Introduction

Despite major advances in peri-operative management techniques, Myocardial Infarction (MI) remain the most common cause of postoperative morbidity and mortality in patient undergoing non-cardiac surgery [1]. Patients experiencing MI in the peri-operative period have a hospital mortality of 15%-25% [2-5]. The high mortality rate could be due to difficulty in detecting peri-operative MI because typical Electrocardiographic (ECG) changes and classical clinical symptoms are often absent [6]. As a growing number of elderly patients at risk of cardiac diseases are undergoing surgery, management of such complication will remain a significant clinical and economical challenge in the future.

The diagnosis of MI traditionally relies on rise and fall of cardiac enzymes such as Creatinine Kinase (CK), creatine kinase muscle and brain isoenzyme (CK-MB), Troponin I and T. With evidence of ischemia [clinical symptoms such as chest pain, supportive electrocardiographic changes] [3]. Troponin is more sensitive and specific, and correlate more closely with the amount of cardiac damage that occurs than CK-MB and is the favoured cardiac enzyme for testing. Troponin T has been found to have a higher positive and negative predictive values, sensitivity and specificity than either troponin I or CK-MB [7]. A rise in troponin T is not normally associated with musculoskeletal trauma [7,8]. Troponin levels begin to rise 4-6 h after the onset of symptoms, similar to CK-MB. Peak values occur 18-24 h after the onset of symptoms. Serum troponin persists for 7-14 days due to its slow release and degradation which allows for increased detection time window of cardiac events [9].

However, cardiac ischemia can be difficult to recognize in the post-operative period because of their silent nature and electrocardiograph changes may be hard to detect, often being non-q wave in origin. However, given there is no current consensus about what defines an infraction in the post-operative setting, perhaps all that can be deduced is that an elevation in troponin, for example, might indicate myocardial injury and provide prognostic information [3].

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (an acute phase reactant protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some type of bacteria) in order to activate the complement system via CIQ complex to facilitate their destruction by the phagocytes [10].
CRP is synthesized by the liver in response to factors released by adipocytes [11,12]. It is a member of the pentraxin family of proteins [11]. C-reactive protein was the first Pattern Recognition Receptor (PRR) to be identified [13].

The power of preoperative hs-CRP levels in predicting cardiac events in patients undergoing noncardiac surgery was stated in few reports with conflicting results [14]. The effect of using Lumbar Epidural Anesthesia (LEA) combined with general anesthesia on the acute inflammatory response as well as myocardial injury after major abdomino-pelvic surgery in cancer patients has not been studied before.

The primary end point of this study was to assess the influence of lumbar epidural anesthesia on postoperative inflammatory response and myocardial damage after abdominal cancer surgery.

Methods

After obtaining approval from hospital ethics committee and written informed consent from the patient, we enrolled 60 ischemic patients (identified from the patients history and from the ECG) scheduled for elective major abdominal cancer surgery with one or more of the following risk factors (previous history of MI, diabetes, hypertension, obesity (BMI >25 kg/m²) and/or heavy smoking).

Patients with polymyositis, serum creatinine over 200 mmol/L, platelet count <150x109 L, international normalized ratio >1.1, active neurological disease, cutaneous disorder at the epidural insertion site, and patients with infections or previous laparoscopic procedures in the last 2 weeks were excluded from the study.

All patients were evaluated preoperatively for the assessment of the operative risk by a cardiologist according to Lee index [15]. ECG was recorded and analyzed for the preoperative ischemic changes. Patients pre-operatively were instructed in how to evaluate their own pain using the Visual Analog Scale (V AS) ranging from 0 to 10 (with 0=no pain and 10=the worst pain imaginable) [16]. Five mg oral diazepam was received night before surgery.

On arrival in the operative room, IV line was inserted and before an infusion of lactated ringsers solution was started a venous sample was taken for serum troponin and hs-CRP; then an on line research randomizer (http://www.randomizer.org), patients were randomly allocated into 2 groups; group 1 (G1) who received standard general anesthesia and group 2 (G2) who received standard general anesthesia and epidural anesthesia.

