The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 6745- 6753

Comparison Study between Three Analgesic Techniques in Ischemic Heart Disease Patients Undergoing Hip Replacement Surgeries

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ABSTRACT

Background: Unmanaged perioperative pain may trigger the sympathetic nervous system, the surgical stress response, and the coagulation cascade, all of which may increase the risk of cardiac morbidity. Myocardial oxygen demand can rise due to increased sympathetic nervous system activity via raising heart rate, arterial blood pressure, and contractility. Additionally, sympathetic activity may increase perioperative hypercoagulability, which might lead to coronary thrombosis or vasospasm and decrease the amount of oxygen delivered to the myocardium.

Objective: To compare the effect of three analgesic techniques used during hip arthroplastic surgery for patients who are at risk for, or had, ischemic heart disease as regards hemodynamic stability, incidence of ischemia, pain control and incidence of complications.

Patients and Methods: This study was carried out in Al-Azhar University Hospital Assiut and Aswan University Hospital in period from March 2020 to March 2022, following written informed agreement and Ethics Committee permission, 60 adult patients with ASA III and IV had hip arthroplasty and were enrolled in the study.

Results: Continuous epidural analgesia attenuated NT-proBNP release in patients undergoing hip arthroplasty. More likely, the addition of local anesthetic bupivacaine to fentanyl epidurally had enhanced this effect. Increased left ventricular wall stress secondary to transitory myocardial ischemia and short bouts of myocardial dysfunction may have contributed to the considerably higher plasma BNP levels in individuals who received IV controlled analgesia.

Conclusion: Epidural analgesia concomitant with general anesthesia by opioids with local anesthetics is a good choice for hip arthroplasty in ischemic heart patients that it is accompanied with less postoperative complications, more stable hemodynamics and less neuroendocrinal stress response. Also, NT-proBNP is a marker of choice for detecting subclinical myocardial ischemia during perioperative periods.

Keywords: Analgesic techniques; Ischemic heart disease; Hip replacement surgeries.

INTRODUCTION

The perioperative phase after major surgery is stressful for the cardiovascular system. Stress causes an increase in cardiac output, which may be readily tolerated by healthy people but has the potential to cause significant morbidity and death in people with heart disease[(1)].

The mortality rate in a group without surgery, adjusted for age and risk, is four times higher on the first day following operation. Cardiovascular injury is the primary cause of more than 50% of these fatalities [(2)]. Stable angina or myocardial ischemia, myocardial infarction (MI), dysrhythmias, and congestive heart failure (CHF) are referred to as these insults. The urgency, size, and level of the surgery, as well as the patient's level of hemodynamic stress, are all connected to the chance of developing a perioperative cardiac event[(3)].

Matching the cardiac reserve to the blood flow demands imposed by surgical stress and the underlying illness condition is the foundation of preoperative preparation for the cardiac patient. Any organic heart illness or coronary artery disease that might put myocardial tissue at risk of ischemia when the demand for cardiac output rises requires functional assessment as part of the evaluation[(4)].

For patients to receive the best postoperative care, effective pain management is crucial. However, patients continue to endure significant pain following surgery despite breakthroughs in our understanding of the biology of pain, the pharmacology of analgesics, and the development of more effective strategies for pain relief[(5)].

A catheter is inserted into the epidural space during epidural anesthesia, a kind of regional anesthesia. By preventing the transmission of pain signals through nerves in or close to the spinal cord, the injection can result in both loss of feeling (anesthesia) and lack of pain (analgesia)[(6)].

The pathobiology and prognosis of perioperative myocardial ischemia are better understood because of cardiac biomarkers[(7)]. In individuals with or at high risk for coronary artery disease, perioperative myocardial ischemia is the single most significant predictor of poor cardiac outcome, which is defined as myocardial infarction, unstable angina, and sudden death[(8)].

BNP is a sensitive and precise predictor of first cardiovascular event and mortality in the general population as well as left ventricular systolic dysfunction. Pro-BNP should be used for independent perioperative prognosis in cardiac patients having non-cardiac surgery, according to the most recent recommendations [(9)]. The use

Received: 19/03/2023
Accepted: 16/05/2023

of cardiac biomarkers like troponin and brain natriuretic peptide by measuring its levels in the perioperative periods had given a very sharp indicators of perioperative cardiac insults[10].

The aim of this work was to compare the effect of three analgesic techniques used during hip arthroplastic surgery for patients who are at risk for, or had, ischemic heart disease as regards hemodynamic stability, incidence of ischemia, pain control and incidence of complications.

PATIENTS AND METHODS

This study was carried out in Al-Azhar University Hospital Assiut and Aswan University Hospital in period from March 2020 to March 2022. 60 adult patients with ASA III and IV had hip arthroplasty and were enrolled in the study.

