Original Article

Hyperbilirubinemia After Open Cardiac Surgery

Mohamad Golitaleb,[1] MS; Faranak Kargar,[2] MD; Farzaneh Gol Aghai,[1] MS; Mehdi Harorani,[1] MS; Ali Jadidi,[1] MS; Homan Bakhshande Abkenar,[2] MD; Mehrdad Haghazali,*[2] MD

ABSTRACT

Background: Postoperative hyperbilirubinemia is one of the complications of cardiopulmonary bypass. The purpose of this study was to investigate the incidence and nature of postoperative jaundice in patients undergoing cardiac surgery, to analyze the determinants, and to identify the clinical significance of this complication with regard to the associated morbidity and mortality.

Methods: This prospective, descriptive study was conducted on 600 patients between 2014 and 2015 in Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran. Six hundred adult patients candidated for open heart surgery were divided into 3 groups. Group A comprised 200 patients who underwent coronary artery bypass grafting (CABG), Group B 200 patients who underwent aortic valve replacement (AVR)+CABG, and Group C 200 patients who underwent mitral valve replacement (MVR)+CAB. Aminotransferases (ALT and AST), alkaline phosphatase, and both types of bilirubin (total bilirubin and indirect bilirubin) were determined at admission. Liver function tests were conducted preoperatively, immediately after surgery, and on the 1st, 3rd, and 7th postoperative days. These data were categorized and analyzed. The presence of jaundice was associated with elevated serum bilirubin levels above 3 mg/dL.

Results: Hyperbilirubinemia developed in 150 (25%) patients. The incidence of postoperative jaundice was higher in the patients who underwent MVR+CABG than in those who underwent CABG and AVR+CABG. Hyperbilirubinemia was correlated with prolonged cardiopulmonary bypass time (P<0.001), aortic cross-clamp time (P<0.001), hypotension during the pump (P<0.001), and number of blood transfusions.

Conclusions: Although hyperbilirubinemia seems to be multifactorial, the type of surgery, cardiopulmonary bypass time, aortic cross-clamp time, hypotension during the pump, and number of blood transfusions seem to determine the incidence of jaundice. ***(Iranian Heart Journal 2017; 18(2):30-35)***

Keywords: Jaundice, Open cardiac surgery, Liver function, Liver enzyme change

[1] Faculty of Nursing and Midwifery, Arak University of Medical Sciences, Arak, I.R. Iran.
[2] Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, I.R. Iran.

***Corresponding Author:** Mehrdad Haghazali, MD; Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, I.R. Iran.
E-mail: haghmehr@yahoo.com **Tel:** 09121158275

Received: 19 February, 2017 **Accepted:** 2 April, 2017

According to the previous studies, postoperative jaundice after open cardiac surgery is associated with 25% of deaths.[1] Postoperative hyperbilirubinemia has been cited as a cause of mortality in several studies. Gastrointestinal complications following cardiac surgery are associated with high morbidity and mortality rates, prolonged hospital stay, and increased cost of hospitalization. [2,3] Open cardiac surgery requires the use of cardiopulmonary bypass (CPB) pump, which takes over the function of the heart, lung, and circulatory system. The pump or extracorporeal circulation has important effects on body organs, including the liver, due to the activation of the coagulation system and the complement system, hemodilution, decreased tissue perfusion, neuroendocrinological abnormalities, hypothermia, and existence of non-pulsatile perfusion. The most important complication of the pump is the disturbance of oxygen transport, of metabolism, and of the hepatic blood flow. [1, 4] The pump-induced disturbed hepatic blood flow is in the form of contracted arteries and decreased oxygen consumption, which leads to a 50% decrease in the hepatic blood flow compared to the normal state. The decreased blood circulation is more observable while cooling and heating patients during the pump. [5] The liver is a strong organ that resists for many years against biochemical toxins and for hours against hypoxia. However, despite these excellent and significant abilities, cardiac surgery imposes degrees of liver failure on 2.3% of patients. As liver failure happens, the mortality rate significantly increases too. The most important factors causing postoperative liver failure after open cardiac surgery are pharmaceutical factors for anesthesia, primary heart failure, and cardiopulmonary pump. [6] Despite the advances made in the areas of anesthesia, extracorporeal circulation, surgery techniques, and postoperative cares, the postoperative rate of hyperbilirubinemia is still high. Given the importance of liver function for health, an increase in the levels of liver enzymes introduces damage to hepatocytes, which leads to longer hospital stay of patients and more costs. [7] However, in more recent retrospective studies, it has become apparent that postoperative jaundice occurs in a substantial number of cases and its incidence is estimated to be more than 20%. [8]

The purpose of the present study was to investigate the incidence and nature of postoperative jaundice in patients undergoing cardiac operations, to analyze the determinants, and to identify the clinical significance of this complication *vis-à-vis* morbidity.

