Monitoring Adverse Drug Reactions in Coronary Thrombosis Patients Admitted to Intensive Cardiac Care Unit in a Tertiary Care Hospital

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ABSTRACT

Adverse drug reaction (ADR) has been considered as a major threat to healthcare. Many studies continue to explore the incidence, causality and preventability of ADRs in different setup of healthcare so as to minimize or avoid them and to ensure better health care. The main objective of the study was to monitor, record, and analyze suspected ADRs in coronary thrombosis patients admitted to intensive cardiac care unit (ICCU). The study was conducted at tertiary care hospital for duration of six months. Patients aged more than 18 years of either gender with established diagnosis of coronary thrombosis admitted to ICCU or referred to the hospital were included in the study. During the study period, a total of 86 patients were monitored, of which 44 patients experienced ADRs which accounted for 51.16% of incidence and totally 130 ADRs were observed. Each patient on an average experienced at least 2.95 ADRs. Anti-anginals (30.76%) were one of the most common drug class implicated especially nitroglycerin (23.84%) in causing ADR like hypotension (39.23%). Cardiovascular system (CVS) [47.69%] was the most common organ system affected. Out of 44 patients with ADRs, drug was withdrawn in 33 patients and specific treatment was administered to 11 patients in view of clinical status. Full recovery was observed in 25 patients. Majority of the suspected reactions were reported to be possible (73.84%), not preventable (83.84%) and mild (79.23%) on causality, preventability and severity assessment. Higher incidence of ADRs was reported in coronary thrombosis patients admitted to ICCU. Strategies to avoid preventable ADRs will certainly minimize the hospital stay and healthcare cost.

Keywords: Adverse drug reactions, Coronary thrombosis, Causality, Severity, Preventability.

INTRODUCTION

Adverse drug reaction (ADR) has been considered as a major threat to healthcare. Various prospective studies have proved that it poses healthcare burden not only in terms of morbidity and mortality but also in terms of enhanced healthcare cost. Many studies continue to explore the incidence, causality and preventability of ADRs in different setup of healthcare so as to minimize or avoid them and to ensure better health care. With increasing human life span as a result of improved health care system, non-communicable diseases are drastically contributing for increased mortality and morbidity. It has been estimated that every minute an American die of heart attack. As per WHO survey, burden of cardiovascular disorders is quite prevalent in developing countries like India. With the evolution of effective modern therapeutic interventions, mortality rate has drastically come down but drug related problems like adverse drug reactions, drug interactions are still prevailing. In USA, ADR is estimated to be the 4th to 6th leading cause of death. Previous studies have reported the prevalence of hospital admissions due to ADRs which ranged from 2.4 to 12.0%. The incidence of fatal adverse drug reactions in hospitalized patients has been reported to be ranging from 0.05% to 0.44% while the incidence in patients experiencing ADRs during hospital stay ranges from 0.05% to 0.19%. In another study, the incidence of fatalities caused by ADRs in hospital was found to be 6.4%. It is well known that cardiac patients are aggressively treated in ICCU. Drugs which are used to treat cardiac patients could lead to ADRs or other drug related problems which in turn could affect their clinical condition, outcome of therapy and also may add up to their overall healthcare cost. There is a need to investigate the incidence, causality and preventability of ADRs in cardiac patients so as to develop strategies to prevent or effectively manage ADRs. However, there is dearth of literature on study of ADRs among cardiac patients. Therefore, the present study was undertaken to estimate the...
incidence of, and to analyze the ADRs among patients of coronary thrombosis admitted to intensive cardiac care unit (ICCU).

The main objective of the study was to monitor, record, and analyze suspected ADRs in coronary thrombosis patients admitted to ICCU, in order to report their incidence, pattern, their relation to patients' demographics, drug class implicated, organ system affected, their management and outcome aspects. The secondary objective of the study was to analyze the observed ADRs to assess their causality, severity and preventability.

