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Research Article

Drug-Device Combinations And Materiovigilance In The Cardiology Department Of A Tertiary Care Private Corporate Hospital

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ABSTRACT

Plan:
To categorize the drug-device combination products used in the Cardiology department and identify and report any adverse reactions related to these products.
Preface: The Materiovigilance Program plays a vital role in ensuring medical device safety in India by monitoring, identifying and reporting, and reacting to undesirable occurrences.
Methodology:
Various diagnostic, monitoring and therapeutic medical devices routinely used in the Cardiology department were systematically classified according to their associated risk. These devices were meticulously monitored and any suspected adverse reactions linked to medical devices were promptly reported to the NCC-MvPI via the materiovigilance centre of the study site.
Outcome:
A total of 1029 medical devices were enlisted and monitored, with the majority being used for therapeutic applications. Among them, 6.1% comprised of drug-device combinations, specifically, drug-eluting stents, pace makers and others. The study identified, documented and reported eighteen suspected adverse reactions associated with cardiology medical devices. Significantly, the study effectively implemented a materiovigilance program within the Cardiology department of a multispecialty hospital.

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INTRODUCTION

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. These products are helpful for patients enduring with serious illnesses and conditions like cancer, cardiovascular disease, sclerosis, diabetes, etc. On the contrary, drug-device combination products have also brought forth a contemporary dimension in medical product development and regulatory approval [1]. Examples of combination products include prefilled syringes, pen injectors, auto-injectors, inhalers, transdermal pumps and patches, kits containing drug administration devices or components, drug-eluting pacemaker leads, antiretroviral-loaded intravaginal rings, drug-coated balloon catheters, hormonal subcutaneous implants, etc [2]. As per section 62(4) of the Medical Devices Regulations, a medical device incident refers to an occurrence associated with a failure of a medical device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions to be used that has led to the death or a consequential deterioration in the state of health of a patient, user, or another person. Drug-device combination products are of important role within the diagnosis, monitoring, and management of various diseases. While the employment of medical devices benefits patients immensely, they also carry possible threats and potential risks. So, it is important to make sure the safety and efficacy of the medical devices during each stage of their development [3]. This study focuses on materiovigilance program in assessing the benefits and risks related to medical devices and combination products. The thought of materiovigilance was first originated when Johnson & Johnson hip replacement system was withdrawn globally due to their complications and harmful effects. One of the important aspects of this program is to monitor medical device-associated adverse events (MDAE), and it also helps to generate awareness among the healthcare professionals about the importance of MDAE reporting. They also play a vital role in analyzing the risk-benefit ratio of medical devices and collaborating with other healthcare organizations and international agencies for the exchange of information and data management [3]. Materiovigilance includes the identification, collection, reporting, and analysis of any unwanted occurrences related to the use of medical devices and also the protection of a patient's health by preventing its recurrences. Drugs Controller General of India established the Materiovigilance Program of India (MvPI) at Indian Pharmacopeia Commission (IPC), Ghaziabad on July 6, 2015. In 2017, the Government of India issued the Medical Device Rules for regulating medical devices used throughout the country and these rules came into effect on 1st January 2018. The government had regulated or notified 37 categories of medical devices as drugs until February 11, 2020. On February 11, 2020, the Government of India gazetted two important notifications – a new definition of medical devices and the Medical Devices (Amendment) Rules, 2020. These rules came into effect on April 1, 2020. As per this rule, all medical devices in India will be regulated as "drugs". All medical devices which weren't notified until February 11, 2020, will then be covered by the new definition of medical devices and can be observed as "Non- Notified Medical Devices". The Central Drugs Standard Control Organisation (CDSCO) released two notices on September 3, 2020, including the classification of non-notified medical devices and in-vitro diagnostic devices (IVDs). The CDSCO has classified almost 1866 medical devices and 80 IVDs. There are 24 categories of medical devices and 3 Categories of Non-Notified In-Vitro Diagnostic Medical Devices defined by CDSCO.

