



Esmolol hypotension maintains tissue perfusion during myomectomy judged by Masimo monitoring of regional cerebral oxygen saturation and pleth variability index

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ABSTRACT

Objectives: To evaluate outcome of elective abdominal myomectomy under esmolol hypotensive anesthesia (HA) compared to normotensive anesthesia (NA).

Methods: Patients were randomly divided into NA Group received NA and HA Group received esmolol (0.5 mg/kg) bolus then infusion (0.05–0.3 mg/kg/min) to maintain mean arterial pressure at 60–70 mmHg till completion of myomectomy. Masimo Radical 7 was used to monitor regional cerebral oxygenation (rSO₂), total hemoglobin (Hb.) and pleth variability index (PVI). Fluid therapy (FT) included initial bolus of 5% human plasma protein followed by intraoperative (IO) Lactated Ringer's (LR) solution. Amount of IO blood loss, blood transfusion and urine output (UOP) were determined. Postoperative (PO) Hb. conc. was measured at laboratory (Lab). **Results:** IO blood pressure was significantly lower, while PVI was significantly higher with significantly lower ΔPVI with HA than NA. Operative time was significantly shorter with significantly less IO blood loss and blood transfusion with HA. Regional cerebral and peripheral tissue oxygen saturations showed non-significant difference between both groups. PO Masimo measured and Lab estimated Hb. was significantly higher with significantly lower ΔHb% in HA than NA group. Masimo measurement was significantly higher with significantly lower ΔHb% than lab estimation in both groups. Patients of NA group received significantly greater amount of LR, but UOP was non-significantly higher than in HA group.

Conclusion: Esmolol HA allowed better control of IO bleeding, blood transfusion and FT. Masimo continuous monitoring of rSO₂ assured preserved cerebral perfusion. Masimo measured PVI could non-invasively monitor tissue perfusion.

1. Introduction

Uterine fibroids are common benign neoplasms [1] that can significantly impact woman's health [2]. Myomectomy is the gold standard uterine-sparing surgery [2] but may be associated with excessive bleeding [3]. Hypotensive anesthesia significantly decreases blood loss with no significant changes in organ functions [4] and significantly reduces transfusion requirements [5].

Esmolol is cardioselective short-acting β blocker [6] that so it is highly effective in prevention and treatment of perioperative tachycardia [7]. Esmolol was administered as intermittent intravenous boluses or continuous infusion [8]. Low dose induces vasodilation thus provide cardiac safety [9] but require continuous monitoring [10].

2. Aim of work

Evaluation of outcome of elective abdominal myomectomy under esmolol hypotensive anesthesia (HA) compared to normotensive anesthesia (NA).

3. Setting

Tertiary referral hospital, KSA.

4. Design

Prospective comparative study.

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5. Methods and materials

The current study was conducted since Jan 2014 until March 2016. The study protocol was approved by the Local Ethical Committee. The study intended to include women assigned for myomectomy. Women with multiple myomas necessitating hysterectomy, suspected or proven gynecological malignancy, history of cardiac, renal, hepatic diseases, and history of endocrinopathy or coagulopathy were excluded from the study. All enrolled women signed a fully informed written consent for study participation. Clinical evaluations entail collection of demographic data including age and body mass index data. All patients underwent routine laboratory investigations including complete blood count.

6. Randomization & grouping

Patients fulfilling the inclusion criteria were randomly allocated into two equal study groups according to the applied anesthetic procedure. Randomization was conducted using sealed envelopes prepared by an assistant blinded about target for each group and envelopes were chosen by patient herself. Studied groups are Group NA, which included patients assigned to receive normotensive anesthesia and Group HA, which included patients, assigned to receive hypotensive anesthesia.