**MATERIAL AND METHODS**

This study was conducted at KLES Dr Prabhakar Kore Hospital and Medical Research Center, Belgaum, Karnataka. The tertiary care hospital with 2200 bed capacity provides medical care to cardiac patients of northern part of Karnataka and neighbouring states. The study was carried out for a period of six months from Jan 2009 to June 2009. Ethical approval (KLEU/08-09/D-10508) was obtained from the Institutional Ethics Committee before initiating the study. Informed consent (in vernacular language) was sought from the patients before their enrollment, on the basis of inclusion and exclusion criteria. Patients aged more than 18 years of either gender with established diagnosis of coronary thrombosis admitted to ICCU or referred to the hospital were included in the study. Patients who refused to participate were excluded. During the study, patients were monitored from the day of admission to ICCU till the day of discharge from ICCU. The details were collected in patient profile form designed for the study purpose. The details included demographics, medical history, medication history, history of drug allergy along with causative drug, current therapy, suspected ADR, description of ADR, date of onset, dechallenge and rechallenge details, management and outcome aspects. Suspected ADRs were analyzed using standard assessment scales. Causality assessment was performed using WHO probability scale\(^\text{23}\) in order to categorize suspected drug implication with observed reaction as certain, probable, possible, unlikely, conditional or unclassifiable. Severity assessment was carried out using Hartwig et al scale\(^\text{24}\) categorizing the reaction as mild or moderate or severe. Preventability assessment of observed ADRs was done using modified Schumock and Thornton scale\(^\text{25}\) to categorize the reaction as definitely preventable, probably preventable or not preventable.

**RESULTS**

During the study period, a total of 86 patients were monitored, of which 44 patients experienced ADRs which accounted for 51.16% of incidence and totally 130 ADRs were observed. Majority of the patients (n= 27) experienced 2-5 ADRs, followed by 13 patients who suffered from single ADR, while in remaining 4 patients more than 5 ADRs were suspected; and one of these four patient was suspected to suffer with an exceptionally as high as 10 ADRs. During the study, it was observed that each patient on an average experienced at least 2.95 ADRs.

**Demographics and ADR incidence:**

Among 74 male patients monitored, 34 patients experienced ADRs, with the incidence of 45.94%. On the other hand, 10 out of 12 female patients experienced ADRs with the incidence of 83.33%. Male patients above the age of 60 years were found to have higher incidence (50%), while the incidence rate was greater among female patients irrespective of their age group. Regarding ADR distribution, highest number of ADRs were recorded among males [94 out of 130 (72.30%)] as compared to females [36 out of 130 (27.69%)]. Male patients within the age group of 50-60 years experienced highest number of ADRs [50 (38.46%)] as compared to female patients within the age group of less than 50 years [15 (11.54%)].

Prescription audit revealed that average number of drugs prescribed per patient irrespective of the age and gender was found to be 11.16.

Male patients (n= 20) within the age group of 50-60 years with other co-morbidities such as diabetes mellitus, hypertension etc. were greater in number than female patients (n= 3) within similar age group. All these patients (n= 23) with co-morbidities were found to have highest number of ADRs [62 (47.69%)] when compared to those in other age groups (Table 1).

**Factors associated with ADRs:**

In the present study, mean age was recorded as 53.70 years in patients with ADRs as compared to 52.47 years in patients with no ADRs which was statistically not significant (p=0.43). The mean number of drugs in patients with ADRs was 12.63 as compared to 9.62 in patients with no ADRs which was found to be statistically significant (p=0.002). The mean number of days of ICCU stay was recorded as 8.32 days in patients with ADRs as compared to 5.76 days in patients with no ADRs which was found to be statistically significant (p=0.003). Association between co-morbidity and ADR was analyzed using chi square test. There was no statistical association observed (p= 0.80) (Table 2).

**Risk assessment and ADR incidence:**

Patient's clinical condition was assessed based on risk categories. Patients with multiple diseases or advanced age were categorized under high risk group. In high risk group, 24 out of 49 patients experienced 67 (51.53%) ADRs,
In the present study, the most common adverse drug reaction was reported to be hypotension (39.23%) followed by elevated activated partial thromboplastin time (aPTT) (16.15%), headache (9.23%), bradycardia (6.92%), hypokalemia (3.84%), vomiting (3.84%), nausea (2.3%). Other less common (less than 2%) reactions were acute renal failure, anemia, dry cough, fever with chills, gastritis, elevated serum creatinine, instent restenosis, thrombocytopenia, bleeding, blurring of vision, tachycardia and ventricular tachycardia.

In our study, majority of the patients experienced nitroglycerin induced hypotension (13.07%) followed by heparin induced elevated aPTT (10.77%), streptokinase induced hypotension (8.46%), nitroglycerin induced headache (6.92%), metoprolol induced bradycardia (5.38%), frusemide induced hypotension (4.61%), metoprolol induced hypotension (3.85%), frusemide induced hypokalemia (3.85%) and nicorandil induced hypotension (3.07%) etc.