METHODS

This prospective, descriptive study was conducted on 600 patients between December 2014 and 2015 in Rajaie Cardiovascular, Medical, and Research Center, Tehran, Iran. Six hundred adult patients candidated for open heart surgery were divided into 3 groups. Group A consisted of 200 patients who underwent coronary artery bypass grafting (CABG), Group B 200 patients who underwent aortic valve replacement (AVR)+CABG, and Group C 200 patients who underwent mitral valve replacement (MVR)+CABG.

Aminotransferases (ALT and AST), alkaline phosphatase (AKP), and both types of bilirubin (total bilirubin and indirect bilirubin) were determined at admission. Liver function tests were conducted preoperatively, immediately after surgery and on the 1st, 3rd, and 7th postoperative days. These data were categorized and analyzed. The presence of jaundice was associated with elevated serum bilirubin levels above 3 mg/dL. The exclusion criteria were comprised of patients with a clinical history of Gilbert's syndrome, clinical history of cardiac arrest and cardiopulmonary resuscitation before surgery, severe and

diagnosed chronic obstructive pulmonary disease before surgery, severe arrhythmia, renal failure, severe failure of the tricuspid valve, severe pulmonary hypertension, hepatitis B and C, patients affected by postoperative compressive pneumothorax and/or difficult intubations due to the complications of anesthesia and accidental decannulation of the tracheostomy tube, patients with an ejection fraction lower than 25%, patients having redo surgeries, and patients reluctant to participate in the study. All the operations were performed by the same group of surgeons, while giving anesthesia according to a standard protocol. CPB was initiated after ascending aorta-to-right atrial or bicaval cannulation. After collecting the information from the patients' records, we analyzed the effects of the mentioned variables—including age, sex, type of anesthesia, type of surgery, history of alcohol use and cigarette smoking, body mass index, cholesterol, LDL, HDL, type of the pump (centrifugal or roller), amount of blood transfusion (≤6 units and >6 units), hypothermia less than or equal to 28 °C and more than 28 °C, duration of the pump (≤100 min and >100 min), duration of aortic cross-clamp (≤60 min and >60 min), and hypotension during surgery (mean blood pressure <50 mm Hg). The data were expressed as means±standard deviations unless they were stated specifically. The data were analyzed by SPSS, version 16, and a *P* value less than 0.05 was considered significant. The χ^2 test was used to compare the qualitative characteristics. Analysis of variance was performed to detect differences between the groups. The Pearson linear, as well as, stepwise multiple regression analysis was employed in order to assess correlations between the variables.

RESULTS

Out of the 600 the patients, 330 (55%) were men and 270 (45%) were women. These subjects were at an age range between 25 and 86 years. Totally, 372 (62.7%) patients underwent the pump for a maximum of 100 minutes and 228 (37.3%) patients experienced it for longer than 100 minutes. Moreover, 348 (58%) patients received a maximum of 6 units of blood and 252 (42%) patients received more than 6 units. In addition, 360 (60%) patients had hypothermia over 28 °C and 240 (40%) experienced hypothermia equal to or below 28 °C. For all the study participants, the mean hypotension during surgery (mean arterial pressure) was 60 mm Hg, mean weight was 65.4 kg, and body mass index was equal to 22.1.

Table 1. Demographic data and operative times among the 3 groups of patients

Variables	CABG	CABG-AVR	CABG-MVR	*P*
Age	64.3±11.2	67±5.3	60.3±8	>0.623
Sex(F/M)	55/45	58/42	61/39	>0.725
Bypass time(min)	65±28	110±45	140±55	< 0.05
Aortic cross-clamp(min)	50±19	85±32	110±40	< 0.05
Type pump(on/off)	180/20	200/0	200/0	>0.605
Mean body surface area(m^2)	1.75±%12	1.25±%17	1.19±%23	>0.827

CABG, Coronary artery bypass grafting; AVR, Aortic valve replacement; MVR, Mitral valve replacement; M/F, Male /female

