Indian Heart Journal 68 (2016) 798–802

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Off-pump coronary artery bypass grafting using continuous heparin infusion☆

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ARTICLE INFO

Article history:
Received 1 March 2016
Accepted 26 April 2016
Available online 18 May 2016

Keywords:
Heparin
Off-pump CABG
Heparin dosing during off-pump CABG
Anticoagulation during off-pump CABG

ABSTRACT

Objectives: Levels of anticoagulation during off-pump coronary artery bypass grafting (OPCAB) remain controversial. Prolonged activated clotting time (ACT) during OPCAB increases blood loss during surgery and can also cause paradoxical increase in postoperative myocardial infarction. Shorter ACT can increase thrombotic complication. Maintaining a steady ACT level is challenging. We have used continuous heparin infusion after initial bolus during OPCAB to maintain a steady low target ACT. The objective of the present study was to assess the effectiveness and safety of heparin infusion in maintaining a steady target ACT level.

Methods: This was a prospective study of consecutive OPCAB patients. ACT was measured after initial bolus dose of heparin. Once ACT of more than 200 seconds was achieved, heparin infusion was started to maintain the required level of anticoagulation. CPK-MB was measured in operation room, 6 and 24 hours postoperatively to rule out ischemic complication.

Results: ACT could be maintained in target range with heparin infusion in 80.1% patients (161/201). Of the 40 patients with one or more ACT reading less than 200 seconds, 38 patients were managed by increasing the dose of heparin infusion and only 2 patients required additional bolus dose of heparin.

Conclusions: Heparin infusion maintains a steady target ACT level and avoids peaks and troughs associated with bolus doses. Lower level of anticoagulation using continuous heparin infusion does not increase ischemic complications. This is the first ever study of use of heparin infusion during OPCAB. We may conclude that heparin infusion is a safe anticoagulation strategy for OPCAB.

1. Introduction

Off-pump coronary artery bypass grafting (OPCAB) is an established method of surgical revascularization. The various techniques of OPCAB continue to evolve. Optimum anticoagulation during OPCAB remains elusive, variable, and debatable.[1] Level of anticoagulation during OPCAB is measured by ACT (activated clotting time). It is generally believed by the cardiac surgeons that longer ACT is better for graft patency and shorter ACT during OPCAB may cause graft blockage. This belief is arbitrarily extrapolated from experience of conventional coronary artery bypass grafting (CABG) using cardiopulmonary bypass and is without any evidence. So there is wide variability in the initial heparin dose, subsequent heparin doses, and target ACT level during OPCAB from center to center across Europe[2,3] and United states.[1] There is no established guideline about the heparin dosing and level of anticoagulation to be maintained during OPCAB. This has resulted in empirical protocols being used during OPCAB.[2] No differences in coagulation indices were detected during OPCAB using high and low dose heparin.[4] But there is no study about OPCAB graft patency with different levels of anticoagulation.[5] Anticoagulation strategy during OPCAB is arbitrarily derived from experience of coronary artery bypass using cardiopulmonary

☆ Meeting presentation: Presented in the Annual Scientific Meeting ISMICS held in Berlin 2015 with the heading "Heparin Infusion During Off-Pump Coronary Artery Bypass Grafting Safely Maintains Steady Level of Anticoagulation" and was judged as the best paper in coronary revascularization category.

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http://dx.doi.org/10.1016/j.ihj.2016.04.024

bypass. But cardiopulmonary bypass induced coagulopathy is absent during OPCAB.

Physiology of OPCAB is different from CABG using cardiopulmonary bypass and probably similar to percutaneous coronary intervention (PCI). It is well established that ACT more than 350 seconds is detrimental to stent patency during PCI paradoxically due to platelet activation.[6] Recent OPCAB study suggests that longer than 350 seconds of ACT during OPCAB is associated with significantly higher incidence of postoperative myocardial infarction.[7] Maintaining a shorter ACT level during OPCAB may have an added benefit of minimizing blood loss during the procedure.[7,8] ACT more than 400 seconds was maintained in OPCAB group in recently published Danish off-pump versus on on-pump revascularization (DOOR) study. It was concluded by the authors of DOOR study that higher level of anticoagulation during OPCAB may result in increased bleeding without improving graft patency.[8,9]

