Effect of preoperative administration of allopurinol in patients undergoing surgery for valvular heart diseases

Sachin Talwar,*, Janardhan Alamanda Sandeep, Shiv Kumar Choudhary, Devagourou Velayoudham, Ramakrishnan Lakshmy, Jeeva Mani Kasthuri, Arkalgud Sampath Kumar

Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi, India
Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Received 2 October 2009; received in revised form 7 January 2010; accepted 12 January 2010; Available online 25 February 2010

Abstract

Objective: To assess the effects of preoperative administration of allopurinol in patients undergoing open-heart surgery (OHS) for valvular heart diseases.

Methods: In this prospective randomised double-blind study, 50 consecutive patients undergoing OHS for valvular heart disease were randomised into two groups of 25 patients each: (a) control group received placebo and (b) test group received allopurinol prior to surgery. Serum troponin T and creatine phosphokinase-MB (CPK-MB) isoenzymes were measured prior to the induction of anaesthesia, at the time of aortic cross-clamp release and 24 h following termination of cardiopulmonary bypass. Postoperatively assessed parameters were inotropic score, rhythm, and duration of mechanical ventilation and occurrence of a low cardiac output state.

Results: Significant differences were observed with respect to inotropic score: median 5 ((0—25) vs 0 (0—25) p = 0.027) and mean 6.44 ± 6.145 versus 3.4 ± 5.54, mean duration of mechanical ventilation (11.1 ± 4.9 vs 7.5 ± 2.5 h, p = 0.002), hospital stay (6.35 ± 1.43 vs 5.04 ± 0.611, p = 0.001) and maintenance of normal sinus rhythm (NSR) (18 vs 25, p = 0.004) between the control groups versus the test group, respectively. There were no significant differences in the levels and trends of troponin T and CPK-MB between the two groups.

Conclusion: The administration of allopurinol prior to OHS for valvular heart diseases is associated with increased conversion and maintenance to normal sinus rhythm, reduced inotropic score and a reduction in the duration of mechanical ventilation and hospital stay. There was, however, no significant difference in the blood levels of CPK-MB and troponin T and a large sample size is required to assess this further.

© 2010 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Open heart surgery; Cardiopulmonary bypass; Allopurinol; Valvular heart diseases

1. Introduction

Cardiopulmonary bypass (CPB) is associated with a systemic inflammatory response syndrome (SIRS) with the activation of the complement system and granulocytes [1]. The latter results in the production of free radicals or reactive oxygen species (ROS), which can produce myocardial damage by lipid peroxidation of the cell membrane [2] that results in loss of cellular homeostasis, leading to myocardial oedema and dysfunction. This ROS-mediated myocardial damage is prominent following the release of aortic cross-clamp when oxygen-rich blood perfuses the myocardium, leading to reperfusion injury.

Myocardial damage can theoretically be minimised or avoided with the use of antioxidants or free-radical scavengers such as allopurinol, vitamin E and pentoxiphylline [3]. Allopurinol has been shown to reduce the production of ROS by inhibiting the enzyme xanthine oxidase (XO) that plays an important role in mediating reperfusion injury [4,5]. Malondialdehyde [5] has been proven to be an end product of lipid peroxidation in earlier studies, and myocardial enzymes troponin T and creatine phosphokinase-MB (CPK-MB) are established markers of myocardial damage. The clinical significance of alterations in these markers is not clear. In this study, we attempted to explore the role of preoperative administration of allopurinol in patients undergoing surgery for valvular heart diseases with particular reference to their clinical course and biochemical alterations.

2. Patients and methods

Between October 2008 and December 2008, 50 consecutive patients with valvular heart diseases undergoing open-heart surgery (OHS) under CPB at the Department of
Cardiothoracic and Vascular Surgery, All India Institute of Medical Sciences, India, were included in this pilot study. Informed consent was obtained from all patients and the institute ethics committee approved the study protocol. Exclusion criteria included patients on preoperative inotropic support, those undergoing surgery on an emergency basis and patients with associated coronary artery disease.

2.1. Randomisation

All 50 patients were randomised into two groups: those receiving allopurinol (test, T) and those who did not receive allopurinol (control, C). The study was double-blinded to avoid bias and patients received either sugar-coated tablets or tablets containing allopurinol 300 mg the night before the surgery and on the morning of the day of the surgery. Baseline blood levels of troponin T and CPK-MB were obtained prior to induction of anaesthesia by drawing 5 ml blood.

