Effects of epidural-and-general anesthesia combined versus general anesthesia alone on the venous hemodynamics of the lower limb

A randomized study

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Summary

Our hypothesis was that, due to its sympatholytic action, epidural anesthesia (EA) administered as part of anesthesia in abdominal surgery would generate a marked venous leg flow enhancement, thus aiding in the prevention of peroperative venous stasis. We studied, and comprehensively quantified the venous haemodynamic changes in the lower limb during and immediately after abdominal surgery performed under EA and general (GA) anesthesia combined, in comparison to GA alone. This is a prospective, randomized, controlled study, stratified for hypertension and smoking, comprising ASA 1-2 patients undergoing elective total abdominal hysterectomy. Those with peripheral vascular or chronic venous disease, prior DVT or BMI>35 were excluded. Eligible recruits received either GA (Group GA) (n = 10; age 36-65, median 50) alone or epidural anesthesia (EA) and GA combined (Group EA/GA) (n = 9; age 32-58, median 46). EA (l1-2) was administered using lignocaine 2%. Both groups had GA induced with fentanyl and propofol, maintained with N₂O and isoflurane; laryngoscopy was facilitated with vecuronium; analgesia was provided either with morphine (Group GA) or epidurally with 2% lignocaine boli (Group EA/GA). Hemodynamics were determined at the popliteal vein in the horizontal supine position at baseline (resting prior to anesthesia), post epidural (20 min after delivery of EA), post induction (15 min after laryngeal intubation), surgery (upon uterus removal) and recovery (30 min after extubation). There was no difference in the mean velocity \( V_{\text{mean}} \) between the 2 groups at baseline \((p = 0.35)\), and post induction \((p = 0.5)\). However \( V_{\text{mean}} \) was significantly higher in Group EA/GA than Group GA, both at surgery \((\text{point estimate} [\text{PE}]: 1.8 \text{ cm/s}; 95\% \text{ CI}: 0.01, 6.3 \text{ cm/s}; p < 0.05)\) and recovery \((\text{PE}: 2.6 \text{ cm/s}; 95\% \text{ CI}: 0.4, 5.1 \text{ cm/s}; p = 0.02)\). Volume flow \( V_Q \) was similar in the 2 groups at baseline and post induction \((\text{both}, p > 0.1)\), but was significantly higher in Group EA/GA at surgery \((\text{PE}: 54 \text{ ml/min}; 95\% \text{ CI}: 18, 159 \text{ ml/min}; p = 0.045)\) and recovery \((\text{PE}: 49 \text{ ml/min}; 95\% \text{ CI}: 16, 129 \text{ ml/min}; p = 0.0037)\). Peak velocity \( V_{\text{mean}} \) and \( V_Q \) increased significantly post epidural in Group EA/GA. Contrary to the venous leg flow attenuation in elective abdominal surgery under GA and upon its recovery, EA administered as part of GA is associated with a significant enhancement of both \( V_{\text{mean}} \) and \( V_Q \). This beneficial hemodynamic effect of EA at the vulnerable stage of recovery may be critically essential in light of enhanced blood viscosity, fibrinolytic shutdown, endothelial/platelet activation and immobility, acting in synergy with putative cardiorespiratory protection. The results of this study lend support to the preferential selection of combined EA/GA in subjects at high risk for venous thromboembolism, particularly when optimal DVT prophylaxis is practically unattainable due to limitations pertaining to the nature of surgery.

Keywords

Epidural anesthesia, venous hemodynamics, stasis

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

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**Introduction**

The benefits of epidural (EA) versus general (GA) anesthesia have been a matter of longstanding debate spanning over 35 years. In a meta-analysis of 141 randomised studies neuroaxial blockade was found to reduce postoperative mortality by about a third (odds ratio 0.70, 95% CI 0.54-0.9) amongst 9559 patients undergoing vascular, orthopedic, urology and general surgery (p=0.0006), in comparison to GA (1). Most notably, neuraxial blockade was associated with a reduced odds of deep vein thrombosis (DVT) by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39% and respiratory depression by 59%, all significant (1). A randomized, controlled Veterans Affairs cooperative study published only months later reported that patients undergoing abdominal aortic surgery under EA and light GA sustained significantly fewer deaths and major complications combined (22%) than those operated upon under GA receiving post-operative analgesia with parenteral opioids (37%), stemming from differences in the incidence of new myocardial infarctions, stroke and respiratory failure between the two groups (2).