Anesthesia technique

Before induction of anesthesia an epidural catheter was placed at the L2-L3 intervertebral space under local anesthesia with the use of a loss of resistance technique and that was followed by injection of 10 ml (100 mg) lidocaine 1%, 10 ml (25 mg) bupivacaine 0.25% and 5 mg morphine. General anesthesia was induced by fentanyl 1.5 µg/kg, propofol 2-3 mg/kg and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cisatracurium 0.5 mg/kg. Anesthesia was maintained by isoflurane 1-1.5 MAC, fentanyl 0.5 µg/kg and cisatracurium 0.03 mg/kg. Patient's were mechanically ventilated to maintain ETCO₂ between 33-36 mmHg.

Outcome definitions

Hypotension was defined as 15% decrease in systolic blood pressure from base-line. It was treated with IV boluses of ephedrine 0.1 mg/kg and normal saline 5 ml/kg and the same doses were repeated if required. Bradycardia was defined as heart rate less than 40 bpm or as inappropriate slow heart rate despite hypovolemia. It was treated with atropine 1 mg IV. Hypoxia was defined as an oxygen saturation value <90%. At the end of the operation muscle relaxation was reversed by neostigmine 50µg/kg and atropine 10 µg/kg. Patients were extubated and transferred to Post Anesthesia Care Unit (PACU). Post operative analgesia comprised Patient-Controlled Analgesia (PCA) with an initial morphine bolus of 0.1 mg/kg once pain was expressed by the patient or if VAS score ≥ 3, followed by 1 mg boluses with a lockout period of 5 min.

Perioperative monitoring

All patients were monitored for 72 hours post-operatively in the post anesthesia care unit. Patients were monitored and transferred to ward after the V AS <3. The first 24 hours, patients were observed in the surgical ward with continuous ECG monitoring and were transferred to the ICU if there were any complications.

Results

A total of 60 patients were included. Demographic data, clinical characteristics and duration of surgery.

Table 1: Demographic data, clinical characteristics and duration of surgery.

| Variables                  | G1      | G2      | P-value |
|----------------------------|---------|---------|---------|
| Age (years)                | 52.4 ± 10.8 | 54.2 ± 13.4 | NS      |
| Weight (kg)                | 77.4 ± 31.2 | 72.5 ± 9.7  | NS      |
| Height (cm)                | 162.5 ± 6.9 | 164.0 ± 1.47 | NS      |
| Male gender                | 16 (53%) | 17 (57%) | NS      |
| Type of surgery            |         |         |         |
| Open coelctomy             | 11 (36.7%) | 7 (23.3%) | NS      |
| Open cystectomy            | 9 (30%)  | 12 (40%) | NS      |
| Abdomino perineal resection| 10 (33.3%) | 11 (36.7%) | NS      |
| Site of ischemia           |         |         |         |
| Lateral                    | 5 (16.7%) | 4 (13.3%) | NS      |
| Inferior                   | 15 (50%)  | 16 (53.3%) | NS      |
| Anterior                   | 6 (20%)  | 7 (23.3%) | NS      |
| Mixed                      | 4 (13.3%) | 3 (10%)  | NS      |
| Risk factors               |         |         |         |
| 1-Previous history of MI   | 1 (3.3%) | 2 (6.6%) | NS      |
| 2-Heavy smoker             | 7 (23.3%) | 6 (20%)  | NS      |
| 3-DM                       | 9 (30%)  | 8 (26.6%) | NS      |
| 4-Hypertension             | 12 (40%) | 14 (46.6%) | NS      |
| 5-Obesity                  | 5 (16.6%) | 4 (13.3%) | NS      |
| Lee index, Risk of MPCE (%) |         |         |         |
| 2, 2.4 (1.3–3.5)           | 22 (73%) | 21 (70%) | NS      |
| ≥ 3, 5.4 (2.8–7.9)         | 8 (27%)  | 9 (30%)  | NS      |
| Duration of surgery (hours)| 3.15 ± 0.87 | 3.30 ± 1.04 | NS      |

Data are expressed as mean ± SD or number (%). CI, confidence interval; NS, Non significant; MPCE, major perioperative cardiac events.