7. Anesthetic procedure

All patients were premedicated by midazolam 0.02 mg/kg; anesthesia was induced using propofol 2 mg/kg, fentanyl 1–2 µg/kg, and rocuronium 0.6 mg/kg. For both groups, balanced anesthesia was continued with sevoflurane, fentanyl and rocuronium adapted to the patient's physiological reaction to surgical stimuli. After intubation of the trachea, the lungs were ventilated with 100% O₂ using a semi-closed circle system. For group HA, esmolol 0.5 mg/kg diluted in 10 ml of 0.9% normal saline was given as an intravenous bolus followed by esmolol (Esmolol hydrochloride 100 mg/10 ml, Baxter Healthcare Corporation, Deerfield, USA) infusion at rate of 0.05–0.3 mg/kg/min to maintain MAP of 60–70 mmHg until myomectomy was completed. Then, esmolol infusion was stopped to allow restoration of blood pressure so that perfect hemostasis could be achieved. For both groups, ventilation was controlled with a tidal volume of 6–8 ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide (ETCO₂) of 30–35 mmHg. Patients were continuously monitored for electrocardiogram, non-invasive arterial blood pressure (SBP, DBP and MAP), heart rate (HR) and temperature.

The O3 Rad sensor was applied to patient's forehead for continuous monitoring of regional cerebral oxygen saturation (rSO₂). Also O3 monitoring provides ΔSpO_2 defined as the difference between forehead and finger O₂ saturation calculated as SpO₂ minus rSO₂. The sensors were connected to O3 MOC-9 module; the module was connected to one of the Root of MOC-9 ports. Masimo Radical 7 finger pulse oximeter device was equipped with a software ver. 7.8.0.1 (Masimo Corp., Irvine, CA, USA) for continuous non-invasive measurement of total hemoglobin (SpHb), SpO₂, perfusion index (PI) which is the ratio of non-pulsatile to pulsatile blood flow through the peripheral capillary bed [11]. Pleth variability index (PVI) which is an automatic measure of the dynamic change in PI that occurs during the respiratory cycle and equals PI (maximum-minimum) divided by PI maximum; PVI helps to predict fluid responsiveness [12]. ΔPVI was calculated as PVI measured at 30-min, 60-min and immediate postoperative (PO) minus baseline PVI.

8. Fluid therapy targets and policies

Both groups received an initial bolus of human plasma protein (5%; Octapharma, Octapharma AG, Switzerland) in a dose of 5 ml/kg over 15–20 min and Lactated Ringer's (LR) solution in a dose of 5 ml/kg/h

throughout operative time. Intraoperative supplemental fluid therapy consisted of additional blouses of LR according to the target of each study group. The target for group HA to maintain MAP in range of 60–70 mmHg and mean arterial blood pressure (MAP) \geq 75 mmHg in group NA around the post-induction MAP so as to get urine output (UOP) $>$ 0.5 ml/kg/h for both groups.

9. Evaluated parameters

1. IO blood loss was calculated as the sum of the amount of blood collected in the suction canister and the calculated net weight of gauze swabs.
2. At end of surgery, blood sample was obtained for immediate PO estimation of hemoglobin concentration. In addition, hemoglobin concentration measured by Masimo was recorded. Hemoglobin deficit for both estimation modalities was calculated versus the preoperative concentration.
3. The frequency of the need and amount of intra and postoperative blood transfusion. Blood loss of \geq 20% of patient's estimated blood volume was replaced by blood transfusion in 1:1 ratio.
4. Calculated amount of Urine output (UOP).

10. Statistical analysis

Sample size was calculated using the standard nomogram proposed by Kraemer & Thiemann [13] and a sample size of \geq 40 patients per group was determined to be sufficient to detect a difference at the 5% significance level and give the trial 80% power [14]. Sample size and power were re-calculated and assured using Power and Sample Size Calculation Software program provided by Department of Biostatistics, Vanderbilt University. Obtained data were presented as mean \pm SD, ranges, numbers and ratios. Results were analyzed using Student *t*-test and Chi-square test (*X*² test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. *P* value $<$ 0.05 was considered statistically significant.

11. Results

The study included 86 patients with mean age of 34.9 ± 7 ; range: 24–44 years and mean BMI 29.6 ± 2.5 ; range: 23.4–37.2 kg/m² with non-significant (*p* $>$ 0.05) difference between both groups. Intraoperative (IO) blood pressure and heart rate measures were significantly lower in patients of group HA compared to patients of group NA. Details of IO hemodynamic findings are shown in Table 1.

Despite of induced hypotension in group HA, arterial blood oxygenation was non-significantly (*p* $>$ 0.05) lower compared to patients who received normotensive anesthesia throughout duration of surgery. Details of regional cerebral and peripheral arterial blood oxygen saturation data are shown in Table 2.