Materiovigilance Programme of India provides a robust, sustainable, and scaled surveillance of all medical devices, thereby encouraging patient safety related to medical devices employed within the healthcare industry in India [4]. Several serious medical devices associated adverse events (MDAE) were received by the Indian Pharmacopeia Commission till now. Numerous types of cardiac implants, including pacemakers, Implantable Cardioverter Defibrillators (ICDs), Left Ventricular Assist Devices (LVADs), Cardiac Resynchronization Therapy devices (CRTs), Transcatheter Aortic Valve Replacement (TAVR), cardiac monitoring devices, artificial heart valves etc. are widely being used for treating various cardiac disorders [5]. Devices such as drug-eluting stents and bioabsorbable stents incorporate drugs like sirolimus, everolimus, zotarolimus, paclitaxel etc. in microfabricated drug reservoirs on the surface. These medications help to inhibit the growth of cells that can cause the artery to become narrowed or blocked again [6]. Various reports had shown possible hypersensitivity reactions related to the utilization of the sirolimus-eluting stent, a few of which are fatal and patients receiving the sirolimus-eluting stent should be monitored for hypersensitivity associated symptoms such as rash, hives, itching, fever, difficulty breathing, pain, and blood pressure change. Thrombosis, anxiety, and bronchospasm caused by drug eluting pacemaker lead, epinephrine autoinjector, and inhalers were also reported. In multiple instances, some devices were recalled due to the risks and damages they caused to users. Thus, drug-device combination products are not devoid of adverse events [7]. Therefore, strict vigilance of drug- device combination products used for diagnosis, monitoring or treatment of various cardiovascular diseases is the need of the hour in order to ensure health safety patients and reduce the recurrence of the events. Therefore, this study aimed to categorize the medical devices and collect, collate and analyse the data on medical device related adverse reactions in the Cardiology department, with special focus on drug-device combinations.

MATERIALS AND METHOD

A prospective observational study was carried out in the Cardiology department of a tertiary care private corporate hospital for a period of 6 months from July to December 2022. All medical devices and drug-device combinations for diagnostic, monitoring and therapeutic purposes, both external and implanted devices used in the Cardiology department were categorized into "notified medical devices" or "newly notified medical devices" using the CDSCO classification. All inpatients of the Cardiology department were closely monitored for any medical device associated adverse reactions and all types of adverse reactions, whether serious or non-serious, pre-known or unknown were recorded after confirming with the clinician's report, irrespective of established causal relationship between event and medical device. The biomaterial used in each medical device and its safety profile was also thoroughly reviewed. Data on suspected adverse reactions related to medical devices were reported to the NCC-MvPI through the materiovigilance centre of the hospital using the Medical Device Adverse Event reporting form Version 1.1, a five-page editable form. Information such as the description of the suspected adverse reaction, details of the device, reporter, manufacturer and the regulator etc. were furnished through this form. The data thus collected were pooled and analyzed at the end of the study period. They were classified into serious, non-serious, preknown or unknown adverse reactions. Description of the device and associated risks to the users were studied thoroughly. The devices were also classified as Class A- Low risk devices; Class B- Low to moderate-risk devices; Class C- Moderate to high-

risk and Class D- High-risk devices by following the CDSCO categorization.

RESULTS

One thousand and twenty-nine devices used in sixty patients of the Cardiology department were closely monitored during the study period for any possible medical device associated adverse reactions. The mean age of the study subjects was 53.47±21.83 years (range:1 to 85 years) and the mean duration of hospitalization was 4.97±2.28 days (range:2-7 days) Of these, 45 (75%) were male patients. The demographic details are presented in table 1.