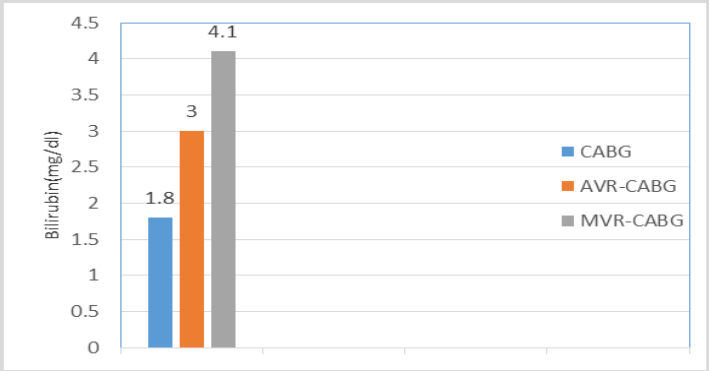

Figure 1. Postoperative jaundice levels between the groups.
Group A: CABG, Group B: AVR+CABG, Group C: MVR+CABG
CABG, Coronary artery bypass grafting; AVR, Aortic valve replacement; MVR, Mitral valve replacement

The patients with early development of postoperative hyperbilirubinemia had a longer intensive care stay and higher mortality rate, while the late appearance of hyperbilirubinemia was associated with a prolonged hospital stay (Table 2).

Table 2. Mortality and morbidity in the patients with and without postoperative hyperbilirubinemia

	Without Hyperbilirubinemia	With Hyperbilirubinemia	*P*
Mortality	0%	3%	< 0.005
Mean intensive care stay (d)	3.5±3.17	7.35±6.75	< 0.05
Mean hospital stay (d)	13.5±2.5	29.25±8.75	< 0.05

According to our logistic regression analysis, the number of the valves replaced, right atrial pressure, and preoperative total serum bilirubin level were risk factors for postoperative hyperbilirubinemia (Table 3).

Table 3. Logistic regression analysis of risk factors for postoperative hyperbilirubinemia

	Regression Coefficient	Partial Correlation Coefficient	Standard Error of the Mean	*P*
No. of the valves replaced	0.591	0.123	0.265	< 0.05
Right atrial pressure	0.212	0.117	0.317	< 0.05
Preoperative total serum bilirubin	0.131	0.229	0.051	< 0.05

DISCUSSION

Although gastrointestinal complications after open cardiac surgery in patients undergoing CPB is about 2% to 3%, the mortality rate in these patients varies from 11% to 59%. Because of the non-pulsatile blood flow, the pump or extracorporeal circulation causes decreased tissue perfusion and disturbed liver tissue oxygenation. [9] The incidence of postoperative hyperbilirubinemia was 25%, which is similar to the data reported by Chu et al, [10] Collins et al, [11] and Wang et al. [12] Chetty et al [13] conducted a research, entitled "Liver Blood Flow During Cardiac Surgery", on 10 patients using clarins indocyanine green (ICG) and considering exclusion criteria that included not having a clinical history or liver disorders, appropriate left ventricular ejection fraction, and CABG surgery with

hypothermia up to 30 °C. The authors found that inducing anesthesia had no effect on the liver blood flow. They also reported that bypass at 30 °C decreased the liver blood flow and it took 4 to 6 hours for the liver blood flow to increase and 24 hours to reach the normal range. In another physiological study, Jacob et al [14] investigated the peripheral and central blood flows in the organs. The authors looked into the changes in the blood flow of the hepatic arteries, femoral artery, and visceral organs in 17 patients and concluded that increased peripheral blood flows and increased oxygen uptakes in certain parts of the body might cause a mismatch between the visceral organs and metabolic needs, but this mismatch was not associated with disturbed liver function. Collins et al [11] investigated the incidence of postoperative jaundice after open cardiac surgery. One of the most important factors in their study was blood transfusion. The number of patients was 20 and other blood products were integrated into the study as well as red blood cells (whole or packed blood). Also, the researchers divided the amount of blood transfusion (packed globule) into 2 categorized variables (<6 units and ≥6 units) and compared the increases in liver tests and bilirubin with them. The limitation of the study by Collins et al was both the low number of patients and the integration of other blood products into the study. Chu et al [10] posited that hypotension in the early postoperative period might reduce hepatic perfusion and hypoxemia might further decrease the hepatic oxygen supply. The pathogenesis of hepatic lesions is complex and multifactorial; nonetheless, the major factor implicated in cardiac surgery is reduced systemic blood flow, which leads to inappropriate oxygen delivery and energy deficit. D'Ancona et al [15] argued that during the intraoperative phases, hypovolemia, prolonged bypass, prolonged aortic cross-clamp time, and administration of inotropes could cause hypoperfusion. In most of the cases, jaundice is reversible with no harmful results. However, the more hyper-bilirubinemia persists and ascends, the more frequent the mortality is. Michalopoulos et al [16] concluded that hepatic dysfunction follows other perioperative complications such as low cardiac output syndrome, necessitating the administration of inotropic agents and the usage of the intra-aortic balloon pump, as well as perioperative shock or arrest. Postoperative jaundice is believed to occur because the liver is "shocked" by hypotension, hypoxia, or hypothermia or chronically congested by right-heart failure. Furthermore, there is a clear relationship between the development of jaundice and the type of surgery as severe hepatic dysfunction may occur far more frequently in patients undergoing MVR or multiple valve surgery requiring more time and blood than in those receiving coronary bypass graft procedures. [17] In addition, these patients have a higher rate of postoperative infection, and hyperbilirubinemia is associated with prolonged mechanical ventilation and ICU stay.

