and CVP intraoperative values at measurements points are presented in Table 2. A normovolemic status existed during liver dissection despite 2 h of fluid restriction. FTc was 327 (320–341) msec, and PVI was 11.50 (11.00–14.00) %. CVP also reflected a state of normovolemia in TED group 11.00 (10.00–12.00) vs. 9.00

Table 3 The volume of intraoperative guided infusion of crystalloids and colloids in transesophageal Doppler (TED) group versus pleth variability index (PVI) group

	Group		*p*-value
	TED	PVI	
Crystalloid (ml)			
• *n*	20	20	$Z_{(MW)} = 1.035$ $p = 0.301$ NS
• Min-max	2000.00–500.00	2000.00–3500.00	
• Mean ± std. deviation	2975.00 ± 715.89	2750.00 ± 444.26	
• 95% CI for mean	2639.952–3310.047	2542.079–2957.920	
• Median (IQR)	3000.00 (2500.00–3500.00)	2500.00 (2500.00–3000.00)	
• KS test of normality	$D = 0.168$, $p = 0.140$ NS	$D = 0.263$, $p = 0.001$*	
Colloids (ml)			
• *n*	18	18	$Z_{(MW)} = 1.418$ $p = 0.156$ NS
• Min-max	500.00–1000.00	500.00–1500.00	
• Mean ± std. deviation	666.67 ± 242.54	805.56 ± 303.84	
• 95% CI for mean	546.05–787.27	654.45–956.65	
• Median (IQR)	500.00 (500.00–1000.00)	1000.00 (500.00–1000.00)	
• KS test of normality	$D = 0.421$, $p = 0.000$*	$D = 0.294$, $p = 0.000$*	

Abbreviations: *n*, number of patients; *min-max*, minimum-maximum; *CI*, confidence interval; *IQR*, interquartile range; *KS*, Kolmogorov-Smirnov; *MW*, Mann-Whitney *U*-test; *statistically significant ($p < 0.05$); *NS*, statistically not significant ($p \geq 0.05$)

(9.00–11.50) mmHg in PVI group, $Z_{(MW)} = 1.055$, $p = 0.2$. No difference in infused total volumes of intraoperative crystalloids (Ringer's acetate), $p = 0.30$ or colloids (HES), $p = 0.15$ were observed when guided by FTc or PVI (Table 3). Table 4 demonstrates the details of intraoperative blood loss, volume of consumed packed red blood cells (PRBCs), and fresh frozen plasma (FFP) in milliliter, respectively. Normovolemia was tolerated with minimal blood transfusion requirements and with a transfusion-free surgery in a significant number of the patients. Negligible correlations existed between FTc, PVI, and CVP, $p > 0.05$ (Figs. 2, 3 and 4).

ICU stay (day) was similar 1.00 (1.00–1.00) vs. 1.00 (1.00–1.00), $Z_{(MW)} = 1.416$, $p = 0.15$. No significant difference in postoperative complications was noted between the two groups. Respiratory complications are as follows: 0 (0.00%) vs. 1 (5.00%), $Z = 1.012$, and $p = 0.31$. Nausea is as follows: 9 (45.0%) vs. 4 (20%), $Z = 1.687$, and $p = 0.0910$, and vomiting is as follows: 1 (5%) vs. 2 (10%), $Z = 0.6003$, and $p = 0.548$ (Mann-Whitney *U*-test). Invasive blood pressure and calculated parameters of TED as COP and SVR demonstrated hemodynamic stability at all phases of surgery. Repeated measures analysis is $p > 0.05$.

Discussion

The results of this trial performed during liver surgery demonstrated the ability of PVI to guide equal volumes of intraoperative fluids as the FTc of TED, despite the poor correlations that existed between both parameters. Previous studies conducted during other surgical procedures demonstrated variable findings. Weak or insignificant correlations were observed with other devices during abdominal major surgery, as reported by Warnakulasuriya et al. (2016) and Abdullah et al. (2012). Bahlmann et al. (2016) study similarly reported that the PVI and Doppler-based stroke volume poorly agreed during surgery, but despite that, they were being able to guide similar volumes of fluids. PVI signals are affected by external factors. Le Guen et al. (2018) explained this by the effect of stress and the released catecholamine on PVI signals; they reported that PVI compared to TED is not an accurate predictor for fluid responsiveness during kidney transplantation. The need to infuse vasopressor as phenylephrine in complex surgical situations as liver resection can affect the readings of PVI through inducing peripheral vasoconstriction. Other surgical factors as hypothermia, low cardiac output, vasoactive drugs, and changes in the autonomic nervous system are among other listed factors. These factors usually associate complex surgery and lead to a decrease in the finger plethysmography signals. Broch et al. (2011) and Monnet et al. (2013) confirmed that plethysmography waveforms were affected by changes in the peripheral vascular tone. In liver surgery, Vos and his colleagues compared the PVI to other dynamic preload variables, as stroke volume and pulse pressure of the FloTrac-Vigileo device. They reported the ability of PVI to predict fluid responsiveness, but again, they confirmed that PVI was unable to tracked fluid changes, particularly when norepinephrine is infused (Vos et al., 2013). Other reasons for the lack of correlation between PVI and TED FTc could