Patients who had documented compensated heart failure due to coronary artery disease (CAD) were included. Existence of CAD was determined by a history of myocardial infarction, typical angina, or atypical angina with a positive stress test, documentation of the disease state was by history. The patient was judged to be at risk for CAD if they had at least two of the following cardiac risk factors[11]: Previous investigations and echocardiography were both included in the research, age >65 years, diabetes mellitus, high blood pressure, current smoking, and serum cholesterol >240 mg/dl. The study's exclusion criteria included severe left ventricular dysfunction (ejection fraction 40%), heart failure caused by conditions other than CAD, symptoms of mitral or aortic valvular disease, liver dysfunction (alanine amino transferase, aspartate amino transferase > 40 U/L), renal insufficiency (S. creatinine > 2 mg/dl), known drug allergies, and contraindications to epidural puncture. Abnormal blood coagulation tests (international normalized ratio > 1.6, platelet count < 100.000 cmm)[12], pulmonary thromboembolic insults during the study period and finally patients who refused any of the techniques. Using the closed-envelope method, patients were allocated into three groups at random, twenty patients each: Group I (GA group) received general anesthesia followed by IV controlled analgesia (continuous, precalculated parenteral analgesics given by syringe infusion pump), Group II (GEO group) received combined general anesthesia with continuous lumbar epidural opioid analgesia, and Group III (GEOL group), received combined general anesthesia with continuous lumbar epidural opioid analgesia with local anesthetic.

All patients had a regular clinical evaluation prior to the trial, which comprised a detailed medical history, a comprehensive physical examination, and laboratory testing, which included: complete blood picture, coagulation profile, renal function tests (blood urea, serum creatinine), liver function tests (alanine transaminase, aspartate transaminase), chest radiography, 12-lead ECG, and transthoracic echocardiographic examination (ECHO) were all used to assess serum electrolytes (Na, K, Ca) and arterial blood gases.

Lactated Ringer's solution (5 ml/kg) was used to hydrate all patients before to surgery. On arrival in the operation room and prior to induction of general anesthesia for patients in groups II and III, a lumbar epidural catheter was placed at the level of L4-L5 utilising a midline approach and loss of resistance method to air.

For all groups, tracheal intubation was performed with sleeping dosages of propofol (1 mg/kg), fentanyl (1 g/kg), and atracurium (0.5 mg/kg). Following anesthesia induction, a central venous line was inserted through the right internal jugular vein. A urinary catheter was introduced to monitor urine output, and an arterial line was implanted to monitor invasive blood pressure.

In all groups, maintenance of anesthesia was carried out by using isoflurane 1.2% in 100% oxygen and additional bolus injections of atracurium 0.15 mg/kg was given on need guided by nerve stimulator. Ventilation was mechanically controlled by VC - CMV.

ABO matched whole blood units were prepared with colloid and crystalloid fluids to maintain the patients hemoglobin level ≥ 10 g/dl during and after the operation.

Intraoperative analgesia in group I was achieved with continuous IV infusion of fentanyl (1 µ/kg/h, fentanyl, Hameln pharmaceutical, Germany, 50 ug/ml) by syringe infusion pump (Injectomat Agilia; Fresenius Kabi, India), while in group II was achieved with initial lumbar epidural bolus injection of 100 µ fentanyl in 10 ml saline followed by continuous epidural infusion of 50 µ/h fentanyl at rate 5 ml/h by syringe infusion pump. In group III, initial lumbar epidural bolus of 10 ml of saline was injected containing 12.5 mg bupivacaine 0.5% (Sunnypivacaine) and 50µ fentanyl mixture followed by continuous epidural infusion of 5µ fentanyl and 1.25 mg bupivacaine/ml mixture at rate 5 ml/h by syringe infusion pump.

Doses for anesthetics were titrated to maintain the MABP 20% below the baseline values in all groups. All patients were sent to the ICU after the procedure and stayed there for at least 48 hours.

Postoperative analgesia: Patients in group I (GA group) received an IV bolus injection of morphine 0.1 mg/kg alone or combined with IV paracetamol 1 gm immediately after admission until a clear decrease of pain reached to get visual analogue scale (VAS) < 4 at rest. After that, the patients were connected to a syringe infusion pump that delivered a continuous intravenous morphine infusion at a rate of 0.02 mg/kg/h for 48 hs postoperatively. Patients in Group II (GEO group) were continued on the fentanyl infusion of 5µg/ml at a rate of 0.1 ml/kg/h via the epidural catheter for 48 hs postoperatively. Patients in Group III (GEOL group) were continued on the mixture of 1.25 mg/ml bupivacaine and 2 µg/ml fentanyl at a rate of 0.1 ml/kg/h via the epidural catheter for 48 hs postoperatively.