The highly significant effect of EA in reducing the risk of DVT (odds ratio 0.56; 95% CI 0.43-0.72) and pulmonary embolism (odds ratio 0.45; 95% CI 0.29-0.69) (1, 3-5) has been associated with a better preservation of fibrinolytic activity (6, 7), an inhibitory action on platelet aggregation (8), thrombo-elasticographic evidence of decreased platelet-fibrinogen interaction particularly in arteriopathies (9), and a stabilising effect on leucocytes and endothelial cells (10), linked to a hyperkinetic blood flow in the lower limbs (11-15). Yet, the venous hemodynamics associated with the administration of EA particularly as part of GA in abdominal surgery have remained largely undetermined despite their being antithetical to the phenomenon of peri-operative venous stasis. Our hypothesis was that, due to its sympatholytic action (16), epidural anesthesia (EA) administered as part of anesthesia in general surgery would generate a marked venous leg flow enhancement, thus aiding in prevention of peroperative venous stasis.

The aim of this prospective randomized study was to quantify the hemodynamic changes that occur in the proximal venous circulation of the lower limb during and upon recovery from elective abdominal surgery performed under combined EA and GA, in comparison to GA used solely.

**Methods**

**Ethics**

Honoring the ethical principles for medical research involving human subjects as set out in the Declaration of Helsinki, the protocol of the study was approved by the institutional review board and, in light of its prospective design, patients’ written informed consent was obtained.

**Design**

This is a prospective, randomized, controlled study with stratification for hypertension and smoking. Following power calculations derived from the data of a previous study (17), ASA 1-2 patients, undergoing elective total abdominal hysterectomy were randomly allotted to receive either GA alone (Group GA) or combined EA and GA (Group EA/GA). Randomization was conducted using four groups of sealed envelopes prepared by an independent public health statistician thus allowing for stratification of randomized subjects for hypertension and smoking (hypertension/smoking; hypertension/non-smoking; normotensive/smoking; normotensive/non-smoking). The method accounted for a correction of the patient allocation between the two groups (Groups GA, and EA/GA) every five new entries.

**Inclusion and exclusion criteria**

Inclusion criteria: ASA 1-2 patients undergoing elective total abdominal hysterectomy, via a Pfannenstiel incision, performed under the care of the same surgical team at the same institution. Exclusion criteria: [1] patients with peripheral vascular disease defined by (a) the absence or attenuation of peripheral pulses, (b) suboptimal ankle brachial pressure indices (< 1.0), (c) the presence of abnormal Doppler velocity waveforms (monophasic or biphasic continuous) in peripheral vasculature (popliteal and crural arteries) at rest in the horizontal position; [2] chronic venous insufficiency determined by the presence of (a) signs and symptoms of venous disease stratified as clinical classes C 2-4 in the CEAP classification (18), (b) presence of abnormal venous reflux (> 0.5 s) (19) in the superficial and deep axial veins of the limb; [3] prior DVT defined by the presence of thrombosis on duplex or the presence of ultrasonographic signs indicating a previous DVT (20), [4] body mass index > 35; [5] patients with collagen tissue disorders; [6] those on nifedipine or beta blockers; [7] previous back surgery or patients refusing to be considered for epidural anesthesia; [8] age > 65; [9] prior lower limb surgery due to arterial or venous trauma.

**Patients**

Overall, 34 patients were initially considered, but only 21 met the stringent inclusion and exclusion criteria of the study, of whom 19 accepted to participate in the study. Ten patients were allotted to receive GA alone (Group GA) and 9 to receive EA and GA combined (Group EA/GA). The demographics of the randomized patients are depicted in Table 1. The 2 groups were matched for age, sex (all females), BMI, ASA physical status (1-2), smoking, hypertension, and dyslipidemia.

**Investigation protocol**

Patients considered for inclusion in the study underwent a detailed medical history, careful assessment of their clinical notes, physical examination with emphasis on the cardio-vascu-
lar system, classification according to ASA physical status and CEAP classification, duplex investigation of the lower limb arteries and veins and measurement of the resting ankle brachial pressure indices. Those of the above who participated in the study had their venous hemodynamics evaluated in the popliteal vein preoperatively at rest [Baseline], 15 min after tracheal intubation [Post-Induction], upon uterus resection [Surgery] and at 30 min after tracheal extubation [Recovery]. In addition those in Group EA also had a full set of hemodynamic measurements performed 20 min after the administration of effective EA [Post-epidural] before GA was induced. The protocol of investigations in the randomized patients is depicted in Table 2. DVT prophylaxis (enoxaparin 20 mg) was administered to all patients.