Table 2: VAS score postoperative at rest.

| VAS | G1      | G2      | P value |
|-----|---------|---------|---------|
| T0  | 4.06 ± 1.76 | 2.13 ± 0.43 | <0.0001 |
| 4h Postoperative | 2.53 ± 0.50 | 2.10 ± 0.30 | <0.0001 |
| 8h Postoperative | 2.43 ± 0.50 | 2.03 ± 0.18 | <0.0001 |
| 12h Postoperative | 3.01 ± 0.99 | 2.00 ± 0.00 | <0.0001 |
| 16h Postoperative | 2.96 ± 0.88 | 2.03 ± 0.41 | <0.0001 |
| 20h Postoperative | 2.80 ± 0.88 | 2.03 ± 0.31 | <0.0001 |
| 24h Postoperative | 2.90 ± 0.99 | 2.00 ± 0.26 | <0.0001 |
| 32h Postoperative | 2.80 ± 0.72 | 2.46 ± 0.73 | NS      |
| 40h Postoperative | 2.66 ± 0.92 | 2.20 ± 0.40 | 0.014    |
| 48h Postoperative | 3.03 ± 0.88 | 2.20 ± 0.48 | <0.0001 |
| 60h Postoperative | 3.46 ± 0.89 | 2.30 ± 0.53 | <0.0001 |
| 72h Postoperative | 3.03 ± 0.66 | 2.36 ± 0.49 | <0.0001 |

Data are expressed as mean ± SD.To, immediate postoperative, NS, Non significant, h, hours.
postoperative care unit: standard monitoring (Non Invasive Blood Pressure (NIBP), oxygen saturation (SO2 %) and ECG), Central Venous Pressure (CVP) was inserted intraoperatively and measured intra- and postoperatively. VAS and post operative consumption of analgesic in the form of PCA morphine was recorded. Twelve-lead ECGs were recorded once a day for 3 days postoperatively. ECGs were assessed by a cardiologist, who was unaware of cTnT values or clinical symptoms and outcome. ECGs were assessed for new persistent Q waves >0.04 second in days 1, 3 postoperatively in G1 but not in G2 compared to baseline value. However, there was no significant difference between G1 and G2 in troponin level all over the study period (Table 4). Five patients in G1 (16.6%) and 2 patients in G2 (6.6%) showed serum troponin T level >0.03 ng/ml. Regarding ECGs changes, 2 patients (6.6%) in G1 (with peak serum troponin level of 0.15 ng/ml and 0.18 ng/ml) and one patient (3.3%) in G2 (with peak serum troponin level of 0.10 ng/ml) showed new ischemic changes postoperatively in the form of depressed ST segment >1 mm. Nausea and vomiting but not itching were significantly less in G2 compared to G1 (Table 5).

Discussion

The present study found that combined general and epidural anesthesia was associated with less myocardial damage in the perioperative period, which was not the case using general anesthesia alone, also the use of LEA with general anesthesia was associated with less pain perception in all post operative time as assessed by VAS and increase in mean time to first request for rescue analgesic compared to general anesthesia alone. Levy et al. suggested that an increased troponin measurement after surgery is an independent predictor of mortality, particularly within the first year [19]. He also suggested that the burden of mortality is higher within the first year after surgery for patients with a postoperative troponin rise.