Table 1: Demographic Details Of Cardiac Patients (N=60)

Sr. No	Age group	Mean duration of hospitalization (±SD)	No. of patients	Percentage (%)
1	Children (1 to 17 years)	3.50 ± 1.05	6	10.0
2	Adult (18 to 59 years)	4.58 ± 1.32	24	40.0
3	Old (60 years & above)	5.57 ± 2.85	30	50.0

Various clinical conditions observed in study population were Coronary Artery Disease (20.5%), Diabetes Mellitus (12.4%), Systemic Hypertension (15.5%), Ischemic Heart Disease (10.5%), Acute Coronary Syndrome (9.9%) etc. Patients also had other conditions such as Pulmonary Arterial Hypertension, Atrial Septal Defect, Atrial Fibrillation, Complete Heart Block, Ventricular Septal Defect, Rheumatic Heart Disease, Heart Failure and Deep Vein Thrombosis.. Six hundred and five drugs belonging to 31 categories were prescribed in the study subjects. These included antiplatelets (20%), antianginals (8%), statins (8%) analgesics (7.6%), beta-blockers (5%), anticoagulants (5%) and others. Aspirin, heparin, atorvastatin, rosuvastatin, trimetazidine, metoprolol, hydrocortisone, spironolactone, furosemide paracetamol, fentanyl, human insulin, ceftriaxone, pantoprazole and ondansetron were some of the most frequently prescribed medications. The medical devices of Cardiology department were categorized into “notified” or “newly notified” medical devices based on the CDSCO classification. There were 36 different types of medical devices, of which 21 devices were notified medical devices and 15 newly notified medical devices. Risk based classification of the above devices indicated that only 6 devices belong to class A (low risk), followed by 14 class B (low-moderate risk), 12 class C (moderate-high risk) and 4 class D (high-risk) category (Fig 1).

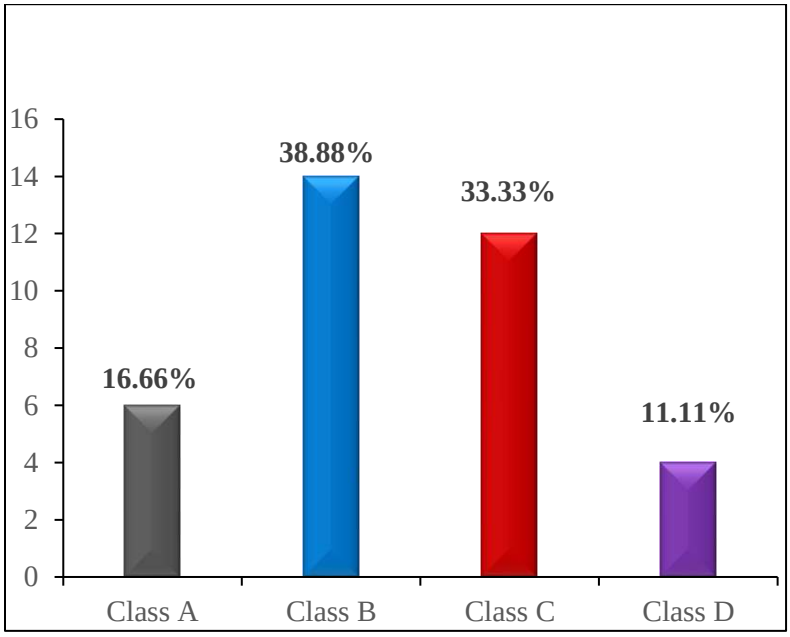

Figure 1: Risk Based Classification Of Medical Devices In Cardiology Department (N=36) A-Low Risk, B-Low-Moderate Risk, C-Moderate-High Risk, D- High Risk.

Of the 1029 devices, 63 (6.1%) were drug-device combinations. These included 3 different types of drug eluting stents such as sirolimus, everolimus and zotarolimus eluting stents (Table 2).

Table 2: Types Of Drug Eluting Coronary Stents (n=63)

Sr. No.	Drug used	Frequency
1	Sirolimus	31
2	Everolimus	20
3	Zotarolimus	12

Majority of the medical devices were used for therapeutic purposes (61.5%) followed by 23% for monitoring and 15% for diagnostic purposes. The details of the various diagnostic devices, therapeutic devices and monitoring devices are summarized in table 3, 4 and 5.