Venous hemodynamics
Investigation of venous hemodynamics included the peak velocity [V peak], mean velocity [V mean], minimum velocity [V min], volume flow [VQ], and pulsatility index [V pulsatility index]. The V pulsatility index was calculated by the following formula: \( \frac{(V_{\text{peak}} - V_{\text{min}})}{V_{\text{mean}}} \). The VQ was estimated using the following formula: \( \pi \times \text{Diameter}^2/4 \times V_{\text{mean}} \). All these hemodynamic parameters were measured at the popliteal vein, level to the medial femoral condyle using duplex ultrasonography. Measurements were obtained strictly in the horizontal position. The reproducibility of these measurements has been previously reported both in the setting of small (21) and medium (22) caliber veins.

**Duplex ultrasonography**
All duplex investigations were performed using a contemporary duplex scanner fitted to a 5.5/7.5 MHz linear scanhead. The settings of duplex software were optimized at the preliminary stages of the study and were thus consistently maintained throughout. Hemodynamics were obtained under resting conditions in the horizontal supine position using real-time gated Doppler sonography superimposed on real-time B mode imaging. The combination of these modes enabled a continuous appreciation of the positioning of the Doppler gate in relation to the lumen of the vessel examined, ensuring optimal data retrieval. The venous flow velocity profiles were enveloped automatically using dedicated flow measuring software. The V peak, V mean and V min were instantly obtained, thus permitting V pulsatility index calculation using the afore-mentioned formula. Determination of the popliteal diameter enabled calculation of the VQ. Venous hemodynamics were estimated on the basis of consecutive Doppler spectra spanning 5-7 sec long and the average of a minimum of 4 measurements was calculated for each parameter, per examined limb, per time-point evaluated. All the data were recorded on S-VHS Video thus allowing an accurate account of all individual values. On all occasions the left limb was investi-

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**Table 1: Demographic profile of the female patients in Group GA (general anesthesia) and Group EA/GA (both epidural and general anesthesia).** Continuous data are reported as median and range. Statistical difference calculated with the Mann-Whitney test (p) or the χ² (*p). Please refer to the Methods section for details on the study criteria.

<table>
<thead>
<tr>
<th></th>
<th>Group GA</th>
<th>Group EA/GA</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Patients</td>
<td>10</td>
<td>9</td>
<td>-</td>
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<tr>
<td>Age</td>
<td>50 (36-65) years</td>
<td>46 (32-58) years</td>
<td>p&gt;0.2</td>
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<tr>
<td>BMI</td>
<td>27.8 (18-33.5)</td>
<td>27.2 (19.6-35)</td>
<td>p&gt;0.2</td>
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<tr>
<td>Hypertension</td>
<td>3</td>
<td>2</td>
<td>*p&gt;0.2</td>
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<td>Smoking</td>
<td>2</td>
<td>2</td>
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<td>Dyslipidimia</td>
<td>1</td>
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<td>Diabetes</td>
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<tr>
<td>Prior DVT</td>
<td>Excluded</td>
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**Table 2: Schematic representation of the hemodynamic assessment protocol in Group GA (general anesthesia alone) and EA/GA (both epidural and general anesthesia), across the sequence of the study time points.**

<table>
<thead>
<tr>
<th>Hemodynamic assessment</th>
<th>V peak</th>
<th>V mean</th>
<th>Diameter</th>
<th>VQ</th>
<th>V min</th>
<th>V pulsatility index</th>
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<td>Group EA/GA alone</td>
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<td>Both Groups</td>
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<td>Both Groups</td>
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gated. An environment of strict temperature control (21 ± 1°C) was ensured throughout the study. All hemodynamic data were obtained by a single examiner (K.T.D.).