2.2. Anaesthesia and surgical technique

Anaesthesia was induced and maintained by weight-related doses of thiopental, fentanyl, midazolam and pancuronium. All patients received ceftazidime as antibiotic prophylaxis after induction of anaesthesia and during the next 48–72 h. CPB was carried out using a non-pulsatile roller pump, membrane oxygenators and standard (uncoated) extracorporeal circuits under normothermia allowing for a drift in temperature during CPB towards mild hypothermia (34 °C). The circuit was primed with appropriate amounts of Ringer’s Lactate solution, mannitol and sodium bicarbonate. Blood was added when the haemoglobin was less than 7 g/100 ml. Valve replacement/repair was carried out using standard surgical techniques. No patient in both the groups underwent Maze procedure or left atrial reduction surgery. A 5-ml blood sample was collected immediately after aortic unclamping. Inotropes were not started on elective basis in these patients and were added only if required. In the absence of methods to determine the cardiac index, the type, dose and duration of inotropic support were based on the overall clinical status of the patients and followed the accepted clinical critical care guidelines.

After surgery, all patients were transferred to the intensive care unit (ICU) and received standard ICU care. Inotropic support was optimised as per requirement and the dose and duration of the inotropic support was recorded. No steroids or non-steroidal anti-inflammatory drugs were given throughout the investigation period. Opioids were administered for postoperative analgesia. A second sample of 5-ml blood was withdrawn 24 h after the first sample.

No patient received amiodarone or calcium-channel blockers in the postoperative period. Postoperatively assessed parameters were rhythm, requirement of inotropic support, duration of ventilation and occurrence of a low cardiac output state. Inotropic requirement was assessed in terms of the standard inotropic score [6] that is calculated as follows:

Inotropic score

\[
= \text{dose in mcg kg}^{-1} \text{min}^{-1} \times (\text{dopamine} + \text{dobutamine}) \times 1 + \text{milrinone} \times 30 + (\text{epinephrine} + \text{norepinephrine}) \times 100
\]

CPK-MB was estimated using a solid phase, NAC-activated enzyme-labelled immunological UV test (Centronic GmbH-Germany). The normal value of CPK-MB using this test kit is less than 24 units l\(^{-1}\). Troponin T was estimated by a solid phase, enzyme-labelled chemiluminescent immuno-metric assay (ELECSYS, Troponin T Third Generation Kit, Roche Diagnostics, GmbH, Mannheim, Germany). The normal value of troponin T using this test kit ranges from 0.5 to 2 ng ml\(^{-1}\).

Transthoracic echocardiography was performed on postoperative day 0 and day 1 for complete assessment of the valves and biventricular function.

2.3. Statistical methods

Statistical analysis was carried out using STATA 9.0 (College Station, Texas, USA). Data were presented as number (%) or mean ± SD/median (range). Continuous characteristics were compared between the groups using Student’s t-test or Wilcoxon rank sum test for non-normal data and categorical variables were compared using Fisher’s exact test. The generalised estimating equation was used to compare the differences in mean values of troponin T and CPK-MB between the groups since the data were correlated. The p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient population, pre-procedure variables and operative characteristics (Tables 1–3)

A total of 50 patients were studied in two groups of 25 each: those who received allopurinol (test, T) and those who received placebo (control, C). The mean age was 35.04 ± 13.73 years in the control group and 27.08 ± 13.33 years in the test group. The male/female ratio was 14:11 in the C group and 13:12 in the T group. The demographic profile, pre-procedure variables and operative characteristics were no different in the two groups.

3.2. Postoperative characteristics (Table 4)

There were two deaths in the control group: one was due to accidental liver injury during chest-tube insertion and another due to cardiac tamponade on the sixth postoperative day. There was a statistically significant difference in inotropic requirements (5 (0–25) vs 0 (0–25) \(p = 0.027\)), requirement of postoperative mechanical ventilation (11.08 ± 4.92 vs 7.48 ± 2.52 days, \(p = 0.002\)) and hospital
AF: atrial fibrillation; NSR: normal sinus rhythm.

Preoperative AF to Postoperative NSR:AF 18:7 25:0 0.004

Mean hospital stay (days) 6.35/C6

Mortality 2 (8%) 0 0.49

Following surgery in either group.