Table 3: Diagnostic Devices Used In Cardiology Department (n=272)

Sr. No	Diagnostic Devices	Frequency	%
1	Angiogram Machine	60	22.75
2	Stethoscope	60	22.7
3	ECG Machine	60	22.7
4	Thermo-Meter	60	22.7
5	Glucometer	25	9.19
6	Ryle's Tube	7	2.57

Table 4: Therapeutic Devices Used In Cardiology Department (n=516)

Sr. No	Therapeutic Devices	Frequency	%
1	Balloon	100	19.35
2	Drug Eluting Stent	63	12.2
3	Syringe Pump	60	11.6
4	Cannula	60	11.6

5	Guide Wire	46	8.91
6	Infusion Pump	45	8.72
7	Guiding Catheter	40	7.75
8	Sheath	37	7.17
9	Urinary Catheter	20	3.87
10	Catheters	10	1.93
11	Ryle's Tube	7	1.35
12	Run-through Guidewire	7	1.35
13	Guide Line	4	0.77
14	Septal Occluder	4	0.77
15	Permanent Pacemaker	4	0.77
16	Ductal Occluder	3	0.58
17	Temporary Pacemaker	2	0.38
18	Mechanical Valve	2	0.38
19	Pulse Generator	1	0.19
20	Double J Stent	1	019

Table 5: Monitoring Devices Used In Cardiology Department (n=332)

Sr. No	Monitoring Devices	Frequency	%
1	Multiparameter Machine	60	13.2
2	Thermometer	60	13.2
3	Blood Pressure Monitoring Apparatus	60	13.2
4	Bedside Monitor	60	13.2
5	Pulse Oximeter	60	13.2
6	Glucometer	25	5.53
7	Central Venous Pressure Stand Monitor	3	0.66
8	Central Supply Suction	3	0.66
9	Mechanical Ventilator	1	0.22

Eighteen suspected adverse reactions due to medical devices were detected and reported during the study period. These included hematoma, fever, headache, swelling, nausea, vomiting, blisters, discoloration, shortness of breath, chest pain, pain at puncture site due to drug-eluting coronary stent (66.6%), hematoma due to permanent pacemaker (11.1%), fever due to duct occluder (5.55%), chest pain due to septal occluder (11.1%) and abdominal pain, urge to urinate and mild chills due to DJ stent (5.55%.) Fig. 2 shows the details of medical device associated adverse reactions.