**Anesthetic protocols**

Patients in both groups received oral temazepam (20mg) 2 hours before going to theatre. Fentanyl 1.5 μg/kg and propofol 1-2.2 mg/kg were administered until loss of consciousness and vecuronium or rocuronium, if a rapid sequence induction was indicated, enabled tracheal intubation (23). Anesthesia was maintained using isoflurane titrated to effect in 60% N₂O and oxygen. Those in Group GA received morphine up to 0.3 mg/kg as required. Normocapnia was maintained by controlled ventilation with airway pressures constantly below 25 cm H₂O. A forced warm air blanket ensured normothermia.

Those in Group EA/GA had their EA sited, before GA induction, in the high lumbar region aiming at the space between the first two lumbar vertebrae (L₁₂). Lignocaine 2% plain was the only anesthetic administered via the epidural catheter. An initial test dose excluded subdural placement of the catheter. A total of 15 ml of lignocaine was given (23). Fifteen minutes after this, the extent of the epidural block was established. Once the patient was unable to straight leg raise and to feel cold up to the level of the tenth lumbar dermatome bilaterally, hemodynamic assessment commenced. A further 5 ml bolus of lignocaine were given as required to achieve this block height. Upon completion of hemodynamic assessment, GA was induced and maintained in the same manner as described for those in Group GA, except that morphine was not given. Ten ml of lignocaine were given as required to achieve this block height. Anesthesia was always provided by the same anesthesiologist.

**Surgical procedure**

All subjects investigated underwent elective total abdominal hysterectomy for benign disease performed via a Pfannensteil incision by the same surgical team.

**Statistical analysis**

Statistical evaluation of the data was performed using non-parametric analysis. Comparison of paired quantitative data involving three or more time points was conducted using the Friedman’s two-way analysis of variance test. Following the Friedman’s test, identification of the exact location of the paired differences was performed using the Wilcoxon’s rank test, making due allowance for multiple testing with the Bonferroni correction (*) (24).

Comparison of data between the two study groups was conducted using the Mann-Whitney test, with Bonferroni correction (*) when applicable. Differences are supported by quotation of the estimated median difference (EMD) for the Wilcoxon’s rank test, the point estimate (PE) for the Mann-Whitney test, and their 95% confidence intervals (95% CI). The quoted EMDs and 95% CIs in the Wilcoxon’s test refer to the baseline values of the parameter in consideration. Differences in proportions are determined using the χ² test. A p-value of less than 0.05 was considered as significant. Data are reported as median and interquartile range, unless otherwise stated.

**Results**

### Peak velocity (V<sub>peak</sub>) (Fig. 1A)

Changes in V<sub>peak</sub> at the different time points of the study were insignificant overall in patients receiving GA (Group GA: p >0.2 [Friedman]). In this group the median V<sub>peak</sub> increased by 19% after GA induction (EMD: 1.5 cm/s; 95% CI: -1.1, 4.5 cm/s) and by 37.6% at surgery (EMD: 1.3 cm/s; 95% CI: -0.9, 3.7 cm/s), on both occasions significance being missed due to overlapping 95% CIs.

In Group EA/GA median V<sub>peak</sub> increased by 70.7% after EA administration and before GA induction (EMD: 4.4 cm/s; 95% CI: 1.8, 7.7 cm/s; p = 0.013 [Wilcoxon]). V<sub>peak</sub> decreased to baseline levels after induction of GA (EMD: 1.4 cm/s; 95% CI: -1.15, 4.3 cm/s), increased at surgery (EMD: 3.7 cm/s; 95% CI: -0.8, 9 cm/s) to decline at recovery (EMD: 1.1 cm/s; 95% CI: -1.6, 8.4 cm/s).

Differences in V<sub>peak</sub> between the two groups were insignificant at baseline, GA induction, surgery and recovery (p >0.23 [Mann-Whitney]). However, V<sub>peak</sub> after EA and before GA in Group EA/GA was markedly higher than V<sub>peak</sub> in Group GA at baseline (PE: 4.9 cm/s; 95% CI: 1.8, 9.7 cm/s; P = 0.012 [Mann-Whitney]) and recovery (PE: 4.9 cm/s; 95% CI: 0.9, 9.4 cm/s; P=0.024 [Mann-Whitney]).

### Mean velocity (V<sub>mean</sub>) (Fig. 1B)

In Group GA, V<sub>mean</sub> showed marked changes overall in the study time points (p <0.01 [Friedman]), due to its decrease at surgery (EMD: -2.2 cm/s; 95% CI: -3.1, -0.7 cm/s; p = 0.011 [Wilcoxon]) and recovery (EMD: -2.1 cm/s; 95% CI: -3.6, -0.4 cm/s; p <0.006 [Wilcoxon]).