Maintaining low steady ACT is challenging as any further drop in ACT may result in thrombus formation leading to unwanted graft blockage. This is particularly true during a prolonged procedure. This apprehension of thrombus formation may lead to higher heparin doses resulting in prolonged ACT. The conventional method of heparin dosing is initial bolus and followed by intermittent bolus doses to maintain ACT above a predetermined target value. This practice is mostly derived from conduction of cardiopulmonary bypass where ACT is maintained above 480 seconds. A little higher dose is considered harmless as higher ACT induced bleeding can easily be managed since blood from operative field is returned using cardiotomy suction. Moreover, intermittent bolus doses result in peaks and trough which may be unwanted during OPCAB. We have used continuous heparin infusion after initial bolus dose during OPCAB to maintain a steady low target ACT. Our target ACT was between 200 and 300 seconds in this study. The objective of the present study is to assess the effectiveness and safety of heparin infusion in maintaining a steady target ACT level.

2. Patients and methods

The study was conducted in accordance with the principles of the declaration of Helsinki. All cases of consecutive unselected isolated off pump coronary artery bypass grafting (OPCAB) operated by the first author were included in this prospective study. Heparin is used as anticoagulant during OPCAB. We used initial bolus dose to achieve target ACT above 200 seconds. After this target level is achieved, we used heparin infusion instead of intermittent bolus doses. Heparin is used as infusion in all clinical conditions. This study had used the conventional method of heparin administration as infusion during OPCAB and hence no IRB approval was obtained.

3. Anticoagulation protocol during OPCAB

Initial heparin bolus dose: 100 units/kg of heparin (heparin sodium) is used as bolus – 25% of this is given before disconnecting the internal mammary artery and the remaining 75% is given before initiation of bypass grafting procedure. ACT was checked 5 minutes after the total 100 units/kg heparin dose. Blood samples were always collected from arterial line for ACT measurement. We targeted an ACT of more than 200 seconds after bolus dose. If target ACT is not achieved, additional dose of heparin is given to achieve ACT $>$ 200 seconds. We used heparin vial of 25,000 units in 5 ml in all cases. Out of this, 10,000 units were diluted in 10 ml (1000 units/ml). This solution was used for bolus doses.

Heparin infusion: After target ACT of more than 200 seconds was achieved, heparin infusion was started. Heparin infusion was prepared by mixing 10,000 units of heparin diluted in total volume 50 ml in a syringe with concentration of 200 units per ml. Heparin infusion was administered using syringe pump through central line. Dose of heparin infusion was adjusted according to ACT of the patient. ACT was measured every hour. Infusion was stopped after the last distal anastomosis was completed. Total amount of heparin used was calculated and 50% of the total heparin dose was reversed using protamine. Additional dose protamine was used only if post-protamine ACT was not normalized.

Monitoring thrombotic complication: The surgical team was vigilant and looked for clots in the operating field. If a clot was detected, it was informed to the anesthetist, ACT measurement was repeated, and bolus dose of heparin was given if required. CPK-MB was measured in operation room, 6 and 24 hours postoperatively to rule out ischemic complication due to bypass graft dysfunction.

Data analysis: Heparin dosing and ACT was recorded prospectively. Change in ACT was calculated as positive if ACT increased and negative if ACT decreased. After data collection, data analysis was done with the help of PSPP Software. Quantitative variables were presented with mean and standard deviation. Correlation among various study parameters was assessed with Pearson's correlation coefficient. Qualitative data was presented as frequency and percentage tables, and P value <0.05 was taken as level of significance.

4. Results

An initial bolus dose of 100 unit/kg was adequate in 185 (92%) patients to achieve ACT more than 200 seconds. Remaining 16 patients required additional bolus dose to achieve initial ACT more than 200 seconds. Figs. 1 and 2 show the correlation between the heparin dose and ACT.