Table 4 Consumed packed red blood cells (PRBCs) and fresh frozen plasma (FFP) in milliliter respectively. PRBCs unit (350 ml), FFP unit (200 ml). Intraoperative blood loss and urine output in ml/h. Preoperative and postoperative hemoglobin (Hb) g/dl

	TED $n = 20$	**PVI** $n = 20$	***P***
FFP (ml)			0.326
• *n*	4 (20.0%)	7 (35.0%)	
• Min-max	200–400	200–400	
• Mean ± std. deviation	250 ± 100	314.29 ± 106.90	$Z_{(MW)} = 0.982$ $p = 0.326$ NS
• 95% CI for mean	90.87–409.12	215.415–413.155	
• Median (IQR)	200 (200–300)	400 (200–400)	
• KS test of normality	$D = 0.441, p = 0.000$*	$D = 0.360, p = 0.007$*	
PRBCs (ml)			
• *n*	6 (30.0%)	8 (40.0%)	
• Min-max	350–700	350–700	$Z_{(MW)} = 1.241$ $p = 0.215$ NS
• Mean ± std. deviation	408.33 ± 142.89	525.00 ± 187.08	
• 95% CI for mean	258.38–558.28	368.59–681.40	
• Median (IQR)	350 (350–350)	525 (350–700)	
• KS test of normality	$D = 0.492, p = 0.000$	$D = 0.325, p = 0.013$*	
Blood loss (ml)			
• Min-max	250–3500	300–2500	
• Mean ± std. deviation	1247.50 ± 909.23	1340 ± 803.05	$Z_{(MW)} = 0.530$ $p = 0.596$ NS
• 95% CI for mean	821.96–1673.03	964.15–1715.84	
• Median (IQR)	950 (675–1925)	1500 (475–2000)	
• KS test of normality	$D = 0.257, p = 0.001$*	$D = 0.202, p = 0.031$*	
Urine output (ml/h)			
• Min-max	40–100	35–90	
• Mean ± std. deviation	70.00 ± 15.30	57.25 ± 13.23	
• 95% CI for mean	62.837–77.162	51.05–63.44	$Z_{(MW)} = 2.776$ $p = 0.005$*
• Median (IQR)	70 (62.5–80)	60 (47.5–65)	
• KS test of normality	$D = 0.150, p = 0.200$ NS	$D = 0.132, p = 0.200$ NS	
Hb (preoperative) (g/dl)			
• *n*	20	20	$Z_{(MW)} = 0.081$ $p = 0.935$ NS
• Min-max	9.90–17.00	11.00–15.90	
• Mean ± std. deviation	13.36 ± 1.52	13.40 ± 1.22	
• 95% CI for mean	12.643–14.066	12.825–13.964	
• Median (IQR)	13.60 (12.15–14.35)	13.10 (12.50–14.40)	
• KS test of normality	$D = 0.156, p = 0.200$ NS	$D = 0.127, p = 0.200$ NS	
Hb (24 h postoperative) (g/dl)			
• *n*	20	20	
• Min-max	10–14.5	9.00–13.90	
• Mean ± std. deviation	11.73 ± 1.43	10.72 ± 1.41	$Z_{(MW)} = 2.307$ $p = 0.021$*
• 95% CI for mean	11.053–12.396	10.054–11.375	
• Median (IQR)	11.60 (10.30–12.90)	10.35 (9.75–11.25)	
• KS test of normality	$D = 0.143, p = 0.200$ NS	$D = 0.182, p = 0.080$ NS	

Abbreviations: *n*, number of patients; *min-max*, minimum-maximum; *CI*, confidence interval; *IQR*, interquartile range; *KS*, Kolmogorov-Smirnov; *MW*, Mann-Whitney *U*-test; *statistically significant ($p < 0.05$); *NS*, statistically not significant ($p \geq 0.05$); *FFP*, fresh frozen plasma; *PRBCs*, packed red blood cells; *Hb*, hemoglobin

be from the esophageal Doppler device side. The calculated TED parameters as cardiac output and FTc depend on changes in aortic dimensions with sympathetic activity. Esophageal Doppler monitor is also a personal operator dependent and requires frequent repositioning of the esophageal probe as observed during this current trial. Esophageal probe had to be readjust repeatedly with surgical manipulations of the liver. They were inserted and manipulated by only one anesthesiologist in this current trial (Schober et al., 2009).