In Group EA/GA V<sub>mean</sub> also changed significantly overall (p <0.01 [Friedman]). This was due to the marked elevation of V<sub>mean</sub> after EA administration and before GA induction (EMD: 3.4 cm/s; 95% CI: 1.3, 5.7 cm/s; p = 0.009 [Wilcoxon]). After GA induction V<sub>mean</sub> declined to baseline levels (EMD: 0.16; 95% CI: -1.5, 1.4 cm/s), but increased again at surgery (EMD: 1.5 cm/s; 95% CI: -0.9, 4.5 cm/s) and recovery (EMD: 1.2 cm/s; 95% CI: -0.5, 4.5 cm/s).

The disparity in V<sub>mean</sub> between Groups EA/GA and GA was small at baseline (p = 0.35 [Mann-Whitney]), and induction (p = 0.5 [Mann-Whitney]). However the V<sub>mean</sub> was significantly higher in Group EA/GA than Group GA, both at surgery (PE: 1.8 cm/s; 95% CI: 0.1, 6.3 cm/s; p <0.05 [Mann-Whitney]) and recovery (PE: 2.6 cm/s; 95% CI: 0.4, 5.1 cm/s; p =
The $V_{\text{mean}}$ after EA in Group EA/GA was markedly higher than $V_{\text{mean}}$ in Group GA at surgery (PE: 4.8 cm/s; 95% CI: 2.7, 7.4 cm/s) and recovery (PE: 4.5 cm/s, 95% CI: 1.7, 7.3 cm/s).

**Diameter (Fig. 2A)**

Popliteal vein diameter in Group GA increased slightly at GA induction and surgery (both $p > 0.6$ [Wilcoxon]), and decreased at recovery (EMD: -0.096 cm; 95% CI: -0.16, 0.001 cm; $p = 0.07$ [Wilcoxon]). Overall diameter changes in Group GA were not significant ($p > 0.1$ [Friedman]).

Popliteal vein diameter in Group EA/GA did not change after EA ($p = 0.7$ [Wilcoxon]); it increased after GA induction (EMD: 0.08 cm; 95% CI: 0.001, 0.14 cm; $p = 0.044$ [Wilcoxon], failing significance after a Bonferroni correction) and surgery (EMD: 0.04 cm; 95% CI: -0.008, 0.01 cm; $p = 0.098$ [Wilcoxon]), decreasing to baseline levels at recovery (EMD: 0.0005 cm; 95% CI: -0.058, 0.059 cm).

No difference was found between the two groups in the popliteal vein diameters at baseline, GA induction, surgery and recovery ($p > 0.1$ [Mann-Whitney]).

**Volume flow ($V_Q$) (Fig. 2B)**

$V_Q$ in Group GA changed little after GA induction ($p > 0.7$ [Mann-Whitney]) compared to baseline, but decreased markedly at surgery (EMD: -32 ml/min; 95% CI: -93, -13 ml/min; $p < 0.011$ [Wilcoxon]), and recovery (EMD: -47 ml/min; 95% CI: -108, -18 ml/min; $p = 0.006$ [Wilcoxon]), yielding intragroup changes significant overall ($p < 0.001$ [Friedman]).

In Group EA/GA, $V_Q$ increased after EA, before GA induction (EMD: 76 ml/min; 95% CI: 25, 133 ml/min; $p = 0.009$ [Wilcoxon]), compared to baseline. It remained higher than baseline after GA induction (EMD: 21 ml/min; 95% CI: -20, 55 ml/min) and surgery (EMD: 59 ml/min; 95% CI: -3, 138 ml/min), but leveled with baseline at recovery (EMD: 36 ml/min; 95% CI: -56, 92 ml/min).

$V_Q$ was similar in the 2 groups at baseline and after GA induction (both, $p > 0.1$ [Mann-Whitney]), but was significantly higher in Group EA/GA at surgery (PE: 54 ml/min; 95% CI: 18, 159 ml/min; $p = 0.045$ [Mann-Whitney]) and recovery (PE: 49 ml/min; 95% CI: 16, 129 ml/min; $p = 0.0037$ [Mann-Whitney]). $V_Q$ after EA before GA induction in Group EA/GA was markedly higher than $V_Q$ in Group GA at surgery (PE: 75 ml/min; 95% CI: 24, 130 ml/min) and recovery (PE: 96 ml/min; 95% CI: 49, 144 ml/min).