After ACT more than 200 seconds was achieved, heparin infusion was started to maintain ACT between 200 and 300 seconds. Figs. 3 and 4 show the change in ACT with different doses of heparin infusion. There was wide variation among patients in the heparin dose required to maintain the target ACT. Infusion dose of 40 units/kg of body weight/hour maintained almost the same ACT, lower doses decreased and higher doses increased ACT. In 80.1% patients (161/201), ACT was maintained in target range with heparin infusion. Of the 40 patients with one or more ACT reading less than 200 seconds, 38 patients were managed by increasing the dose of heparin infusion and only 2 patients required additional bolus dose of heparin. One patient in our series had significant CPK-MB rise postoperatively in spite of ACT being higher than desired level. He had diffuse coronary artery disease and required mid and distal LAD endarterectomy. As the ACT level was higher than desired level and patient had mid and distal endarterectomy, this CPK-MB rise cannot be attributed to inadequate level of anticoagulation.

5. Discussion

OPCAB techniques continue to evolve in India in spite of widespread skepticism about the long-term result of OPCAB.[10] Coronary artery bypass grafting is a palliative procedure and effectiveness of the procedure is directly proportional to graft patency. To improve graft patency the target activated clotting time is maintained between 250 and 300 seconds in India[11] But there is no study of peri-operative myocardial infarction rate with this target ACT level between 250 and 300 seconds. Wide variation in ACT level maintained during OPCAB is reported from different parts of the world.[1–3] A study from Korea revealed that ACT more than 350 seconds are associated with paradoxically higher incidences of peri-operative myocardial infarction.[7] In DOOR study, ACT longer than 400 seconds was maintained in OPCAB group and may have resulted in higher rate of vein graft failure due to paradoxical platelet activation.[8] Prolonged ACT increases blood loss during OPCAB without improving graft patency.[9] The physiology of OPCAB is

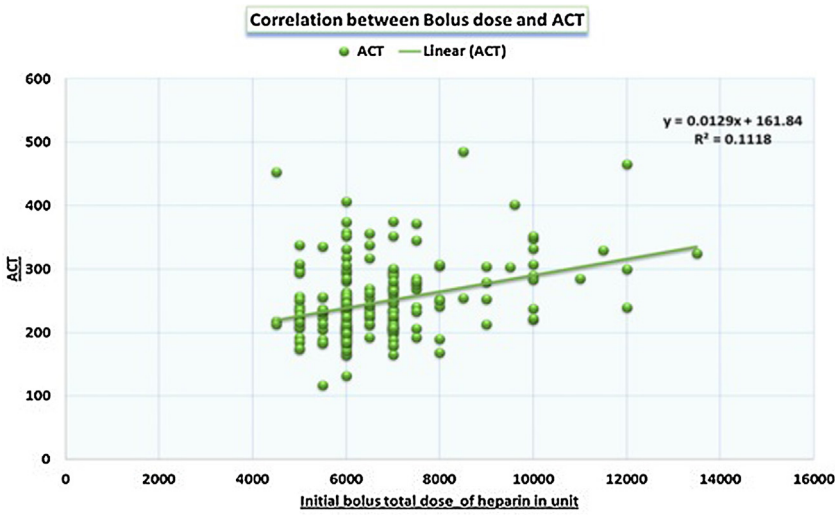

Fig. 1. Correlation between initial bolus dose of heparin in units and ACT 5 minutes after the bolus dose.

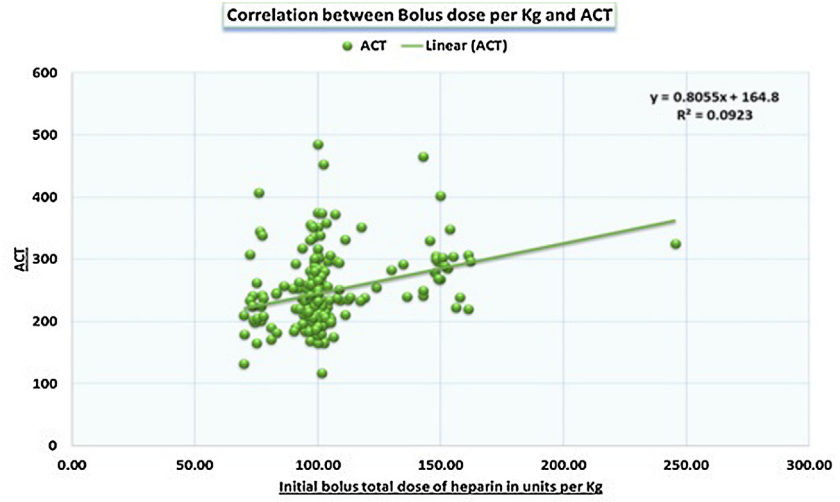

Fig. 2. Correlation between initial bolus dose of heparin in units per kg of body weight and ACT 5 minutes after the bolus dose.