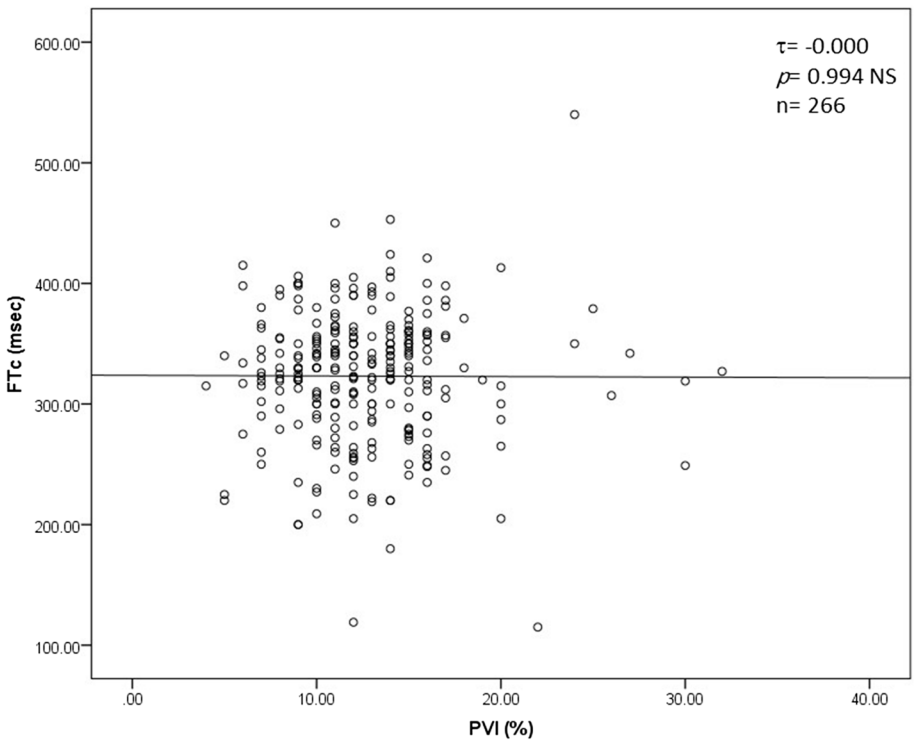

Fig. 2 Simple scatter plot with regression (best fit) line and correlation between transesophageal Doppler corrected flow time (FTc, msec) and pleth variability index (PVI, %)

Another specific condition related to liver surgery is the effect of extensive abdominal retraction necessary to mobilize the liver during resection. This retraction can reduce blood perfusion to the fingers by compressing the subclavian artery between the first rib and the clavicle (Dulitz et al., 2005).

Morbidity and stay

Warnakulasuriya et al. and Bahlmann et al. reported no difference in morbidity, outcome, or stay in PVI group compared to TED during surgery (Bahlmann et al., 2018; Warnakulasuriya et al., 2016). However; Thiele RH et al. in 2015 demonstrated a beneficial role for the PVI in reducing stay and morbidity when included in the perioperative care of colorectal surgery protocols (Thiele et al., 2015).

Economics and cost

PVI probe is reusability and cheap compared to the cost of the TED probe. TED probe is of a single use with an average cost of 5000 Egyptian pounds. This is expensive in developed countries. However, TED probes provide more hemodynamic function details; this includes the cardiac output and systemic vascular resistance, which is not possible with the figure probe of PVI. TED remains an important monitor during major surgery particularly for patients with compromised cardiovascular functions or with significant intraoperative hemodynamic changes (Mahmoud et al., 2016).