**Minimum velocity ($V_{\text{min}}$) (Fig. 3A)**

$V_{\text{min}}$ changes in Group GA were insignificant overall ($p > 0.2$ [Friedman]), although a decrease was noted both at surgery (EMD: -2 cm/s; 95% CI: -5.6, 1.6 cm/s) and recovery (EMD: -2.7 cm/s; 95% CI: -6.1, 0.9 cm/s), $V_{\text{min}}$ in Group EA/GA increased markedly after EA, before GA (EMD: 2.8 cm/s; 95% CI: 0.7, 6.8 cm/s; $p = 0.024$ [Wilcoxon]), compared to baseline; $V_{\text{min}}$ decreased after GA induction (EMD: -1.8 cm/s; 95% CI: -4.4, 0.03 cm/s) and at surgery (-2.9 cm/s; 95% CI: -5.8, 1.3 cm/s), to increase upon recovery (EMD: 0.7 cm/s; 95% CI: -1.1, 6.5 cm/s), the overall changes noted being highly significant ($p < 0.001$ [Friedman]). Differences in $V_{\text{min}}$ between Groups GA and EA/GA were small ($p > 0.1$) at baseline, GA induction, surgery...
Delis, et al.: General and epidural combined versus general anesthesia alone on venous hemodynamics and recovery. This also applied to $V_{\text{min}}$ after EA before GA induction in Group EA/GA when compared to $V_{\text{min}}$ in Group GA ($p > 0.1$ [Mann-Whitney]).

**Venous pulsatility index** ($V_{\text{pulsatility index}}$) (Fig. 3B)

$V_{\text{pulsatility index}}$ in Group GA increased stepwise from baseline to GA induction (EMD: 0.4; 95% CI: -0.2, 2.2), through to surgery (EMD: 1.4; 95% CI: 0.5, 2.4; $P = 0.014$ [Wilcoxon]) and recovery (EMD: 1.2, 95% CI: 0.14, 2.9; $p < 0.006$ [Wilcoxon]). In Group GA, $V_{\text{pulsatility index}}$ increased significantly post epidural ($p = 0.024$). $V_{\text{pulsatility index}}$ in Group EA/GA increased significantly with advancing procedural stage ($p < 0.05$). $V_{\text{pulsatility index}}$ in Group EA/GA decreased significantly post epidural ($p < 0.025$). For details refer to the results section.
EA/GA and that in Group GA at surgery (PE: -1.1; 95% CI: -1.7, -0.1; P = 0.024[Man-Whitney]).

Other parameters
There was no significant difference (p >0.2) between the two study groups in the blood loss and length of surgery. None of the study patients sustained a DVT (predischarge duplex) or pulmonary embolism (clinically). There were no complications requiring return to the theatre, high dependency care, prolonged hospitalization or readmission.

Discussion

Previous studies (13, 15, 25-29) have examined the arterial flow dynamics of the lower extremity during different types of surgery, including prostatectomy (13, 28) elective total abdominal hysterectomy and uterine myomectomy (25), femoropopliteal, femorocrural (15, 27, 29) and aortofemoral reconstructions (29), total hip arthroplasty (26) and inguinal hernia repair (27). These studies, three of which were randomized (26-28), using different techniques, such as $^{133}$Xe clearance (29), radio-active ($^{99}$mTc) labeled erythrocytes in whole body scintigraphy (30), ankle brachial indices (31) venous occlusion impedance plethysmography (13, 25-28), electromagnetic flowmetry (15, 29), laser Doppler flowmetry (27), and Doppler ultrasound (11, 13, 17), indicated that implementation of EA generated a significant enhancement of the arterial leg inflow contrasting the flow attenuation sustained with GA. Yet, extensive literature review revealed only one study on the effects of EA on the venous hemodynamics of the leg (17), based on a long outdated Doppler (1983) methodology. The broad applicability and clinical efficacy of EA and GA in current surgical practice associated with the EA-related prevention of hypercoagulability and thromboembolism, compelled a comprehensive determination of their effects in the venous circulation of the limb, particularly in light of high-resolution vascular imaging and the automated determination of blood flow dynamics offered by contemporary duplex.