Ethical approval:

The Ethics Committee of Al-Azhar University Faculty of Medicine granted the study approval. All participants signed an informing consent after a thorough explanation of the goals of the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

The SPSS computer programme from IBM V. 22 was used for the statistical analysis. All data were presented as means and standard deviations (SD) as well as counts (percent). Then appropriate statistical analyses were applied. It was considered statistically significant at $p \leq 0.05$.

While descriptive statistics for qualitatively scattered data were calculated as number and percentage, they were calculated for quantitative normally distributed data as the minimum and maximum of the range, mean, and SD.

RESULTS

There was no statistically significant difference between groups regarding age, weight, and gender (Table 1).

Table (1): Comparison between the three studied groups regarding the demographic data

No.	**Age (years)**	**Weight (kg)**	**Gender**
Group I			
Min	66	45	M = 12
Max	80	119	F = 8
Mean	71.55	82.85	
S.D.	4.94	13.78	
Group II			
Min	65	50	M = 11
Max	80	122	F = 9
Mean	73.55	76.8	
S.D.	5.08	13.47	
Group III			
Min	65	60	M = 12
Max	80	105	F = 8
Mean	71.95	76.45	
S.D.	5.27	10.34	
P1	**0.107**	**0.084**	**0.749**
P2	**0.403**	**0.052**	**1.00**
P3	**0.167**	**0.464**	**0.749**

P1 = comparison between group I and II,
P2= comparison between group I and III
P3 = comparison between group II and III

There was no statistically significant difference between groups regarding cardiac risk factors (Table 2).

Table (2): Comparison between the three studied groups regarding cardiac risk factors.

	Cardiac risk factors						**p**
	GI		**GII**		**GII**		
	No.	%	No.	%	No.	%	
Compensated HF	3	15.0	2	10.0	3	15.0	0.231
Previous MI	4	20.0	3	15.0	5	25.0	0.365
Typical angina	5	25.0	6	30.0	5	25.0	0.421
Atypical angina	6	30.0	5	25.0	5	25.0	0.311
HTN	15	75.0	13	65.0	14	70.0	0.285
Diabetes mellitus	10	50.0	10	50.0	12	60.0	0.415
Smoking	11	55.0	9	45.0	10	50.0	0.355
Hyper-cholesterolemia	8	40.0	7	35.0	9	45.0	0.254

There was statistically significant decrease in heart rate in group I after induction and a statistically significant increase in heart rate after ICU admission (P= 0.0039, 0.0047 respectively). There was statistically significant decrease in heart rate in group II after induction (P= 0.0025). There was statistically significant decrease in heart rate in group III after induction and 15 min after induction (P= 0.0413, 0.0008 respectively).

When comparing the three studied groups, the heart rate in group III was statistically significantly lower than group I and II 15 min after induction, although, the heart rate in group I was statistically significantly higher than group II and III at ICU admission and 1 hr after ICU admission. In the present study, there were no significant differences between all studied groups as regards ECG ischemic changes during the perioperative periods (Table 3).

These results reflect efficacy of the three techniques to block pain pathway that activate sympathetic afferent nerves with subsequent extreme increase in heart rate, inotropy and blood pressure that lead to increase indices of myocardial demand and result in myocardial ischemia.

Table (3): Comparison between the three studied groups regarding the HR (Beat/min)

No.	Preoperative	After induction	After 15 min.	After 30 min.	After 45 min.	After 60 min.	After 75 min.	After 90 min.	After 105 min.	After 120 min.	ICU	After 1 hr	After 2 hr	After 3 hr	After 4 hr	After 5 hr
Group I																
Mean	67.95	59.3	66.5912	67.9	66.05	66.7	63.85	66.6	65.75	63.8	74.9	67.6	65.8	65.5	67.05	63.95
S.D.	9.76	9.75	8.51	12.93	9.41	8.71	8.59	10.40	9.46	10.94	5.82	11.47	10.19	11.03	9.13	8.81
Group II																
Mean	63.3	55.185	62.342	62.45	63.55	63.05	60.5	63.65	66.65	63.55	62.7	62	61.65	65.25	62.5	66.55
S.D.	9.10	8.10	8.63	9.93	8.52	13.14	11.46	10.17	11.32	12.43	10.90	9.09	9.72	10.22	9.94	7.86
Group III																
Mean	63.20	58.14	54.15	63.30	64.80	61.65	61.00	62.10	61.75	62.65	59.75	61.70	62.70	63.25	62.50	62.95
S.D.	9.33	8.59	7.53	12.17	11.56	10.98	10.37	10.99	8.61	11.06	11.06	6.20	10.84	9.53	9.60	11.26
P1	**0.064**	**0.077**	**0.063**	**0.072**	**0.192**	**0.153**	**0.151**	**0.185**	**0.393**	**0.473**	**<0.001***	**0.048***	**0.098**	**0.471**	**0.070**	**0.166**
P2	**0.062**	**0.346**	**<0.001***	**0.127**	**0.355**	**0.058**	**0.175**	**0.096**	**0.085**	**0.371**	**<0.001***	**0.025***	**0.179**	**0.247**	**0.066**	**0.378**
P3	**0.486**	**0.135**	**0.001***	**0.405**	**0.350**	**0.358**	**0.443**	**0.323**	**0.066**	**0.405**	**0.200**	**0.452**	**0.374**	**0.263**	**0.500**	**0.124**