**Drug class implicated and organ system affected with ADRs:**

Majority of ADRs were found to be due to cardiac medications (93.84%) compared to non-cardiac medications (6.15%). Anti-anginals (30.76%) were one of the most common drug class implicated with ADRs followed by anti-hypertensives (26.15%), anti-coagulants (13.84%), and fibrinolytics (13.07%). Cardiovascular system (47.69%) was the most common organ system affected due to ADRs followed by haematological system (20.76%), central nervous system (9.23%), and gastrointestinal system (8.46%) [Table 3].

**Suspected drug, ADRs and affected system:**

Among the anti-anginals, the most common drug implicated with ADRs was nitroglycerin (23.84%) followed by heparin (13.84%), streptokinase (10%), metoprolol (9.23%), frusemide (8.46%), nicorandil and ramipril (5.38% for each), aspirin (4.6%) clopidogrel and reteplase (3.07% for each). Drugs like atenolol, cefotaxim, ceftriaxone and drug eluting stent contributed for minimal number of ADRs with the incidence of 1.54% for each. Other drugs with minimum number of ADRs (less than 1% each) were amlodipine, artesunate, abciximab, atenolol plus hydrochlorothiazide, cefuroxime, cefpodoxime, ciprofloxacin, isosorbide dinitrate and isosorbide mononitrate.

In the present study, the most common adverse drug reaction was reported to be hypotension (39.23%) followed by elevated activated partial thromboplastin time (aPTT) (16.15%), headache (9.23%), bradycardia (6.92%), hypokalemia (3.84%), vomiting (3.84%), nausea (2.3%). Other less common (less than 2%) reactions were acute renal failure, anemia, dry cough, fever with chills, gastritis, elevated serum creatinine, instent restenosis, thrombocytopenia, bleeding, blurring of vision, constipation, haematoma, itching, tachycardia and ventricular tachycardia.

In our study, majority of the patients experienced nitroglycerin induced hypotension (13.07%) followed by heparin induced elevated aPTT (10.77%), streptokinase induced hypotension (8.46%), nitroglycerin induced headache (6.92%), metoprolol induced bradycardia (5.38%), frusemide induced hypotension (4.61%), metoprolol induced hypotension (3.85%), frusemide induced hypokalemia (3.85%) and nicorandil induced hypotension (3.07%) etc. [Table 4].

**Table 1: Demographics and ADR incidence**

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of patients (n=86)</th>
<th>No. of patients with ADRs (n=44)</th>
<th>No of ADRs (n=130)</th>
<th>Average no. of drugs prescribed</th>
<th>No. of patients with co-morbidities (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>M: 16 F: 3</td>
<td>M: 8 F: 2</td>
<td>M: 17(13.07)</td>
<td>9(6.92)</td>
<td>11.06</td>
</tr>
<tr>
<td>Total</td>
<td>M: 74 F: 12</td>
<td>M: 34 F: 10</td>
<td>M: 94</td>
<td>36</td>
<td>-</td>
</tr>
</tbody>
</table>

M: Male; F: Female; Patients with co-morbidities such as diabetes mellitus, hypertension, asthma and others. Figure in parenthesis denotes percentage.

**Table 2: Factors associated with ADRs**

<table>
<thead>
<tr>
<th>Factors</th>
<th>During hospitalization in ICCU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years*</td>
<td>No ADR (n=42)</td>
</tr>
<tr>
<td>Mean no. of drugs*</td>
<td>52.47 (49.56-55.39)</td>
</tr>
<tr>
<td>Mean no. of days of ICCU stay*</td>
<td>9.62 (9.0-10.23)</td>
</tr>
<tr>
<td>Co-morbidity*</td>
<td>5.76 (4.22-7.31)</td>
</tr>
<tr>
<td>Co-morbidity*</td>
<td>25</td>
</tr>
</tbody>
</table>

*Mann-Whitney test for statistical analysis; *Chi square test for statistical analysis.
Management and outcome aspects of ADRs:

Out of 44 patients with ADRs, drug was withdrawn in 33 patients and specific treatment was administered to 11 patients in view of clinical status. Full recovery was observed in 25 patients and rest of the patients had partial recovery.

Regarding the treatment, suspected drug was withdrawn in 48.46% of ADR reports, with which the recovery was seen in 33.07%. Dose of suspected drug was altered in 6.15% of reports, and the recovery was observed in 3.85%. Rechallenge was considered in 5 patients in view of clinical condition but symptoms reappeared in one patient after rechallenge.

Specific treatment for the management of suspected reaction was administered in 36.92% of ADR reports. Symptomatic treatment (8.46%) was also considered in case of minor ADRs. Recovery was seen in 36.15% when both treatment modalities were opted. On the contrary, recovery was also seen in 39.23% without using any treatment modality as most of the mild reactions were self-subsided.