The present study has shown that patients undergoing elective abdominal surgery under GA sustain a significant attenuation of the $V_{\text{mean}}$ and $V_Q$ during surgery and recovery, their median values decreasing by 27% and 15% at surgery and 21.5% and 41% at recovery, respectively. On the contrary, in patients under combined EA and GA the median $V_{\text{mean}}$ and $V_Q$ increased by 40% and 61% during surgery and by 58% and 20% on recovery, respectively. We estimated that the median $V_{\text{mean}}$ in Group EA/GA was 40% higher at surgery and 62% higher at recovery than that in Group GA, linked to a higher (median) $V_Q$ by 62% and 78%, respectively. In the only pertinent study available to date, Poikolainen et al (17) examined the effects of lumbar EA versus GA on the venous hemodynamics of the limb during retropubic prostatectomy. They identified a 120% increase in the femoral venous flow velocity with EA, associated with a 47% increase in peak flow and a 188% increase in minimum flow, contrasting GA patients who sustained a peak flow velocity decrease of 24-40%. Immediately after GA induction flow velocity in the femoral vein approached 0 cm/s but gradually rose and after 8 minutes stabilized at 40% below the preoperative velocity level. Despite its randomized design, their study did not investigate the effects of combined EA and GA, nor did it evaluate the hemodynamic changes in the recovery period whilst flow determination was based on a method which has since been superseded by all generations of duplex/Doppler ultrasound.

In the present study, patients undergoing elective abdominal surgery under GA sustained no significant changes in their $V_{\text{peak}}$ and $V_{\text{min}}$ in relation to baseline, yet the significant concurrent attenuation of $V_{\text{mean}}$ caused a marked stepwise increase of $V_{\text{pulsatility index}}$, from GA induction through to surgery and recovery. On the other hand those receiving EA/GA demonstrated a 71% increase in (median) $V_{\text{peak}}$ upon EA administration, compounded by a 90% elevation in (median) $V_{\text{min}}$ and a 126% rise in (median) $V_{\text{mean}}$, resulting in a notable attenuation of $V_{\text{pulsatility index}}$: upon induction of GA Group EA/GA patients manifested a marked attenuation of the venous flow velocities attained before with EA, nonetheless they maintained venous hemodynamics at levels similar to or higher than baseline, evidently contrasting with their counterparts receiving GA.

Assuming an unimpaired inflow in the arterial circulation, it is the outflow resistance that determines the nature of blood flow dynamics, the pulsatility index being a relatively dependable indicator of the outflow status (32). By inference, and assuming an unimpaired venous outflow anatomically, a high volatility of venous flow velocity (high $V_{\text{peak}}$ to $V_{\text{min}}$ differential) in the presence of a diminished $V_{\text{mean}}$ (i.e. high $V_{\text{pulsatility index}}$) are indicative of factors impeding venous outflow, including cardio-respiratory, mechanical, and iatrogenic. On the other hand a low flow velocity volatility (low $V_{\text{peak}}$ to $V_{\text{min}}$ differential) associated with a high $V_{\text{mean}}$ (i.e. low $V_{\text{pulsatility index}}$) are indicative of low outflow impedance. The rising levels of $V_{\text{pulsatility index}}$ in Group GA with advancing stage from GA induction through to surgery and recovery, should be interpreted as suggestive of an increasing venous outflow impedance. This could be attributable to the institution of mechanical ventilation after GA induction and the temporary abolition of negative mediastinal pressure with its beneficial effects on venous return. Sympathetic overflow causing peripheral vasoconstriction (33) and manipulation of the abdominal organs should be viewed as additional factors of outflow impartment during surgery. The increase in abdominal pressure due to surgical edema and the enhanced abdominal muscle contraction after tracheal extubation (34) could account for the outflow impedance in recovery. The increasing $V_{\text{pulsatility index}}$ from baseline to recovery in Group GA is in keeping with biologic plausibility, particularly in light
of the stress response to surgical trauma, the release of catecholamines and the resulting shutdown effect in peripheral vasculature. On the other hand, the attenuation of $V_{\text{pulsatility index}}$ after EA should be viewed as a decrease in venous outflow impedance, caused by the peripheral sympatholytic action of EA (16) and a subsequent relaxation of venous wall tone. Yet it should be recognized that for the same outflow impedance, venous inflow alterations would cause $V_{\text{mean}}$ changes impacting on $V_{\text{pulsatility index}}$. Thus, $V_{\text{pulsatility index}}$ should be interpreted cautiously more as a qualitative indicator rather than as a robust quantitative marker of venous outflow.