Normovolemia during dissection

The state of normovolemia during the dissection phase in a significant number of patients was not associated with increase in blood loss or the need for blood transfusion. The surgical technique of liver dissection adopted in this trial (anterior parenchymal resection) and avoiding the selective vascular occlusion of the hepatic inflow (Pringle maneuver) with the preservation of the middle hepatic vein played an important role in preserving the hemodynamics (Chen et al., 2000). Optimization of perfusion and oxygen delivery to the residual and cirrhotic liver tissues during surgery is important. As previously mentioned published data still recommends that CVP should be less than 5 mmHg (Hughes et al., 2015; Li et al., 2014), but Wang et al in a study among healthy liver donors reported that a CVP levels of 8.1 ± 1.9 mmHg during dissection were not associated an increase in blood loss. This is similar to the CVP readings reported in our current trial during the resection phases. Wang et al. believe that the extreme lowering of the CVP needs to be avoided. Low CVP could lead

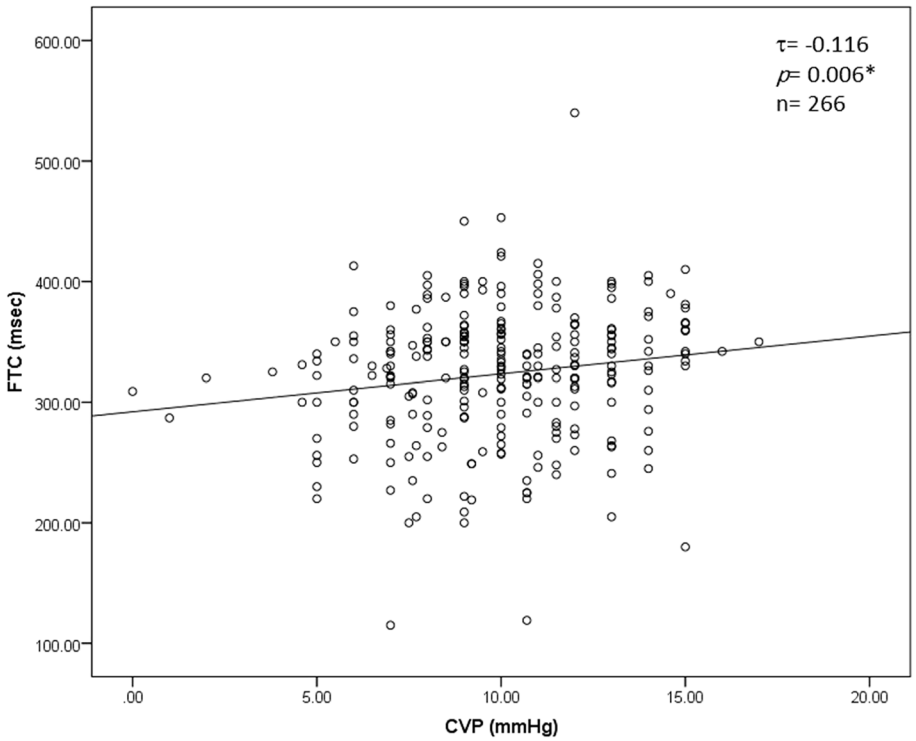

Fig. 3 Simple scatter plot with regression (best fit) line and correlation between transesophageal Doppler corrected flow time (FTc, msec) and central venous pressure (CVP, mmHg)

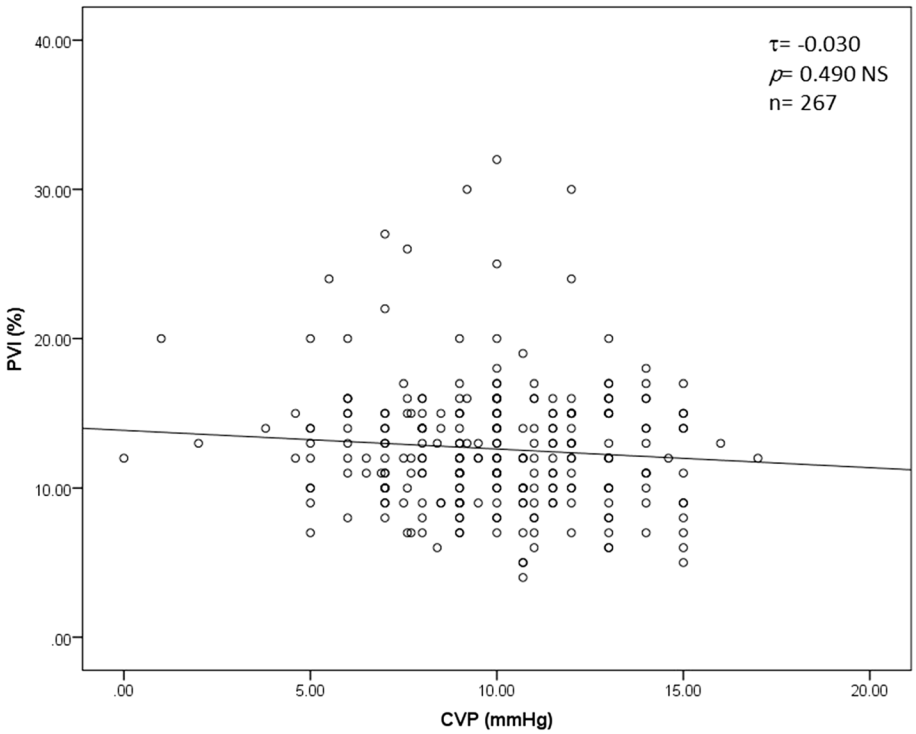

Fig. 4 Simple scatter plot with regression (best fit) line and correlation between pleth variability index (PVI, %) and central venous pressure (CVP, mmHg)

to air embolism. Unrecognized hepatic vein lacerations can endanger the patients more than blood loss (Wang et al., 2017).