Intraoperative PVI measurements were significantly lower compared to baseline PVI measurements for both groups. PVI was significantly higher with significantly lower ΔPVI in group HA compared to group NA. Immediate PO PVI was non-significantly higher, but ΔPVI was significantly lower with HA than with NA. Details of PVI measurement are shown in Table 3.

Hypotensive anesthesia was associated with significantly lower IO blood loss with and significantly shorter operative time than NA. Masimo measured Hb. Conc. was significantly higher than laboratory estimated Hb. Conc. in both groups. At end of surgery Masimo and laboratory estimated Hb. conc. was significantly lower than preoperative measures with significantly lower measures but significantly higher $\Delta\text{Hb}\%$ in NA group than in group HA. Patients of group NA received significantly greater amount intraoperative LR solution compared to patients of group HA. Details of operative findings are showed in Table 4

Table 1
Patients' hemodynamic data.

Group Data		Group NA (n = 43)	Group HA (n = 43)	P value
SBP (mmHg)	Baseline	119.1 ± 4.6	117.8 ± 5.9	NS
	Post-induction	112.5 ± 7.4	86.5 ± 4.2	0.001
	30-min	111 ± 9.2	83.2 ± 6.5	0.001
	60-min	111.8 ± 11.2	76.4 ± 6.6	0.001
	Immediate PO	110.7 ± 11.9	104 ± 13.8	0.019
DBP (mmHg)	Baseline	74.2 ± 2.8	73 ± 3.6	NS
	Post-induction	69.2 ± 2.6	60.6 ± 1.4	0.001
	30-min	66.1 ± 2.7	59.6 ± 2.6	0.001
	60-min	64.4 ± 2.9	61.4 ± 2.2	0.001
	Immediate PO	65.1 ± 2.7	63.8 ± 3.1	0.037
MAP (mmHg)	Baseline	89.1 ± 2.7	87.9 ± 3.3	NS
	Post-induction	83.7 ± 3.2	69.2 ± 1.4	0.001
	30-min	81.1 ± 3.6	67.5 ± 2.9	0.001
	60-min	80.2 ± 3.8	66.4 ± 2.4	0.001
	Immediate PO	80.3 ± 4.5	77.1 ± 5.2	0.001
HR (beat/min)	Baseline	82.4 ± 3.1	81.1 ± 4	NS
	Post-induction	76.4 ± 4.3	72.4 ± 4.7	0.015
	30-min	73.5 ± 4.8	69.7 ± 3.2	0.010
	60-min	71.7 ± 3.4	66.3 ± 2.9	0.023
	Immediate PO	72.4 ± 3	70.4 ± 3.9	0.025

Data are presented as mean ± SD; Group NA: received normotensive anesthesia; Group HA: received hypotensive anesthesia; SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure; HR: Heart rate; PO: Postoperative; NS: Non significant difference; p < 0.05: significant difference

Table 2
Regional cerebral and peripheral arterial blood oxygen saturation in patients of both groups.

Group time		Group NA (n = 43)	Group HA (n = 43)	P value
Baseline	SpO ₂	99.1 ± 0.5	99 ± 0.6	NS
	rSO ₂ %	67.8 ± 7.8	68 ± 7.3	NS
	ΔSpO ₂	31.3 ± 7.6	31 ± 5.3	NS
30-min	SpO ₂	98.9 ± 1	98.7 ± 0.8	NS
	rSO ₂ %	67.3 ± 7.9	68.4 ± 8.9	NS
	ΔSpO ₂	31.6 ± 8.4	30.3 ± 6.3	NS
60-min	SpO ₂	98.8 ± 0.8	98.6 ± 1	NS
	rSO ₂ %	67.4 ± 8.2	67.9 ± 7.1	NS
	ΔSpO ₂	31.4 ± 9.2	30.7 ± 4.2	NS
Immediate PO	SpO ₂	98.7 ± 1	98.5 ± 0.9	NS
	rSO ₂ %	67.6 ± 9.7	68.7 ± 8.9	NS
	ΔSpO ₂	31.1 ± 10.2	29.7 ± 8.7	NS