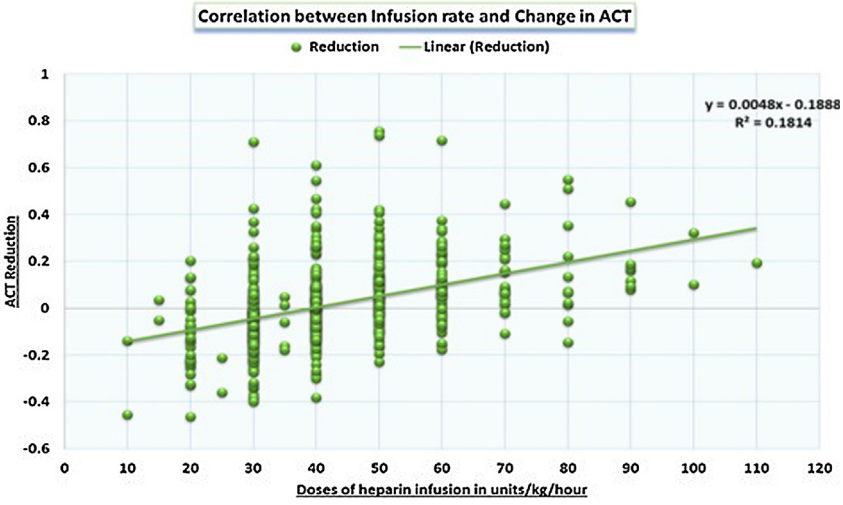

Fig. 3. Correlation between infusion rate of heparin in units per kg of body weight per hour and change of ACT.

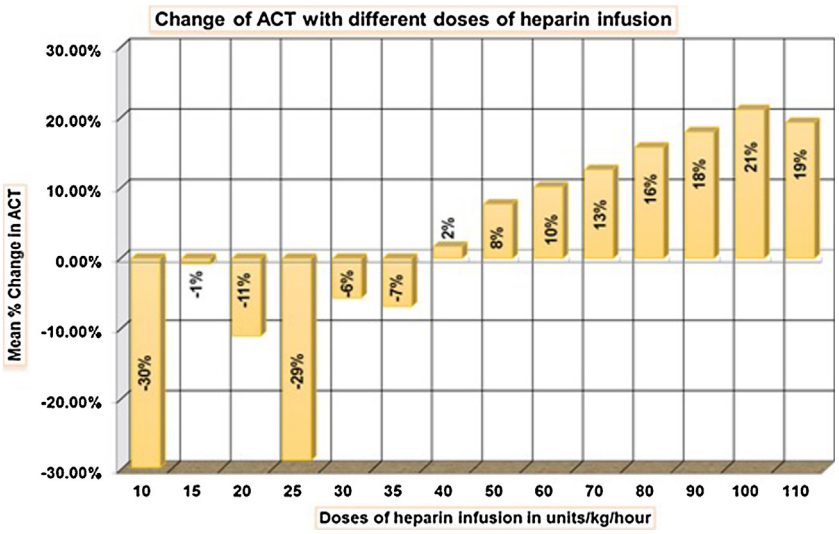

Fig. 4. Correlation between infusion rate of heparin in units per kg of body weight per hour and change of ACT in percentage.

different from coronary artery bypass grafting using cardiopulmonary bypass and probably similar to PCI.[12]

Longer ACT (more than 350 seconds) is avoided during PCI as it does not increase stent patency rate but increases bleeding complications. Similarly in DOOR study, ACT more than 400 seconds in the OPCAB group may have caused increased bleeding without improving graft patency.[8,9] It may be concluded that ACT less than 350 seconds (between 200 and 300 seconds) may be optimal for OPCAB with least incidence of postoperative myocardial infarction and minimal intra-operative blood loss.[12]