P1 = comparison between group I and II, P2= comparison between group I and III
P3 = comparison between group II and III**;** ***: Significant**

Table (3 Cont.): Comparison between the three studied groups regarding the HR (Beat/min)

No.	After 6 hr	After 9 hr	After 12 hr	After 15 hr	After 18 hr	After 21 hr	After 24 hr	After 27 hr	After 30 hr	After 33 hr	After 36 hr	After 39 hr	After 42 hr	After 45 hr	After 48 hr
Group I															
Mean	66.7	65.25	64.6	64.2	66.4	64.3	66	64.6	67.9	66.7	63.35	64	64.5	64.1	63.6
S.D.	10.06	11.02	9.58	10.07	12.05	11.79	8.52	9.68	8.91	8.81	9.07	8.50	9.84	9.55	8.65
Group II															
Mean	64.85	62.75	64.2	66	64.65	60.3	62.95	62.7	67.3	63.05	64.9	67.6	63.85	62.8	64.55
S.D.	8.91	10.70	11.31	8.37	11.32	9.75	10.44	8.77	7.82	8.48	8.19	8.92	9.56	9.79	11.00
Group III															
Mean	62.20	61.90	63.40	62.50	62.70	64.20	64.40	65.00	64.60	66.40	65.25	66.30	62.10	65.45	67.75
S.D.	8.84	9.11	9.94	7.90	8.55	11.19	10.23	8.30	9.65	8.95	10.81	7.95	8.11	8.69	8.22
P1	0.271	0.236	0.452	0.271	0.319	0.125	0.159	0.260	0.411	0.095	0.287	0.100	0.417	0.337	0.382
P2	0.071	0.151	0.350	0.278	0.135	0.489	0.297	0.445	0.134	0.458	0.275	0.191	0.203	0.321	0.064
P3	0.175	0.394	0.407	0.091	0.271	0.124	0.330	0.200	0.169	0.116	0.454	0.315	0.268	0.185	0.152

There was a statistically significant decrease of the MABP in group I after induction and during the operative time. Also, there was a statistically significant decrease of the MABP through all the postoperative ICU time (P< 0.05). In group II; there was a statistically significant decrease of the MABP after induction and during the operative time. Also, there was a statistically significant decrease of the MABP through all the postoperative ICU time (P< 0.05). In group III; there was a statistically significant decrease of the MABP after induction and during the operative time. Also, there was a statistically significant decrease of the MABP through all the postoperative ICU time (P< 0.05). When comparing the three groups, there was no statistically significant difference between the three groups at preoperative values (P>0.05). The MABP in group III was lower than MABP in group II which was lower than MABP in group I. But it was statistically insignificant through all the study time except statistically significant decrease of the MABP in group III 15 min and 30 min after induction than in group I and II and statistically significant increase of the MABP in group I at ICU admission than in group II and III (P<0.05) (Table 4).

Table (4): Comparison between the three studied groups regarding the MABP (mm/Hg)