No patient converted from NSR to AF NSR. Postoperative cardiac rhythm was stable in both the

of eight patients from the control group converted from AF to NSR, which was maintained till discharge while only one out

patients with preoperative AF in the test group converted to

significantly higher in patients receiving allopurinol. All four

The conversion to NSR from atrial fibrillation (AF) was

normal sinus rhythm (NSR) as compared to the control group.

However, there were no significant differences in post-

operative mediastinal drainage and hospital mortality.

 Patients in the T group showed better maintenance of

normal sinus rhythm (NSR) as compared to the control group.

The conversion to NSR from atrial fibrillation (AF) was significantly higher in patients receiving allopurinol. All four patients with preoperative AF in the test group converted to NSR, which was maintained till discharge while only one out of eight patients from the control group converted from AF to NSR. Postoperative cardiac rhythm was stable in both the groups till discharge. No patient converted from NSR to AF following surgery in either group.

Results of cardiac enzyme analysis between the two groups are presented in Table 5 and the trend analysis is shown in Figs. 1 and 2. Base-line levels of CPK-MB were within normal range in all patients in both the groups. These levels increased marginally, immediately after aortic unclamping but were still within the normal range. Higher values were noted in three patients in the C group, but the highest value among them was 24 u l\(^{-1}\). Higher values were noted even in the T group in seven patients and the highest value among them was 30 u l\(^{-1}\). Data from samples collected after 24 h showed further elevation in CPK-MB levels but 50% of patients in both the groups had values within the normal range. However, when the mean values were compared, there was a threefold increase in the CPK-MB levels from the base line in both the groups. The highest recorded value was 35 u l\(^{-1}\). The ’t’ test performed to compare the CPK-MB levels of patients

stay (6.35 \pm 1.43 vs 5.04 \pm 0.611 days, \( p = 0.001 \)) with results being better in the T group than in the C group. However, there were no significant differences in postoperative mediastinal drainage and hospital mortality.

Patients in the T group showed better maintenance of normal sinus rhythm (NSR) as compared to the control group. The conversion to NSR from atrial fibrillation (AF) was significantly higher in patients receiving allopurinol. All four patients with preoperative AF in the test group converted to NSR, which was maintained till discharge while only one out of eight patients from the control group converted from AF to NSR. Postoperative cardiac rhythm was stable in both the groups till discharge. No patient converted from NSR to AF following surgery in either group.

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C</th>
<th>Group T</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>RHD MS</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>RHD MR</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>RHD AS</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>RHD AR</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>RHD MS AS</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RHD MR AR</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RHD MS AR</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>RHD MR AS</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Associated TV involvement</td>
<td>2</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>Reduced LV function</td>
<td>3</td>
<td>1</td>
<td>0.297</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C</th>
<th>Group T</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td>MV repair</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>MVR</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>MV repair, AVR</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DVR</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>MVR, AV repair</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Associated TV repair</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>AOXL (min)</td>
<td>60.6 \pm 25.37</td>
<td>78.92 \pm 40.92</td>
<td>0.064</td>
</tr>
<tr>
<td>CPB (min)</td>
<td>80.12 \pm 27.72</td>
<td>110.16 \pm 54.14</td>
<td>0.07</td>
</tr>
</tbody>
</table>


![Fig. 1. Comparison of trend of serum CPK-MB. X axis denotes the enzyme values and the numbers 1, 2 and 3 indicate the readings at preoperative levels, following aortic clamp release, and at 24 h, respectively. Group: \( p = 0.405 \), time: \( p = 0.001 \), time \times group interaction: \( p = 0.280 \), not statistically significant.](image1)

![Fig. 2. Comparison of trend of troponin T. X axis denotes the enzyme values and the numbers 1, 2 and 3 indicate the readings at preoperative levels, following aortic clamp release, and at 24 h, respectively. Group: \( p = 0.598 \), time: \( p = 0.001 \), time \times group: \( p = 0.165 \), not statistically significant.](image2)
in both the groups showed insignificant difference between both the groups at all three points at a 95% confidence interval.

Similar comparison was performed for serum troponin T levels. All patients in both the groups had a normal base-line serum troponin T value except one patient in the T group who had a higher value at the base line. Post-aortic unclamping levels of troponin T showed that more than 50% of patients in both groups had blood levels above the normal range. The highest value in the control group was 3.2 ng ml\(^{-1}\), while the same in the T group was 3.5 ng ml\(^{-1}\). Troponin T levels after 24 h in both the groups were beyond the normal range. Six patients in both groups had levels within the normal range. The highest recorded value in both the groups was 4 ng ml\(^{-1}\). The ‘t’ test performed to compare the troponin T levels of both the groups showed insignificant difference between both the groups at all three points at a 95% confidence interval.