Data are presented as mean ± SD; Group NA: received normotensive anesthesia; Group HA: received hypotensive anesthesia; PO: Postoperative; SpO₂: Peripheral arterial blood oxygen saturation; rSO₂: regional cerebral oxygen saturation; ΔSpO₂: difference between peripheral and regional cerebral oxygen saturation; P value: P value of significance of difference between both groups; NS: Non-significant difference

12. Discussion

The current study relied on an intraoperative (IO) bolus of human plasma protein as colloid fluid therapy (FT) to minimize the amount of infused fluid, thus allowing induction of controlled hypotension without compromising tissue perfusion. Additional FT was provided as Lactated Ringer's (LR) solution; hypotensive anesthesia (HA) allowed significant reduction of amount of LR infused compared to normotensive anesthesia (NA). The applied policy allowed sparing of the recently [15–17] reported variability of response to crystalloid FT alone during major abdominal surgeries.

In support of efficacy of the applied policy for HA in maintaining tissue perfusion, the IO changes of PVI (ΔPVI), a measure of dynamic

Table 3
PVI measurements recorded in patients of both groups.

Group Time		Group NA (n = 43)	Group HA (n = 43)	P value
Baseline		15.77 ± 1.67	15.4 ± 1	NS
30-min	Mean	11.77 ± 2.35*	12.3 ± 1*	NS
	ΔPVI	3.73 ± 1.6	2.86 ± 1.12	0.005
60-min	Mean	11.4 ± 2.56*	12.5 ± 1.1*	0.011
	ΔPVI	4.09 ± 2.08	2.66 ± 1.1	0.001
Immediate PO	Mean	11.76 ± 1.6*	12.07 ± 1.36*	NS
	ΔPVI	3.74 ± 1.54	3.11 ± 1.33	0.043

Data are presented as mean ± SD; Group NA: received normotensive anesthesia; Group HA: received hypotensive anesthesia; PO: Postoperative; ΔPVI: change of Pleth variability index; *: indicates significant difference versus preoperative measurement; P value: P value of significance of difference between both groups; NS: Non-significant difference; p < 0.05: significant difference

change in perfusion index, compared to preoperative PVI were significantly lower till immediate postoperative (PO) with HA than with NA.

Evaluation of tissue perfusion depending on ΔPVI changes illustrated its efficacy for non-invasive patients' monitoring during anesthesia especially HA that required restriction of FT to maintain low blood pressure. This assumption supported that reported by Baker et al. [18] who found fluid responsiveness was associated with a change in PVI, but not a change in heart rate or central venous pressure and documented that this association between Δ PVI and fluid responsiveness may be a surrogate marker of improved cardiac output following a fluid bolus. Also, Lu et al. [19] showed that strong correlations exist among PVI, pulse pressure and systolic pressure variations in the evaluation of volemia, but PVI can serve as a useful, noninvasive indicator of continuous central extracellular fluid volume for patients not requiring invasive hemodynamic monitoring. Yu et al. [20] also documented that PVI-based goal-directed fluid management can reduce the amount of IO fluid, especially the crystalloid. Moreover, Lu et al. [21] documented that PVI is a new continuous, noninvasive and functional hemodynamic parameter that has the same accuracy as invasively monitored stroke volume variation.

Moreover, the reported non-significant difference in regional cerebral oxygen saturation (rSO₂) and peripheral tissue oxygen saturation (SpO₂) assures both the efficacy of applied FT regimen to maintain tissue perfusion despite of induced hypotension and the accuracy of rSO₂ for monitoring cerebral perfusion. The obtained results go in hand with Rhondali et al. [22] who assessed the impact of sevoflurane anesthesia-induced hypotension on brain perfusion in children younger than 6 months and found cerebral blood flow velocities or rSO₂ reflects a good cerebral perfusion when MAP is > 45 mmHg.

The current study reported significantly lower amount of IO bleeding concomitant with reduced transfusion requirement and significantly lower hemoglobin deficit in HA patients compared to NA patients. This illustrates the beneficial effect of induced hypotension on IO bleeding and its sequelae and goes in hand with that previously reported concerning applicability of HA during various surgeries associated with excessive bleeding [5,23,24].