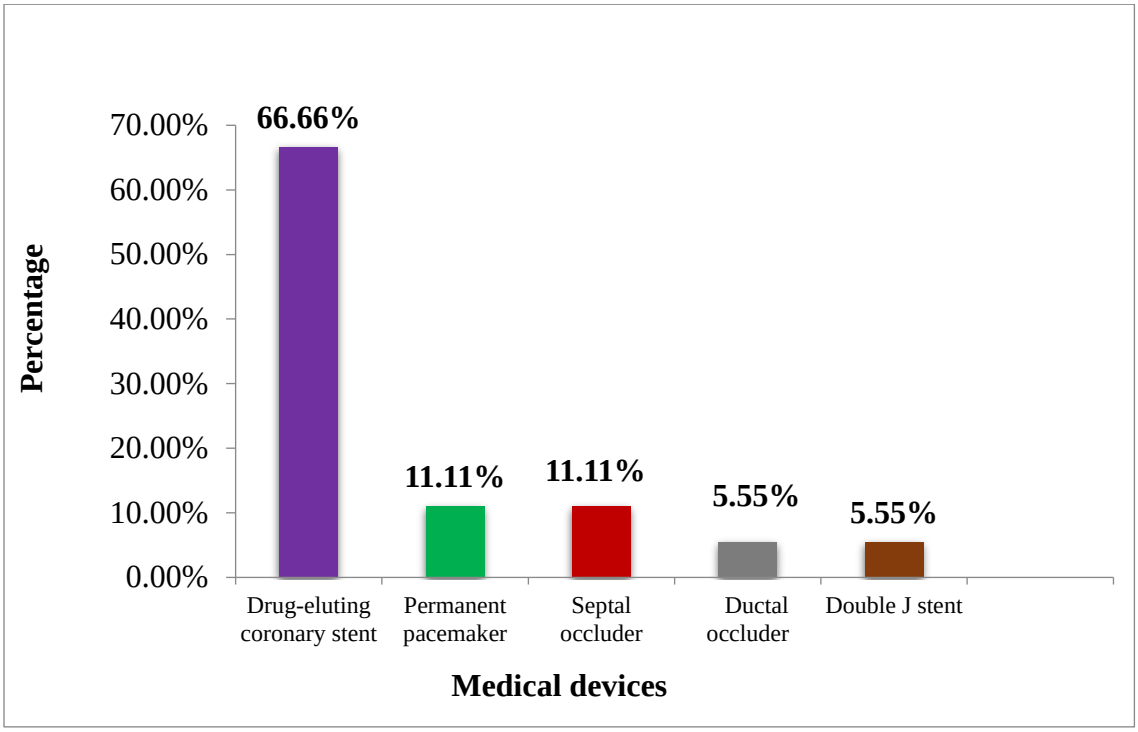

Figure 2: Medical Devices Suspected With Adverse Reactions

The data on suspected adverse reactions due to medical devices were mailed to the Materiovigilance program of India using the Medical Device Adverse Event (MDAE) reporting forms through the Medical Device Monitoring Center (MDMC) of the study site.

DISCUSSION

The current study evidenced that the use of medical devices benefits patients immensely but they also carry significant risks to the patients. The use of cardiac devices including pacemakers, catheters, sheath, balloons, guidewires, drug eluting stents implantation are increasing in number (8). Today a number of different medical devices are available for various cardiac procedures. The MvPI had been established to ensure the safety of medical devices including cardiovascular devices. The US Food and Drug Administration (FDA) defines high-risk devices as those that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury" and include such products as pacemakers, defibrillators, implanted prosthetics, and high frequency ventilators (9).The high-risk medical devices used in the cardiology department during the current study include drug-eluting coronary stents, mechanical valves, pacemaker generators, and pulse generators. The most commonly used high-risk (Class D) medical devices in cardiac patients were permanent pacemakers and drug-eluting coronary stents. Eighteen suspected adverse reactions associated with Class C (moderate-high risk) and Class D (high risk) medical devices in the Cardiology department were identified and reported during the study period. Of these, only one was serious and the patient recovered after device removal and surgical intervention. The remaining were non-serious and does not produce any harm to the study population and the patients recovered within one to three days after exposure to the adverse reactions such as fever, headache, hematoma, blisters etc. The details are presented in Table 6.

Table 6: Medical Device Associated Adverse Reactions Reported During The Study (n=18)

Sr. No	Name of the medical devices	No. of patients (%)	Adverse reactions
1	Drug-eluting coronary stent	12 (66.6%)	Hematoma, fever, headache, swelling, nausea, vomiting, blisters, discoloration, shortness of breath, chest pain, pain at the puncture site
2	Permanent pacemaker	2 (11.1%)	Hematoma
3	Duct occluder	1 (5.55%)	Fever
4	Septal occluder	2 (11.1%)	Chest pain
5	Double j stent	1 (5.55%)	Abdominal pain, urge to urinate, mild chills