No.	Pre-operative	After induction	After 15 min.	After 30 min.	After 45 min.	After 60 min.	After 75 min.	After 90 min.	After 105 min.	After 120 min.	ICU	After 1 hr	After 2 hr	After 3 hr	After 4 hr	After 5 hr
Group I																
Mean	97.6	78.05	85.15	87.337	80.2	75.3	78.9	79.95	72.9	73.2	82.89	78.5	76.7	73.95	76.9	76.75
S.D.	13.060	11.161	7.929	8.216	8.800	11.305	10.412	10.763	9.926	11.893	11.077	11.330	11.323	13.885	11.774	9.657
Group II																
Mean	94.75	78.8	85.65	82.857	78.85	75.95	75.3	75.9	77.3	72.65	76.2825	73	73.9	74.3	73.45	73.05
S.D.	12.540	13.045	11.320	12.314	14.203	11.358	12.712	14.371	9.685	10.007	10.507	12.460	12.096	13.503	11.741	14.118
Group III																
Mean	96.5	73.15	71.335	73.8893	75.85	80.25	73.65	76.1	74.8	77.65	74.468	77.4	73.95	76.3	75.35	71.85
S.D.	11.537	14.658	9.325	11.990	13.120	11.781	11.481	11.059	11.312	11.753	8.599	10.669	10.112	11.471	10.434	11.142
P1	**0.243**	**0.423**	**0.436**	**0.092**	**0.360**	**0.429**	**0.167**	**0.160**	**0.082**	**0.438**	**0.030***	**0.076**	**0.227**	**0.468**	**0.180**	**0.170**
P2	**0.390**	**0.121**	**<0.001***	**<0.001***	**0.113**	**0.092**	**0.069**	**0.136**	**0.288**	**0.121**	**0.005***	**0.377**	**0.211**	**0.281**	**0.331**	**0.073**
P3	**0.324**	**0.103**	**<0.001**	**0.013***	**0.246**	**0.124**	**0.335**	**0.480**	**0.229**	**0.078**	**0.277**	**0.119**	**0.494**	**0.308**	**0.296**	**0.384**

P1 = comparison between group I and II, P2= comparison between group I and III

P3 = comparison between group II and III**;** ***: Significant**

Table (4 Cont.): Comparison between the three studied groups regarding the MABP (mm/Hg)

No.	After 6 hr	After 9 hr	After 12 hr	After 15 hr	After 18 hr	After 21 hr	After 24 hr	After 27 hr	After 30 hr	After 33 hr	After 36 hr	After 39 hr	After 42 hr	After 45 hr	After 48 hr
Group I															
Mean	72.75	72.6	71.9	70.5	75.75	74.7	76.8	76.45	72.3	72.6	72.8	71.95	73.8	71.75	71.2
S.D.	11.050	11.028	12.802	11.993	10.997	10.342	11.377	8.575	9.581	11.496	9.540	12.386	10.611	10.543	8.841
Group II															
Mean	76.9	75.5	70.75	72.1	76.5	70.3	71.5	73.3	77.65	72	73.75	71.35	74.85	71.95	73.55
S.D.	11.845	11.353	9.182	12.243	11.119	9.895	11.072	10.766	9.751	9.819	10.809	6.784	9.010	11.119	10.405
Group III															
Mean	71.85	77.3	72.7	73.4	74.45	71.25	72.35	70.6	72.95	75.45	73.95	76.3	71.2	70.5	71.25
S.D.	12.516	9.303	10.868	8.911	13.012	12.985	10.994	9.827	10.081	11.482	9.350	10.327	8.445	7.674	9.765
P1	**0.130**	**0.209**	**0.373**	**0.339**	**0.416**	**0.089**	**0.072**	**0.156**	**0.064**	**0.430**	**0.385**	**0.425**	**0.369**	**0.477**	**0.223**
P2	**0.405**	**0.077**	**0.416**	**0.195**	**0.367**	**0.179**	**0.108**	**0.076**	**0.418**	**0.219**	**0.351**	**0.118**	**0.198**	**0.335**	**0.493**
P3	**0.099**	**0.293**	**0.272**	**0.352**	**0.298**	**0.398**	**0.404**	**0.206**	**0.071**	**0.157**	**0.475**	**0.091**	**0.097**	**0.317**	**0.238**

There was statistically significant decrease of the VAS value through all the follow up period till the patient discharge in relation to the VAS value at the ICU admission in group I (P< 0.05). In group II, there was no statistically significant difference of the VAS value through all the follow up period till the patient discharge in relation to the VAS value at the ICU admission. In group III, there was no statistically significant difference of the VAS value through all the follow up period till the patient discharge in relation to the VAS value at the ICU admission. When comparing the VAS value between the studied groups; At ICU admission, the VAS value was significantly lower in group III than in group II which is lower than group I (P< 0.05). Starting from 4 hs after ICU admission and through all the follow up period till the patient discharge, the VAS value was statistically lower in group III than in group I and II (P< 0.05) (Table 5).