The conventional method of heparin dosing is initial bolus and followed by intermittent bolus doses to maintain ACT above a predetermined target value.[11] This practice is mostly derived from conduction of cardiopulmonary bypass where ACT is maintained above 480 seconds and a little higher heparin dose is considered harmless. Higher ACT-induced bleeding can easily be managed as blood from operative field is returned using cardiotomy suction. It is possible that cardiopulmonary bypass-induced coagulopathy has protective effects from heparin-induced platelet activation at the level of ACT maintained during the procedure. However, during OPCAB, such protective effect is absent. So during OPCAB, prolonged ACT level may result in paradoxical increase in postoperative myocardial infraction.[7]

Heparin has a short half life which may vary with dose and from patient to patient. Half life of heparin increases with dose when administered as bolus. The disappearance of anticoagulant activity of heparin follows nonlinear kinetics – combination of saturable and linear mechanism. There is a threshold below which heparin level rises only slowly and above which rises rapidly in a linear fashion correlating with dose.[13] Biological half life of heparin increases from 30 minutes after a dose of 25 units/kg IV bolus to 60 minutes with IV bolus dose of 100 units/kg and 150 minutes with bolus dose of 400 units/kg.[14] The problem with intermittent supplemental dosing of heparin is that if a patient has a short half life, the ACT level may fall below the critical level of 200 seconds. This may lead to thrombus formation leading to graft blockage. So the normal response to a lower ACT is to supplement a higher dose of bolus heparin. Higher dose of heparin may increase the heparin half life with increase of ACT above 350 seconds with detrimental effects on graft patency due to platelet activation.[8,9,12]

In the protocol of heparin infusion adopted by us, it is clearly demonstrated that it is possible to achieve a steady ACT level with heparin infusion. Initial dose of 100 units/kg was adequate in most patients to achieve ACT more than 200 seconds. Infusion dose of 40–50 units/kg/h was adequate to maintain the desired ACT level. Higher infusion dose was used to increase the ACT and vice versa. Moreover, even when ACT dropped to less than 200 seconds, there was no clot formation in the operative field. In such situation, we increased the infusion rate to increase ACT. Bolus doses were given in two patients when clot formation was detected in the operating field. Desired level of ACT can be achieved using dose of infusion appropriate for the patient. There is wide variability in heparin dose requirement among the patients to maintain target level of ACT between 200 and 300 seconds. It is easier to fine tune infusion as there is a very minimal risk of ACT dropping below 200 seconds with infusion on-flow. So heparin infusion has resulted in minimal overshooting of ACT in the non-responders.

Study limitations: Several limitations of this study must be recognized. There is no control group in this study. This infusion regime is not compared with intermittent bolus doses of heparin. Moreover, long-term graft patency of such anticoagulation strategy is to be determined by further study. We did not collect the blood loss data prospectively in these patients.

Conclusion: Level of anticoagulation during OPCAB is often neglected. Higher level of anticoagulation is often considered better for OPCAB graft patency but higher level of anticoagulation may lead to paradoxical increase in thrombotic complication.[8] In our series of 201 consecutive OPCAB patients, one patient had postoperative CPK MB rise in spite of ACT being more than the desired level. He had diffuse coronary artery disease and required mid and distal LAD endarterectomy. This study proves that lower level of anticoagulation (ACT between 200 and 300 seconds) is safe and does not increase ischemic complications. Low steady level of target ACT can be maintained using heparin infusion. Heparin infusion also avoids peaks and troughs associated with bolus doses.

Heparin is conventionally used as continuous infusion in various clinical conditions. It has a short half-life so it is pharmacologically correct to use heparin infusion to maintain target ACT after a bolus dose to achieve the target level of anticoagulation. Added advantage of maintaining shorter ACT is reduction in blood loss. In our experience, this regime is safe and effective in maintaining desired level of anticoagulation precisely with no apparent downside. This is the first ever study of use of heparin infusion during OPCAB. We can conclude that heparin infusion is a safe and optimum anticoagulation strategy for OPCAB to maintain precise anticoagulation level.

Funding

None.

Conflicts of interest

The authors have none to declare.

Acknowledgement

The authors thank Dr. Dnyaneshwar M. Gajbhare for his contribution in statistical analysis of this study.

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