The ultimate concept of drug delivery is to achieve maximum therapeutic efficacy and minimum side effect of the therapeutically active agent enhancing the clinical outcomes. The best-known drug-device combination is the drug- eluting coronary stent. In the study, 63 drug- eluting coronary stents manufactured by 9 different companies were identified and monitored. Of these, 31 were sirolimus eluting stents, 20 everolimus eluting stents, and 12 zotarolimus eluting stents. The drug sirolimus of dose 1.25ug/mm2 is used in these stents. These types of stents are mainly used for patients experiencing symptoms of heart disease due to atherosclerotic lesions, who have narrowing in their coronary arteries. The zotarolimus eluting stents of dose 1.6ug/mm2 are usually used in patients with narrowed arteries, high risk of bleeding, and who are in need for chronic or lifelong anticoagulant therapy. Seven bioabsorbable polymer based everolimus-eluting stents (of dose 1ug/mm2) were monitored. These stents are reported to be useful in improving coronary artery luminal diameter in those with high risk of bleeding, diabetes mellitus, stable and unstable angina, and symptomatic heart disease (2). In this study, out of 18 medical device associated adverse events reported, 2 were suspected to be associated with permanent pacemakers. The patients experienced complaints of hematoma which was suspected to be due to the pacemaker used. In a similar retrospective study, the duration of hospitalization and the time from temporary to Permanent Pacemaker (PPM) placement were calculated in 260 patients who underwent temporary transvenous pacing. It was found that a longer waiting period between permanent pacemaker indication and implantation was dangerous as it is associated with an increased risk of adverse events such as infections, syncope, asystole, malignant arrhythmias, cardiac arrest, and death. Thus, PPM implantation should be done within 24 hours after hospitalization with Temporary Pacemaker Implantation (TPI) to ensure lesser adverse effects and better quality of life (10). In the current study, a total of 50 cardiac catheters were closely monitored, revealing no suspected adverse events. A retrospective cohort study was conducted in 262 children with congenital heart disease who received cardiac catheterization, to determine the incidence and risk factors of adverse events associated with paediatric cardiac catheterization. Of 262 patients, adverse events occurred in 31 patients, in children ranging in age from 3 days to 16 years. There were 7 patients with higher severity adverse events, 7 with moderate adverse events and 17 patients with minor adverse events. Vascular complications represented the majority. (11). In this study, a patient was suspected with complaints of fever after implantation of a duct occluder. In a recent case report, complication of an Amplatzer duct occluder (ADO) was reported in which a patient presented increasing hemoptysis owing to ADO eroding the vessel wall and forming a pseudoaneurysm that communicated with the left main bronchus (12). The materiovigilance

program in the Cardiology department could identify and report various adverse reactions associated with medical devices and drug- device combinations, recognize the risk category of the devices and determine the severity of the reactions. This study is a vital initiative by the pharmacist in ensuring the safety of medical devices and drug-device combinations in the Cardiology department. During the study period, the medical devices used in the study population were identified and categorized into notified and newly notified medical devices, with the majority being therapeutic medical devices, followed by monitoring and diagnostic medical devices. Of these, most of the medical devices belonged to class B (low to moderate risk category) followed by class C (moderate to high-risk category), class A (low-risk category) and class D (high-risk category). Adverse reactions associated with class D devices such as drug eluting coronary stents, permanent pacemakers and class C devices such as duct occluder, septal occluder, DJ stent were identified and reported during the study.

Among the medical device-associated adverse reactions identified, the majority were non-serious and were caused due to drug-eluting coronary stents such as sirolimus, zotarolimus, and everolimus-eluting stents. These drugs are immunosuppressants, which are slowly released into the artery wall around the stent and help prevent coronary artery restenosis after the stent implantation. The study was helpful in successfully implementing materiovigilance program in the 25 bedded Cardiology department of the multispecialty hospital. As a result of this study, all devices available in the cardiology department could be enlisted and categorized into notified/newly notified medical devices and closely monitored. Further, categorizations were made based on their purpose and risk involved. Thus, the study has played a major role in supporting the Materiovigilance Programme of India (MvPI) by contributing detailed data on medical device-associated adverse reactions.

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