Table (5): Comparison between the three studied groups regarding the VAS value

		VAS												
	No.	ICU	After 4 hr	After 8 hr	After 12 hr	After 16 hr	After 20 hr	After 24 hr	After 28 hr	After 32 hr	After 36 hr	After 40 hr	After 44 hr	After 48 hr
Group I	**Min**	5	2	1	1	2	4	3	1	3	4	1	3	3
	S.D.	1.142	0.918	1.118	1.750	0.988	0.786	0.988	1.281	0.933	0.768	1.277	1.021	0.988
Group II	**Mean**	4.3	3.8	4.3	4.7	4.2	4.6	4.85	4.5	4.8	4.7	4.45	4.25	4.5
	S.D.	0.923	0.795	0.801	0.979	1.240	1.314	0.933	0.889	1.105	0.801	1.276	1.482	1.051
Group III	**Mean**	2.8	1.3	1.05	1.7	1.35	1.55	1.45	1.65	1.65	1.4	1.2	1.4	1.3
	S.D.	0.768	0.470	0.826	0.801	0.813	0.999	0.605	0.813	0.745	0.940	0.696	0.754	0.865
	P1	**<0.001***	**0.324**	**0.085**	**0.430**	**0.878**	**0.655**	**0.999**	**0.354**	**0.867**	**0.708**	**0.888**	**0.073**	**0.627**
	P2	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***
	P3	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***

P1 = comparison between group I and II, P2= comparison between group I and III

P3 = comparison between group II and III**;** ***: Significant**

The total dose of paracetamol in group I ranged from 1-5 gm with a mean value 3±1.12 gm, the total dose of paracetamol in group II ranged from 1-4 gm with a mean value 2.1±0.912 gm and the total dose of paracetamol in group III ranged from 0-2 gm with a mean value 0.95±0.83 gm. When comparing the total dose of paracetamol between the three studied groups, it was statistically lower in group III than in group II, which was statistically lower than in group I starting from the ICU admission and through all the follow up periods till the patient discharge (P1=0.004, P2=0.000, P3=0.000).

When comparing the incidence of complications, the incidence of nausea, vomiting, pruritus and respiratory depression was statistically lower in group III (Table 6).

Table (6): Comparison between the three studied groups regarding incidence of complications

	Complication						P
	GI		GII		GIII		
	No.	%	No.	%	No.	%	
Nausea	11	55.0	6	30.0	2	10.0	**0.009***
Vomiting	9	45.0	5	25.0	2	10.0	**0.043***
Pruritus	7	35.0	2	10.0	1	5.0	**0.024***
Resp. depression	5	25.0	2	10.0	0	--	**0.046***
Hemo-dynamic instability	2	10.0	1	5.0	0	--	**0.349**
Neuro-logical complications	0	--	0	--	0	--	**1**

***: Significant**

-DISCUSSION

The working hypothesis in this thesis was that ongoing perioperative pain control would modify NT-proBNP release, which is said to be the preferred biochemical marker for assessing the acute risk of non-surgical patients with cardiovascular conditions ranging from acute transmural myocardial infarction and heart failure to asymptomatic myocardial ischemia without ST segment elevation[(13)].

The present study included 60 adult patients undergoing hip arthroplastic surgery. Patients were randomly assigned to one of three groups, 20 patients each. Group I (GA group), patients received general anesthesia followed by IV analgesia (continuous, parenteral analgesics given by syringe infusion pump). Group II (GEO group), patients received combined general anesthesia with continuous lumbar epidural opioid analgesia. Group III (GEOL group), patients received combined general anesthesia with continuous lumbar epidural opioid analgesia with local anesthetics.

In all groups, there was a statistically significant reduction in HRs and MABP after induction, mostly related to the vasodilatation effect of the propofol and its negative chronotropic effect on the heart with the action of fentanyl in decreasing heart rate in these ASA III and IV patients suffering from contracted intravascular volumes[(14)]. But there was no statistically significant difference between the three groups regarding the decrease in HR and MABP after induction.

In group III, there was a statistically significant decrease in HR and MABP 15 min. after induction and decrease in MABP 30 min. after induction than in G I and G II. This is mostly due to the sympathetic blocking action of epidural bupivacaine combined with the effect of inhalational anesthesia and propofol (the superiority of epidural anesthesia to completely block the nociceptive pathways in comparison to the IV opioids). This is also stated in **Rigg *et al.*** [(15)] in their study upon the effect of epidural anesthesia in major surgeries**.**

Through all the operation time there was no statistically significant changes in heart rate in each group and between groups. After ICU admission and at 1st hour after ICU admission, there was a statistically significant increase in heart rate in Group I more than in the Group II and III. Also, after ICU admission there was a statistically significant increase in MABP in Group I more than in the Group II and III. This is due to fading of the effect of IV fentanyl compared to the continuous epidural analgesic effect in group II and III and starting action of IV morphine which increases the heart rate by its histamine like action[(16)].

Through all the ICU stay time there was no statistically significant changes in HR among the groups and in between them.

MABP significantly decreased in all the groups but was kept around 20% of the preoperative values, which was done intentionally aiming to control MABP to prevent excessive blood loss. There were no statistically significant changes between the three studied groups.