MI is the most common major peri-operative vascular complication [20]. It is associated with poor prognosis. However, asymptomatic perioperative MI is as strongly associated as symptomatic MI with 30 day mortality. Therefore, routine monitoring of cardiac biomarkers after surgery is essential. The highest risk for death after perioperative MI is in the first 48 hours; regardless of whether the patient experiences ischemic symptoms. This highlights the need to quickly diagnose and intensely monitor and implement treatments for perioperative MI, just as with nonoperative MI [21-23]. Recent studies suggest that a troponin or CK-MB measurement after surgery may independently

| Table 3: C-reactive protein mg/L. |
| Variables | G1 | G2 | P-value |
| CRP0 | 5.06 ± 1.81 | 5.02 ± 1.85 | NS |
| CRP1 | 38.64 ± 13.64 | 26.85 ± 12.60 | P<0.0001 |
| CRP2 | 31.62 ± 10.13 | 29.84 ± 11.52 | P<0.0001 |
| CRP3 | 33.68 ± 12.7 | 28.80 ± 10.39 | P<0.0001 |

Data are expressed as mean ± SD.
P1, significant compared to baseline value; P2, significant between 2 groups; CRP0, CRP preoperative; CRP1, CRP at first day postoperative; CRP2, CRP at 2nd day postoperative; CRP3, CRP at 3rd day postoperative; NS, Non significant.

| Table 4: Serum troponin T level ng/ml. |
| Variables | G1 | G2 | P-value |
| Serum troponin 0 | 0.017 ± 0.005 | 0.018 ± 0.005 | 0.278 |
| Serum troponin 1 | 0.031 ± 0.04 | 0.019 ± 0.012 | P<0.012 |
| Serum troponin 2 | 0.03 ± 0.038 | 0.018 ± 0.010 | P<0.010 |
| Serum troponin 3 | 0.03 ± 0.039 | 0.019 ± 0.012 | P<0.010 |

Data are expressed as mean ± SD.
P1, significant compared to baseline value; P2, significant between 2 groups; Troponin0, Troponin preoperative; Troponin 1, Troponin at first day postoperative; Troponin 2, Troponin at 2nd day postoperative; Troponin 3, Troponin at 3rd day postoperative.

| Table 5: Side effects. |
| Variables | G1 | G2 | P-value |
| Nausea | 10 (33.3%) | 6 (20%) | 0.042 |
| Vomiting | 8 (26.6%) | 3 (10%) | 0.007 |
| Itching | 2 (6.6%) | 3 (10%) | NS |

Data are expressed as number (%). NS; Non significant.
pericardial effusion, and surgical maneuvers 