In Yu L. et al. (2020) study, low CVP during hepatectomy had no significant effect on intraoperative blood loss (Yu et al., 2020). The authors of this current trial believe that liver surgery among cirrhotic liver tissues is possible without extreme reduction in CVP to avoid increasing the risk of hypoperfusion to the remnant hepatic tissues beside the risk of air embolism. The modified recent surgical techniques for resection reduce the risk of intraoperative bleeding.

Multimodal monitoring

Adopting a multimodal hemodynamic monitoring policy during major liver surgery will avoid the disadvantages of depending on a sole monitor. The additional data provided by the TED as CO and SVR can increase the scope of monitoring. A study by Ratti F. et al. (2016) demonstrated that *intraoperative monitoring* of the cardiac *preload* and CO together with stroke volume (SV) did add to the management of the patients in their study and improved the outcome following laparoscopic *liver surgery* when compared to the traditional sole monitoring of CVP (Ratti et al., 2016).

The CVP has been challenged in many studies by none or minimal invasive fluid guiding parameters that claimed to be better in predicting the response to fluid administration. Two recent meta-analysis studies by Marik PE and his colleagues suggested abandoning the CVP as a guide for fluid therapy (Marik et al., 2008; Marik & Cavallazzi, 2013).

Fu et al. (2012) and Vos et al. (2013) agreed that the best threshold values to predict fluid responsiveness were > 12.5% for SVV and > 13.5% for PVI in the real surgical setting. Later in 2016, Chu et al. systematic review and meta-analysis demonstrated that PVI has a reasonable ability to predict fluid responsiveness. However; the applicability of PVI may be limited by the potential interference from several factors, such as arrhythmia, and low peripheral perfusion (Chu et al., 2016). Wu C. Y. et al. in a diagnostic accuracy prospective study (2016) that included liver cirrhosis patients demonstrated that the multimodal dynamic preload variables (PPV, SVV, and PVI) can predict fluid responsiveness (Wu et al., 2016).

One of the limitations of the study is the small number of the patients enrolled; this could be due to the restrictive inclusion criteria of only adults with hepatitis C liver cirrhosis and undergoing elective open liver surgery. Another limitation is non-blinding of the CVP readings from the attending anesthesiologists, which could subject their observations to possible bias.

Conclusions

Volume of fluids guided by PVI was not different from that by TED, despite lack of correlation. Transfusion-free dissection was possible for a significant number of patients with normovolemia and median values of 11.5% for PVI or 327 msec for FTc.

Abbreviations

TED: Transesophageal Doppler; FTc: Corrected flow time; PVI: Plethysmography variability index; CVP: Central venous pressure; ICU: Intensive care unit; IBP: Invasive blood pressure; SV: Stroke volume; COP: Cardiac output; SVR: Systemic vascular resistance; BIS: Bispectral index; PI: Perfusion index; IQR: Interquartile range; τ: Kendall's tau correlation; SpHb: Noninvasive hemoglobin concentration; Lab Hb: Laboratory hemoglobin; PEEP: Positive end-expiratory pressure; HES: Hydroxyethyl starch; MELD: Model of end-stage liver disease; BMI: Body mass index; FFP: Fresh frozen plasma; PRBCs: Packed red blood cells; Hb: Hemoglobin.

Acknowledgements

We would like to thank Dr. Elsayed Amr Basma for his statistical consultation.

Authors' contributions

HA, FE, AM, and KY have full access to all the data in the study and take responsibility for the integrity of the data. Study concept and design, AM and KY; acquisition of data, HA, FE, AM, and KY; and analysis of data and critical revision of the manuscript, HA, FE, AM, and KY. The authors read and approved the final manuscript.

Funding

None

Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate was obtained from the local ethics committee of the Faculty of Medicine at Menoufia University, Egypt (IRB, 0108/2018). Informed written consent was obtained from each patient. The trial was registered at the South Africa Pan Cochrane Research Registry.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Received: 18 November 2021 Accepted: 4 November 2022
Published online: 08 December 2022

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