Unfortunately, Masimo over-estimated Hb. Conc. with significantly higher concentration compared to laboratory measurements and thus, calculated Hb deficit versus preoperative measurements were lower with Masimo. These findings indicated the unreliability of Masimo hemoglobin measurement and go in hand with Khalafallah et al. [25] who reported that SpHb may enable prompt routine preoperative anemia management, but its precision was lower than expected and Galvagno et al. [26] also found noninvasive SpHb monitoring did not enhance the ability to predict the need for blood transfusion. Recently, Riess & Pagel [27] observed a lack of precision with noninvasive Hb

Table 4
Intraoperative data of both groups.

Group Data			Group NA (n = 43)	Group HA (n = 43)	P value
Operative time (min)			109.8 ± 13.9	103.6 ± 11	0.026
Operative blood loss (ml)	Strata	< 500	9 (20.9%)	17 (39.5%)	0.037
		500–1000	27 (62.8%)	21 (48.8%)	
		> 1000	7 (16.3%)	5 (11.6%)	
		Mean amount	857.7 ± 290	725 ± 326	
Hb. Conc.	Preoperative	Laboratory measurement	10.15 ± 1.37	9.99 ± 1.08	NS
		Masimo measurement	10.82 ± 1.69 [†]	10.63 ± 1.44 [†]	NS
	At end of surgery	Laboratory measurement	Conc. 8.86 ± 0.69 ^{*†}	9.1 ± 0.35 ^{*†}	0.039
			ΔHb% 1.26 ± 0.87	0.92 ± 0.66	0.031
		Masimo measurement	Conc. 9.28 ± 0.84 [*]	9.63 ± 0.71 [*]	0.013
			ΔHb% 1.29 ± 1.02	0.89 ± 0.78	0.043
Blood transfusion data	Frequency	Yes	15 (34.9%)	7 (16.3%)	0.041
		No	28 (65.1%)	36 (83.7%)	
	Number of transfused units	One	10 (23.3%)	5 (11.6%)	0.023
Two		5 (11.6%)	2 (4.7%)		
Fluid therapy	Initial fluid	Colloid	258.3 ± 22.8	256.4 ± 19.4	NS
		Crystalloid	430.6 ± 38	427.3 ± 32.4	NS
	Additional LR fluid	946 ± 267.7	658.2 ± 215.4	0.001	
Intraoperative UOP (ml/kg/hr)	Total received fluid	1462.8 ± 277	1170 ± 228	0.001	
		1.06 ± 0.4	0.94 ± 0.3	NS	

Data are presented as mean ± SD & numbers; percentages are in parenthesis; Group NA: received normotensive anesthesia; Group HA: received hypotensive anesthesia; Hb. Conc.: Hemoglobin concentration; ΔHb%: change of Hb. Conc. than preoperative conc.; UOP: Urine output; LR: Lactate Ringer's solution; ^{*}: indicates significant difference versus preoperative measurement; [†]: indicates significant difference versus laboratory estimated Hb. Conc.; P value: P value of significance of difference between both groups; NS: Non-significant difference; p < 0.05: significant difference

measurement, especially after cardiopulmonary bypass. Also, in trauma patients, Bridges & Hatzfeld [28] found continuous SpHb is not precise enough to serve as sole transfusion trigger and Yang et al. [29] documented that SpHb added no benefit over conventional oximetry to predict urgent packed RBC transfusion for trauma patients.

However, despite of the over-estimated Hb. Conc. using Masimo than laboratory estimation, non-invasive Hb. monitoring during surgery spared the need for repeated IO laboratory estimations and could allow blood transfusion whenever required. In line with such ability, Sümmig et al. [30] found the noninvasive Hb measurement is a reasonable first-line approach for pre-donation Hb screening of blood donors but a second method should be available to retest those with Hb values below the cutoffs. Kim et al. [31] also found continuous Hb monitoring might help to determine the appropriate time to perform an invasive Hb measurement in patients who undergo double-jaw surgery. Moreover, Awada et al. [32] found adding SpHb monitoring to standard of blood management care resulted in decreased blood utilization in high blood loss neurosurgery, while facilitating earlier transfusions.

13. Conclusion

Esmolol HA allowed better control of IO bleeding, blood transfusion and FT. Masimo continuous monitoring of rSO₂ assured preserved cerebral perfusion. Masimo measured PVI could non-invasively monitor tissue perfusion.

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Conflict of interest

None.

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