predict a patient’s intermediate (≤ 12 months) or long-term (more than 12 months) risk of death or a major cardiovascular event [24,25]. So some investigators have advocated monitoring perioperative troponin levels in patients undergoing noncardiac surgery to identify patients at risk [25,26]. Most patients with perioperative ischemia remain asymptomatic, and serum markers of myocardial ischemia, such as CK-MB and cardiac troponins, usually do not increase [27,28]. Perioperative pain is a potent trigger for the stress response, activates the autonomic system [29], and is thought to be an indirect cause of adverse effect on various organ systems, also it can activate sympathetic efferent nerves and increase heart rate, intropoty, and blood pressure, although activation of the sympathetic nervous system can increase indices of myocardial oxygen demand and result in ischemia [30-36]. The perioperative stress is associated with hypercogulability and the release of proinflammatory cytokines into the circulation caused by excessive activity of the neuroendocrine systems, particularly due to insufficient pain control in the postoperative period [37]. Vasospasm caused by this stress response impairs the coronary blood flow and consequently increased contractility of the myocardium disturbs the balance between the supply and the need for oxygen that may lead to outcomes ranging from myocardial ischemia to severe cardiac injury [27,38,39]. Tachycardia-induced increase in shear force on an atherosclerotic plaque, together with stress-induced hypercoagulation, may induce plaque rupture with subsequent myocardial hypoperfusion or ischaemia [26,27,38,39]. Both LEA and analgesia were found to reduce pulmonary and cardiac complications, and improve myocardial oxygenation and tissue reperfusion [40]. This has been attributed to several related mechanisms among which is the LEA-induced analgesia that suppresses the hormonal and autonomous response to surgery by inhibiting afferent stimuli and modulating the neurohormonal pathways to produce anti-ischemic actions and decrease the severity of myocardial ischemia [39,41-43]. Cardiac morbidity was shown to be lower among patients undergoing major vascular surgery after the administration of general anesthesia combined with postoperative epidural analgesia compared to the administration of general anesthesia alone and postoperative systemic opioid analgesia [44]. A meta analysis revealed a significant reduction in venous thromboembolism in patients undergoing surgery for hip fracture under regional anesthesia compared with general anesthesia, but resulted in only a marginally better effect on early mortality [45]. In a study involving 60 patients with risk of Coronary Artery Disease (CAD) scheduled to undergo lower extremity surgery, patients were divided into three groups, one was given general anesthesia followed by intravenous patient-controlled analgesia, the second group was given lumber epidural anesthesia followed by lumbar epidural analgesia and the third group was given general anesthesia combined with intra and postoperative thoracic epidural analgesia. They found that plasma cardiac troponin 1 concentrations were within normal limits (<0.1 mg/L) in all the 3 groups and they concluded that opioids and local anesthetics also contributed to the positive effects of TEA and lumber epidural anesthesia plus analgesia. For high-risk cardiac patients, epidural anesthesia followed by epidural postoperative analgesia should be preferred [46]. In the study of dogan et al. 40 patients were divided into two groups, regional anesthesia group and general anesthesia group, during elective cesarian delivery [47]. Serum troponin T, creatinine kinase-MB, and myoglobin levels were measured preoperatively (baseline) and at 1, 5, and 24 hours postoperatively. In all 40 cases, troponin T levels were in the normal range at all time points studied. In both groups, mean serum creatine kinase-MB and myoglobin levels at one and 5 hours postoperatively were significantly higher than baseline (p<0.05). These high CK-MB and myoglobin levels were returned to normal ranges at the end of the study. In a study of peyton et al. they found that there was no evidence that perioperative epidural analgesia significantly influences major morbidity or mortality after major abdominal surgery [48].Priestly et al. found no difference in troponin levels between General Anesthesia (GA) alone and GA plus High Thoracic Epidural Anesthesia (HTEA) groups, Loick et al. found significantly reduced troponin T levels in their HTEA group [49,50]. In this study, inflammatory response to surgery measured by hs-CRP significantly increased in both groups from the first postoperative day with persistent elevation till the third day. This inflammatory response was less with LEA compared to general anesthesia in the first post operative day. It is considered that hs-CRP is a general marker for inflammation. Recently, it was found that high hs-CRP levels were significantly associated with an increased risk of perioperative MI [51]. Ridker and colleagues, however, suggested, that extremely high hs-CRP levels (>10 mg/L) may be useful for predicting cardiovascular disease and thrombotic events [52]. Use of hs-CRP may add to risk estimation in a limited subset of individuals who are at intermediate predicted risk according to the Framingham risk score (which is a tool designed for adults aged 20 and older who do not have heart disease or diabetes). Low levels in high risk population don't reduce the risk and high levels in low risk groups don't increase the risk [45,53].Rashidinejad et al. in their study found a strong positive correlation between serum hs-CRP and troponin. They also concluded that this positive correlation could be a useful biomarker for predicting extended myocardial involvement in patients with acute myocardial infarction [54]. Since many variables can elevate CRP, this is not a very specific prognostic indicator. Cancer is one of the situations that can raise serum hs-CRP and its level has been linked to the disease extent and possibility of recurrence [55]. This can explain the high baseline hs-CRP level in the studied patient groups.

Conclusion

The LEA combined with general anesthesia in high risk patients with ischemic heart disease undergoing major abdominal cancer surgery provided better pain relief, and a lower CRP in the first 3-days postoperatively than general anesthesia alone. Ischemic cardiac events related to serum troponin T and ECG were similar in both groups. Our findings suggest that LEA with general anesthesia is associated with less perioperative acute inflammatory response and can reduce the perioperative myocardial damage.

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