In fact, the epidural group had a lower mean arterial pressure and the hemodynamic stability was not affected and the mean arterial pressure was kept at adequate ranges to maintain perfect organ perfusion. This is most probably due to limitation of the epidural block to the spinal dermatomes that innervate the surgical field only, preventing the extension of the block to the level that might lead to profound physiological changes, because cardiovascular changes especially arterial blood pressure largely follow a linear dose response curve, with the amount of physiologic change depending on how much the block is present, which is also stated by **Hu *et al.*** [(17)] in their study.

Battista *et al.* [(18)] discovered no effect of epidural plus general anesthesia on heart rate in comparison to the general anesthesia alone**.** Also, **Curatolo *et al.*** [(19)] during the evaluation of the frequency of bradycardia during epidural block, they found no significant effect of epidural block on heart rate during the perioperative periods.

The present study has demonstrated that none of the three anesthetic techniques had any remarkable

depressant effect on respiratory function mainly O_2 saturation during the whole perioperative period and O_2 saturation maintained at appropriate levels in all groups. Although postoperative hypoxemia is frequent, it acts as a marker for individuals who have postoperative pulmonary morbidity and/or is linked to myocardial ischemia.

Following general anesthesia, a reduction in lung expiratory flow and volume is typical. Due to a reduction in diaphragmatic function, these alterations are particularly noticeable in patients following extensive abdominal and thoracic surgeries. Pre-existing lung illness, the length of the surgical incision, morbid obesity, and advanced age are additional risk factors [(20)].

In the present study, despite the superiority of the epidural group in providing adequate analgesia during the perioperative periods more than the balanced general anesthesia group, the three groups did not show any significant reduction in O_2 saturation, which remained at appropriate levels with no incidence of hypoxemic events.

Youssef *et al.*[(21)] found similar results on comparing the effect of epidural analgesia and epidural morphine on morbidity, pain and respiratory complications. The authors explain their results on the basis that the patients were low risk pulmonary patients. The VAS pain scores for the investigated epidural opioids were comparable. These parallels in analgesia may be attributable to widespread practises of combining opioids with epidural local anesthetics and adjusting infusion rates in accordance with a patient's level of discomfort.

In the present study, all the patients in all groups had satisfactory pain score. The epidural analgesia groups of patients had satisfactory and statistically better analgesia at the ICU admission than the IV controlled analgesia group of patients (Group I). These results are reflecting better analgesia provided by comparing opioid parenteral analgesia with epidural analgesia (morphine in the present study). After that; in group III, pain control and satisfaction were statistically significantly better than the other two groups during the whole postoperative period due to the combined effect of epidural local anesthetic with opioids over the epidural opioids alone.

These results could be attributed to the efficacy of epidural anesthesia to completely and provide sufficient and thorough avoidance of both peripheral and central sensitization by effectively blocking afferent nociceptive stimuli and inhibiting efferent sympathetic outflow in response to painful stimuli. This is consistent with the findings of **Frerichs and Janis[(22)]** on preemptive analgesia in foot and ankle surgery.

In line with the findings of the current study, **Block *et al.*[(23)]** reviewed 100 studies in a meta-analysis and found that a better method of controlling postoperative pain is epidural anesthesia. with low VAS measurement than parenteral opioid analgesia during different major surgical procedures (thoracic, abdominal and lower extremity).

In contrast to the current study, **Kostamovaara *et al.*[(24)]**, showed that the addition of ropivacaine 1 mg/ml to epidural fentanyl 10 /ml did not significantly reduce the amount of fentanyl required for pain management following hip replacement surgery. This may be attributed to that these results reported in a small sized trial with different local anesthetic.

As regards postoperative requirement of additional analgesia (IV paracetamol), group III showed statistically significant decrease in total amount of IV paracetamol consumption when compared to group II, which is also statistically lower than group I. These results are reflecting the efficacy of epidural analgesia to provide better and adequate postoperative analgesia than IV controlled analgesia with opioids.

Brodner *et al.*[(25)] agreed to the results of the present study, they demonstrated better pain scores with significant lower rescue analgesia consumption in epidural analgesia treated patients when compared to IV opioids treated patients**.**

In the current study baseline NT-proBNP concentrations were similar in the three groups. This variable showed no statistically significant difference at 90 min from skin incision and at ICU admission. It increased significantly 24 hs and more after 48 hs in the IV analgesia group. Also, it significantly increased 48 hs after ICU admission in epidural fentanyl group while in group III there was no significant change.

After 24 hs from ICU admission, plasma NT-proBNP was higher in group I than in group II and III while after 48 hs from ICU admission the NT-proBNP was higher in group I more than in group II more than in group III.