CONCLUSIONS

We suggest that postoperative hyper-bilirubinemia is a multifactorial process caused by both impaired liver function of bilirubin transport and increased production of bilirubin because of hemolysis. The development of postoperative hyperbilirubinemia was associated with a higher mortality rate, longer duration of artificial ventilation, and longer ICU stay time in our study population.

ACKNOWLEDGEMENTS

We hereby thank all the personnel of Rajaie Cardiovascular, Medical, and Research Center.

REFERENCES

1. Sabzi F, The study of Changes in liver enzymes among the patients Undergoing open heart surgery. Journal of Medical Council of Islamic Republic of Iran 2008, 26 (2) Summer: 222-229 .

2. Rodriguez R1, Robich MP, Plate JF, Trooskin SZ, Sellke FW, J Card Surg. 2010 Mar;25(2):188-97. doi: 10.1111/j.1540-8191

3. Pranav Sharma et al, Hyperbilirubinemia after cardiac surgery: An observational study, Asian Cardiovascular & Thoracic Annals 2015, Vol. 23(9) 1039–1043.

4. Sunil K Ohri and Theo Velissaris Gastrointestinal dysfunction following cardiac surgery, Perfusion 2006; 21: 215_223

5. Govind Chetty, David AC Sharpe, Jay Nandi, Stephen J Butler and Ian M Mitchell; (2004) Liver blood flow during cardiac surgery. Perfusion; 19: 153/156

6. Jai S. Raman, FRACSa*, Kazuhiro Kochi,6.MDa, Hiroshi Morimatsu, MDb, Brian Buxto FRACSa, Rinaldo Bellomo, MDb Severe ischemic early liver injury after cardiac surgery Ann Thorac Surg 2002;74:1601-1606

7. Mahoori AR,et al, Long-term complications leading to hospitalization in the intensive care unit after open heart surgery, Summer 2009 19(2): 139-144.

8. Kikumik Hosotsubo, Hyperbilirubinaemia after major thoracic surgery: comparison between open-heart surgery and oesophagectomy, Critical Care20004:180 ,DOI: 10.1186/cc691.

9. Giuseppe D'Ancona, MD, Richard Baillot, MD, Brigitte Poirier, MD, Determinants of GI Complications in Cardiac Surgery, 2003; 30(4): 280-285.

10. Chu CM, Chang CH, Liaw YF, Shieh MJ: Jaundice after open heart surgery: a prospective study. Thorax 1984, 39:52-56.

11. Collins JD, Bassendine MF, Ferner R, *et al*.: Incidence and prognostic importance of jaundice after cardiopulmonary bypass surgery. *Lancet* 1983, i**:** 1119-1123. 10.1016/S0140-6736(83) 92863-5.

12. Wang MJ, Chao A, Huang CH, *et al*.**:** Hyperbilirubinemia after cardiac surgery. J Thorac Cardiovasc Surg 1994, 108: 429-436.

13. Govind Chetty, David AC Sharpe,et al ,Liver blood flow during cardiac surgery, Perfusion 2004; 19: 153_/156

14. Stephan M. Jakob, and Zeno Stanga(2010), Perioperative metabolic changes in patients undergoing cardiac surgery Nutrition 26 , 349–353

15. D'Ancona G, Baillot R, Poirier B, Dagenais F, de Ibarra JI, Bauset R, et al. Determinants of gastrointestinal complications in cardiac surgery. Tex Heart Inst J 2003;30: 280-205.

16. Michalopoulos A, Alivizatos P, Geroulanos S. Hepatic dysfunction following cardiac surgery: determinants and consequences. Hepatogastroenterology 1997;44:779-783.

17. Bohmer T, Kjekshus E, Nitter-Hauge S. Studies on the elimination of bilirubin pre-operatively in patients with mitral valve disease. Eur Heart J 1994;15:10-16.