Causality and preventability assessment of ADRs:

Causality assessment revealed that majority of the suspected reactions were possibly (73.84%) due to suspected drugs followed by probable (20%) and certain (5.38%) implication of suspected drug. On preventability assessment, majority of the suspected reactions were reported to be not preventable (83.84%) followed by probably preventable (15.38%) and definitely preventable (0.76%) reactions [Table 5].

Severity assessment of ADRs:

Severity assessment indicated that 79.23% of the suspected reactions were mild while 20.77% were moderate and none of them were severe in nature.

### Table 4: Suspected drug, ADRs and affected system

<table>
<thead>
<tr>
<th>Causative drug</th>
<th>System affected</th>
<th>ADR</th>
<th>No. of ADRs</th>
<th>Total No. of ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin, streptokinase, metoprolol, frusemide, nicorandil, ramipril, reteplase, atenolol, isosorbide dinitrate, atenolol plus hydrochlorothiazide</td>
<td>Cardiovascular</td>
<td>Hypotension</td>
<td>51 (39.23)</td>
<td>62 (47.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bradycardia</td>
<td>9 (6.92)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia</td>
<td>1 (0.77)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular tachycardia</td>
<td>1 (0.77)</td>
<td></td>
</tr>
<tr>
<td>Heparin, streptokinase, clopidogrel, nicorandil, nitroglycerin, abciximab</td>
<td>Haematological</td>
<td>Elevated aPTT</td>
<td>21 (16.15)</td>
<td>27 (20.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleeding (oral)</td>
<td>2 (1.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td>2 (1.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia</td>
<td>2 (1.54)</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, nicorandil, isosorbide mononitrate, ceftriaxone, streptokinase, ciprofloxacin</td>
<td>Constitutional symptoms</td>
<td>Headache</td>
<td>12 (9.23)</td>
<td>15 (11.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
<td>2 (1.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itching</td>
<td>1 (0.77)</td>
<td></td>
</tr>
<tr>
<td>Aspirin, clopidogrel, cefotaxim, cefpodoxime</td>
<td>Gastrointestinal</td>
<td>Vomiting</td>
<td>5 (3.84)</td>
<td>11 (8.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>3 (2.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastritis</td>
<td>2 (1.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation</td>
<td>1 (0.77)</td>
<td></td>
</tr>
<tr>
<td>Frusemide</td>
<td>Electrolyte</td>
<td>Hypokalemia</td>
<td>5 (3.85)</td>
<td>5 (3.84)</td>
</tr>
<tr>
<td>Cefotaxim, ceftriaxone, cefuroxime, artesunat</td>
<td>Renal</td>
<td>Acute renal failure</td>
<td>2 (1.54)</td>
<td>4 (3.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased serum creatinine</td>
<td>2 (1.54)</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>Respiratory</td>
<td>Dry Cough</td>
<td>2 (1.54)</td>
<td>2 (1.54)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Ophthalmic</td>
<td>Blurring of vision</td>
<td>1 (0.77)</td>
<td>1 (0.77)</td>
</tr>
<tr>
<td>Drug eluting stent, heparin</td>
<td>Others</td>
<td>Others</td>
<td>3 (2.30)</td>
<td>3 (2.30)</td>
</tr>
</tbody>
</table>

Figure in parenthesis denotes percentage.

### Table 5: Causality and preventability assessment of ADRs

<table>
<thead>
<tr>
<th>Causality assessment</th>
<th>No. of ADRs</th>
<th>Preventability assessment</th>
<th>No. of ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>07 (5.38)</td>
<td>Definitely preventable</td>
<td>01 (0.76)</td>
</tr>
<tr>
<td>Probable</td>
<td>26 (20)</td>
<td>Probably preventable</td>
<td>20 (15.38)</td>
</tr>
<tr>
<td>Possible</td>
<td>96 (73.84)</td>
<td>Not preventable</td>
<td>109 (83.84)</td>
</tr>
</tbody>
</table>

Causality assessment: WHO probability scale 
Preventability assessment: Modified Schumock and Thornton scale
Figure in parenthesis denotes percentage.

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DISCUSSION

Adverse drug reactions were intensively monitored in hospitalized (in ICCU) coronary thrombosis patients. In the present study, ADRs were suspected by careful evaluation of disease condition, laboratory investigation reports and considering the new medical events bearing temporal relation to suspected drug intake. Observed ADR incidence of 51%, in the present study was more than double the incidence reported in non-ICCU patients hospitalized for various health disorders. There appears to be scanty information regarding similar studies in the literature. However, results of a study carried out in the same hospital, but in non-ICCU patients indicate much lower incidence of ADRs; 4.5% (unpublished data). The high incidence of ADRs affecting every alternate patient in the present study could be due to short term study involving smaller sample size as compared to earlier studies. Other contributing factors could be multiple drug administration and presence of co-morbidities.