Numerous studies have supported the association between BNP and the severity of coronary disease in non-surgical patients [(20-24)]. **Sadanandan *et al.*[(26)]** discovered that an increased BNP was linked to greater CAD disease, LAD involvement, and tighter culprit vascular stenosis in individuals with acute coronary syndrome.

Weber *et al.*[(27)], also found during dobutamine stress echocardiography, that BNP was a reliable indicator of ischemia. These investigations revealed that since plasma NT-proBNP concentrations were closely linked to ventricular BNP mRNA expression, myocardial ischemia per se is responsible for the rise in plasma NT-proBNP indicating an enhanced cardiac BNP gene expression in the ischemic left ventricle.

Our study's key finding was that continuous epidural analgesia attenuated NT-proBNP release in patients undergoing hip arthroplasty. More likely, the addition of local anesthetic bupivacaine to fentanyl epidurally had enhanced this effect. Patients who received IV controlled analgesia may have had short periods of myocardial dysfunction and elevated left ventricular wall stress secondary to transitory

myocardial ischemia, which may have contributed to their considerably higher plasma BNP content.

Consequently, this result revealed that continuous epidural analgesia for perioperative pain control in CAD patients promotes anti-ischemic activities through modification of neurohormonal-mediated pathways, which eventually results in reduced and reversible myocardial ischemia, and this was similar to the results of **Nadir *et al.*[28]**.

The fact that using epidural analgesia in the current trial was linked to decreased pain and sympathetic tension, as shown by considerably lower pain levels, corroborated this idea, lower IV analgesia consumption during the postoperative period, slower heart rates, less increase in MABP and less ST-segment changes during the perioperative period and these were similar to data revealed by **Schnabel *et al.*[29]**.

The investigations on the impact of epidural analgesia in surgical and non-surgical CAD patients may provide evidence in support of the findings of the current study. **Olausson *et al.*[30]** discovered that continuous epidural blockade of the upper five thoracic segments with bupivacaine improved the major determinant of myocardial oxygen demand by lowering heart rate without affecting mean arterial pressure or coronary perfusion pressure in non-surgical patients with severe ischemic chest pain refractory to standard anti-anginal therapy.

The link between the significantly elevated NT-proBNP and the insignificant cTnI denoting that NT-proBNP release and cTnI levels didn't parallel each other, proves that an elevation in NT-proBNP is a more general sign of decreased cardiac function secondary to myocardial ischemia than it is a particular sign of structural myocardial damage, and identifying a subgroup of patients that suffering from myocardial ischemia, which if left without aggressive anti-ischemic management may propagate to myocardial damage[31].

Evaluation of postoperative complications revealed that postoperative use of epidural analgesia in group III and II was a safe technique and was associated with fewer complications when compared to parenteral opioid used in group I, nausea (2 versus 6 versus 11 respectively), vomiting (2 versus 5 versus 9 respectively), pruritus (1 versus 2 versus 7 respectively), respiratory depression (0 versus 2 versus 5 respectively) showed by slower respiratory rate in the 3 cases without $SpaO_2$ changes, none of the three groups showed any neurologic complications.

As regards nausea, vomiting and pruritus these results could be attributed to combination of epidural local anesthesia with opioid and the use of epidural opioids alone in low dosages may minimise nausea and vomiting, providing analgesic synergism and improving the general overall outcome when compared with parenteral opioid especially morphine. While parenteral opioids increase the incidence of nausea, vomiting and pruritus[32].

Regarding respiratory depression, it appears that the risk of respiratory depression following epidural injection of opioids both alone and in combination with local anesthetics is dosage dependent. However, delayed respiratory depression very sometimes occurs [33].

On the other hand, application of local anesthetics together with epidural analgesia was not related with any incidence of hemodynamic instability than parenteral opioids group and epidural opioids alone (0 versus 2 versus 1 respectively) with no statistically significant intergroup differences.

In line with the findings of the current study, **Unic-Stojanovic *et al.*[33]** demonstrated that epidural anesthesia is safer with less complication especially if it is continued into the postoperative period than balanced general anesthesia.

In contrast to the present results, **Peyton *et al.*[34]** concluded that, compared to balanced general anesthesia, epidural analgesia did not improve outcomes following major aortic surgery in high-risk patients. But the aortic surgery and level of epidural block were different from the present study.

CONCLUSION

Epidural analgesia concomitant with general anesthesia by opioids with local anesthetics is a good choice for hip arthroplasty in ischemic heart patients that it is accompanied with less postoperative complication, more stable hemodynamics and less neuroendocrinal stress response. Also, NT-proBNP is a marker of choice for detecting subclinical myocardial ischemia during perioperative periods.

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