The hemodynamic findings of this study were carefully controlled by the maintenance of central hemodynamics, reflected by a stable mean arterial blood pressure during surgery and recovery, in relation to baseline. A consistent decrease in the mean arterial pressure occurred early after EA administration and GA induction yet our measurements were obtained 20 min after EA and 15 min after GA induction, when pressure comparability to baseline had been ensured.

Venodilatation has been reported to occur during surgery, particularly amongst the more senior patients, as a humoral response to vasoactive substances released at the wound site during operation (35, 36). In its presence, the relative disproportional exertion of stretch on the intima exceeds its viscoelastic capabilities, impairing its integrity, and exposing subendothelial thrombogenic tissues such as collagen directly to the coagulation cascades of the venous circulation (35, 36). In our study, those undergoing elective abdominal surgery under GA had a 12% increase in the (median) popliteal vein diameter after GA induction and a 6.3% increase at surgery. Due to overlapping 95% CIs, these changes lacked the power of significance. Amongst those receiving EA/GA, similar diameter changes were found after EA, GA induction and at surgery, again missing significance. The young age of patients and the relatively brief operative time may have limited the magnitude of venodilatation in our study.

The venous flow attenuation in patients undergoing surgery under GA is associated with coagulation alterations generating a procoagulant milieu associated to a high thromboembolic incidence. GA for major orthopedic surgery was reported to reduce platelet-mediated hemostasis time by 39±8.6%, clotting time by 21±3% and collagen-induced thrombus formation (10.3±5.9%) (37). By comparison none of these factors was altered significantly under EA. Plasminogen activator inhibitor-1 plasma levels in patients undergoing elective lower extremity reconstruction under GA increased by 50% at 24 hours and returned to baseline at 72 hours in contrast with their counterparts operated under regional anesthesia in whom no change occurred, indicating that GA may significantly inhibit fibrinolysis particularly during the immediate postoperative period (7). The fibrinolytic impairment was causally related to the development of postoperative arterial thrombosis. This is corroborated by reports that in patients receiving GA for total hip replacement, both fibrinolysis and plasminogen activation are associated with an enhanced capacity for activation of factor VIII, contrasting with those under EA (38). These studies (7, 37, 38) indicate that hypercoagulability generated by surgery under GA is prevented by EA implementation. This has been ascribed both to a protective effect that the local anesthetic agents may have on the coagulation system itself or platelet aggregation and to the improved rheologic conditions associated with the sympathetic block of neuraxial anesthesia. It has been proposed that EA abolishes hypercoagulability induced by surgery without affecting physiologic aggregation and coagulation processes (37). This hypothesis is supported by the failure to substantiate a significant impact of EA at clinical relevant concentrations of local anesthetics on aggregation, and the absence of hemostasis-related peroperative bleeding which is so prevalent with anticoagulants.

The flow velocity attenuation in the venous system of patients undergoing elective abdominal surgery under GA, shown by our data in the popliteal vein, reflects a far lower level of flow velocities in the more distal circulation of the limb and highlights the degree of stasis during abdominal surgery. One of the main culprits in Virchow’s triad, venous stasis, disrupts laminar flow and brings platelets into contact with the endothelium, prevents dilution of activated clotting factors by fresh flowing blood, retards the inflow of clotting factor inhibitors, permits the build-up of thrombi and promotes endothelial cell activation (22, 39). In addition, it causes inflammatory cell and platelet activation and aggregation (22, 39, 40).

In the periods of surgery and recovery, venous flow may sustain a critical attenuation particularly in light of enhanced blood viscosity, fibrinolytic shutdown, endothelial/platelet activation and immobility acting in synergy with putative cardiorespiratory protection (30).

When compared to GA, the favourable venous rheology documented in the lower limb during and in the early stages after elective abdominal surgery performed under combined GA and EA highlights the physiology background leading to the lower likelihood of venous thromboembolism reported with the latter. The haemodynamic benefit offered by the combined use of EA and GA may be clinically crucial in preventing venous thromboembolism, particularly when optimal prophylaxis during surgery cannot otherwise be effectively applied.
References