4. Discussion

Stimulated by the documented cardio-protective effects of allopurinol in patients undergoing coronary artery bypass grafting, we started using allopurinol in patients undergoing surgery for valvular heart disease nearly 5 years ago and consistently observed excellent results in these patients. Our experience was, however, not studied or documented and formed the basis for this double-blind randomised study. To the best of our knowledge, there is no double-blind randomised study to assess the efficacy of allopurinol as a cardio-protective agent in patients undergoing surgery for valvular heart disease. We attempted to address this issue in this study.

Our results show that patients receiving allopurinol prior to surgery under CPB fare better as compared to their counterparts who did not receive allopurinol in terms of larger conversion of patients in AF to NSR, better maintenance of NSR, decreased inotropic requirements, decreased duration of postoperative mechanical ventilation and shorter hospital stay. The conversion from AF to NSR was stable despite the fact that left atrial reduction and anti-arrhythmia surgery was not performed in any patient. These findings are similar to other studies in patients undergoing coronary artery bypass surgery (CABG) where it was found that preoperative administration of allopurinol was associated with reduced cardiac complications such as arrhythmias and heart failure [7,8]. Although in both these studies conversion from AF to NSR and vice versa was not studied separately, it was observed by Rashid and William-Olsson [8] that only one patient out of 45 had postoperative AF in the allopurinol group compared with five out of 45 in the group not receiving allopurinol. The Maze procedure has been widely used to achieve conversion from AF to NSR; however, we do not perform this procedure routinely. We also believe that the addition of this procedure in our patients would have complicated our analysis and made it difficult for us to attribute conversion to NSR to the drug or the Maze procedure or to a combination of both.

Patients in the T group had a better cardiac performance in terms of decreased inotropic requirements. However, this did not manifest in terms of better left ventricular function on postoperative transthoracic echocardiography. This also correlates with other studies in patients undergoing CABG receiving allopurinol, where they were found to have decreased inotropic requirements [8,9]. Conclusive demonstration of better cardiac function requires objective determination of cardiac index in these patients; we were, however, hampered by the lack of availability of this investigation. Therefore, we relied on less inotropic score and less duration of mechanical ventilation as indirect evidence of better cardiac function.

Reduced postoperative mechanical ventilatory requirements in patients receiving allopurinol were probably because of the effect of allopurinol acting as a free-radical scavenger that may protect the lungs against free-radical-mediated damage. In the absence of functional parameters of pulmonary function such as pulmonary index or alveolar—arterial oxygen tension difference (A-aDO2), this too seems speculative but our observations are strengthened by previous studies, which have shown that antioxidants, such as allopurinol, protect the lungs by decreasing pulmonary endothelial dysfunction after CPB [10].

The reduced hospital stay in the T group could be due to better cardiac performance reflected in terms of lesser inotropic requirements and hence lesser duration of inotropic and mechanical ventilatory support, which ultimately decreased the hospital stay in patients of the C group.

Trend analysis of blood levels of both the cardiac enzymes is suggestive of myocardial damage during CPB. However, to attribute this to lipid peroxidation due to free radicals would need estimation of lipid peroxidation end products [5] or direct estimation of free radicals [11]. Estimation of CPK-MB and troponin T is suggestive only of myocardial damage and not its cause. It has been found that CPK-MB and troponin T levels rise after cardiac surgery and the peak levels are found at 24 h. The rise in the levels has been shown to correlate with the extent of surgery in terms of CPB time. The maximum rise in CPK-MB levels was 32 u l\(^{-1}\) in the C group and 35 u l\(^{-1}\) in the test group, which is similar to the rise in CPK-MB levels in patients undergoing cardiac surgery under short CPB. Changes in the troponin T levels suggest that troponin T and lipid peroxidation products may increase during uncomplicated cardiac surgery in patients without signs of myocardial infarction. It has, however, been demonstrated previously that following uncomplicated cardiac surgery, moderate increases of cardiac troponin T may not reflect severe cardiac injury [12].