Acute coronary thrombosis requires aggressive therapeutic interventions involving variety of medications such as antiplatelet, anticoagulants, hypotensive agents etc. In the present study, about 11 drugs were prescribed per patient on an average and polypharmacy is a well known factor associated with drug interactions and adverse drug reactions.

The incidence of ADRs was found to be high among female patients as compared to male patients. This could be due to less number of females enrolled in the study. However, similar trend, 3.7% in males and 5.5% in females of non-ICCU patients in the same hospital has been observed in earlier study. There was no difference observed in the incidence of ADRs within age group. The association between the incidence of ADRs and presence of co-morbid conditions was reported to be statistically insignificant (p = 0.80). Other studies showed similar profile as compared to our study but few studies demonstrated lower incidence obviously due to different hospital setup, different patient profile and clinical condition, and diverse pattern in use of drug therapy.

Disappearance of ADRs on drug discontinuation in some patients and reappearance on medication rechallenge not only affirmed the suspected ADRs but also provided the evidence for causal association of drug. In the present study, about 74% of suspected ADRs were ‘possible’ in nature. Almost one third were ‘probable’ and one fifth of them had ‘certain’ causal association with suspected drug. These findings were almost similar to those of other earlier reported studies. On the contrary, dissimilar results were also reported by an earlier study.

Severity assessment indicated that 80% of the suspected reactions were mild while 20% were moderate and none of them were severe in nature. The findings were dissimilar to that of earlier study. The discrepancy could be due to large sample size and different clinical setup in earlier study. Mild reactions were more frequently occurring but there were few reactions which resulted in extension of ICCU stay by almost 2 days.

In the present study, anti-anginals were one of the most common drug class implicated with ADRs especially nitrates followed by other classes viz. anti-hypertensives, anti-coagulants and fibrinolytics. Most of ADRs with anti-anginals had occurred due to the use of intravenous infusion, which was given in the initial management of coronary thrombosis. Headache was one of the most prominent reaction observed with intravenous nitrates which was found to be reversible on discontinuation of infusion. Similar pattern of ADRs with antianginals (both in frequency and severity) have been reported.

In the present study, cardiovascular system was the most common organ system affected due to ADRs followed by haematological system, central nervous system, and gastrointestinal system. Our findings were inconsistent as compared to studies conducted earlier. The discrepancy could be due to different healthcare setup and different management strategies for ICCU and non-ICCU cases. Another factor which might have contributed for high incidence of cardiovascular ADRs could be drugs used in coronary thrombosis mainly targeted CVS.

About 84% of the suspected ADRs were not preventable whereas 16% were preventable. The findings of the present study are inconsistent as compared to those of an earlier study, where more number of preventable ADRs (45%) had been reported. The discrepancy could be due to large sample size and different clinical setup. Preventable ADRs require more specific focus so that hospital stay of the patients and healthcare costs can be minimized.

In the present study, ADRs were managed either by decreasing dose (13.64%) or temporary discontinuation of drug (75%) or using specific antidotes (25%) and/or other drugs (18.18%) to provide symptomatic relief.

Results of the present study clearly indicate that incidence of ADRs is very high in ICCU patients with acute coronary thrombosis. Surprisingly, there was no significant difference in the incidence between different age group patients and incidence was not related to the associated co-morbidities. There was positive co-relation between incidence of ADRs and duration of ICCU stay, which definitely escalates both direct and indirect healthcare costs.
Results of the present study cannot be generalized due to small sample size, a major limitation. Higher incidence of ADRs in females may not be a fact as study includes a very small number of female patients (12 females). Another limitation was lack of independent reviewer as ADR assessment as well as analysis was carried out by investigator and participating clinicians. It is very difficult to comment, the impact of ADRs on treatment outcome in ICCU patients. It is equally difficult to comment regarding their contribution for high mortality rate in coronary thrombosis patients.

CONCLUSION

Higher incidence of ADRs in acute coronary thrombosis patients was mainly due to anti-anginals followed by anti-hypertensives, anti-coagulants and fibrinolytics. The observed high incidence is possibly attributed to polypharmacy and appears to be not related to age, gender and co-morbidity. Strategies to avoid preventable ADRs, though small in number certainly minimize the hospital stay and healthcare costs.

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REFERENCES