4.1. Study limitations

The primary limitation of our study is a small sample size. Assessment of the trends in alterations of cardiac isoenzymes would need a larger number of patients. The samples were not taken beyond 24 h and further changes in these levels are not clear. Another limitation was the lack of estimation of end products of lipid peroxidation or direct estimation of free radicals. We did not monitor cardiac output in either group. Ideally, these measurements in a larger sample size would provide a more conclusive answer and better elucidate the efficacy of allopurinol in these patients. Although there is a paucity of published data as well as lack of firm evidence
regarding conversion from AF to NSR in such patients without anti-arrhythmia surgery, we did not perform the Maze procedure for reasons detailed above. We were seriously hampered by the lack of resources to study the effect of allopurinol objectively by using indices of cardiac and pulmonary function. Better cardiac performance was reflected indirectly by the lesser need for inotropes and shorter time to extubation. Similarly, lesser duration of mechanical ventilation was an indirect indicator of better pulmonary function, although we must confess that the cardiac performance and pulmonary function are often linked to each other and objective criteria are needed to separately assess each parameter. However, we do believe that the strength of this study is its ability to stimulate further research in this direction. Further double-blind randomised controlled clinical trials with objective assessment of cardiac and pulmonary functions along with estimation of products of lipid peroxidation and other inflammatory mediators are required.

5. Conclusion

The administration of allopurinol prior to OHS for valvular heart diseases is associated with increased conversion and maintenance to NSR, reduced inotropic score and a reduction in the duration of mechanical ventilation and hospital stay. There was, however, no significant difference in the blood levels of CPK-MB and troponin T and a large sample size is required to assess this further.

References


Appendix A. Conference discussion

Dr M. Zembala (Zabrze, Poland): It is not easy to discuss this paper because the valve group is certainly not homogeneous. There is a substantial difference between symptomatic aortic stenosis and asymptomatic mitral incompetence you put together. However, I would like to compliment you for choosing this subject for two reasons: first, after 20 years most of the papers focus on patients operated on for coronary artery disease (CABG), you elevate the problem in a broader spectrum. Secondly, in the last three years in the literature there is growing interest in the role of allopurinol in blood rheology rather than cellular metabolism. This brings me to the first important question: what is, in your opinion, the optimal dose of allopurinol?

The literature suggests a dose of at least 600 mg administered 24 h prior to surgery. The second dose should be on the day of surgery, and again 600 mg. What is your theory behind the administration of only half of the recommended dose? What is your explanation for this approach?

Dr Talwar: Regarding the optimal dose of allopurinol, this has been the subject of intense speculation for a long time now. As we all know, the majority of data we have regarding the role of allopurinol is related to patients undergoing CABG, and if you look back at the literature, there is a wide variation. If you look at the literature from the University of Gothenburg, they started to do this preoperatively, and then they gave a dose of 600 mg for two days, then 600 mg prior to the night of the operation, and then another dose in the morning. At the same time, if you look at the 1994 report from the Harefield Hospital.

Dr Zembala: It is difficult to discuss fully the pharmacokinetics, but let’s keep in mind the very strong pharmacology against these doses.

The second, perhaps even more interesting, question is about hyperuricemia, as it is becoming an important marker of metabolism. I would like to know if a patient with elevated uric acid serum level should be treated with allopurinol before surgery? Your paper does not clearly define the margins at which treatment should be initiated. For how long should this treatment be continued? I think it is something which should be incorporated in this very interesting study.

Dr Talwar: I would like to point out here that all these patients had normal serum uric acid levels, so they did not have hyperuricemia. Now, as far as we know, if we are confronted with a patient with hyperuricemia, we should first be prompted to exclude the noncardiac causes of hyperuricemia, and once we know, if we are confronted with a patient with hyperuricemia, I think the management should follow the standard guidelines for hyperuricemia, which are: In cases of mild elevation, a 100 to 200 mg dose per day is enough, for patients with moderate elevation, it is 300 to 600 mg day$^{-1}$, and for severe it is 600 to 900 mg day$^{-1}$. Mind you, the only problem with the higher doses is that it can lead to renal insufficiency.

And coming back to the terminal part of the first question, I think the answer on the optimal dose of allopurinol will have to be addressed by further trials. We need to formulate a study in which we administer three different types of doses for varying periods of time and then assess its effects in a better fashion. That would be a better guideline.

Dr Zembala: I agree with you but a much more homogeneous group should be taken into account.