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A Comparative Study of Active and Passive Adverse Drug Reaction Monitoring Methods in Category I Tuberculosis Patients at a Tertiary Care Hospital in India

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Abstract

***Background & Aims*:** Adverse Drug Reactions (ADRs) are common with drug treatment. They can be collected by active and passive methods. The aim of the study was to compare active and passive ADR monitoring methods in terms of yield and lag period in category I tuberculosis patients.

Materials & Methods: A prospective observational analytical study was done in a directly observed therapy short-course (DOTS) center and pharmacovigilance center of SMS hospital, Jaipur, Rajasthan, India from 1.1.2019 to 31.12.2019. A total of 303 category I tubercular patients on DOTS were divided into groups A (150) and B (153). Group A (active) patients were interviewed personally or telephonically for ADRs on 0,3,7,15,30, 90,180 days of therapy as per pre-structured & pre-validated questionnaire. Group B (passive) patients were asked to report ADRs themselves to pharmacovigilance center directly or through a drop box. Collected ADRs were compared statistically using software Minitab 14, Pennsylvania, USA.

Results: The yield of ADRs in active method was 4.5 times higher than the passive method. GIT related ADRs were similar in both groups, cutaneous were higher in active and CNS concerned were higher in passive method. However, consistency of ADR reporting was more in passive method. Mean lag period between onset and reporting of ADRs by active and passive methods were 5.72 and 22.4 days, respectively.

***Conclusion*:** Active method initially and numerically facilitates ADR reporting together with decreased lag period but passive method gives consistent yield in chronic diseases like TB, hence, an integrated approach to identify and manage ADRs will be most beneficial for patients**.**

***Keywords*:** Tuberculosis, Adverse drug reactions (ADRs), Yield, Lag period, Active and passive monitoring

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Introduction

Adverse Drug Reactions (ADRs) account for 5% of all hospital admissions, occur in 10-20% of hospitalized patients and are the fourth leading cause of death globally (1). The need to identify and address adverse drug reactions (ADRs) can never be overemphasized as mitigating ADRs will increase drug compliance besides reducing the suffering of already sick patients. Its importance was desperately felt as early as in 1952 when FDA started collecting data regarding bone marrow suppression due to chloramphenicol. Further thalidomide tragedy (1961) reiterated the requirement of monitoring the drugs for adverse reactions (2,3). It persuaded WHO to establish Uppsala monitoring center in 1968 with headquarters in Sweden to collect ADRs periodically for all the drugs across the globe(4). India launched its National Program of Pharmacovigilance in 2005 which was renamed as Pharmacovigilance Program of India (PvPI) in 2010 under the same initiative (5). Today WHO based Vigi-Base is the world's largest individual case safety reports (ICSR) database for ADRs. Med Watch program in 1990s allowed USA health care professionals and patients to voluntarily report ADRs of drugs and medical devices and United States Food and Drug Administration (USFDA) Act in 2007 compelled manufacturers to conduct post-marketing surveillance to ensure drug safety and alleviate ADRs are other important milestones of pharmacovigilance program (6,7). To date many drugs like terfenadine, cisapride, phenylpropanolamine, rofecoxib, cerivastatin, gatifloxacin, cisapride,sibutramine, and tegaserod have been withdrawn from the market because of the serious adverse drug reactions they caused(8,9).

Today ADR monitoring can be done by two methods - Active or intensive and Passive or voluntary (10). ADR monitoring studies are also known as drug safety surveillance or drug safety monitoring studies.

In active method, measures are taken proactively to detect ADRs. This is achieved by dynamic monitoring at the start of, during and at times after the end of treatment. Active ADR monitoring can be mainly sentinel site based where ADRs are collected from patients and physicians directly from selected few sites as in institutional and specific settings or cohort event monitoring (CEM) where after acknowledging the patients from electronic records or automated health insurance claims, follow up questionnaire is sent to acquire required data. Its advantages are that it discerns incidence rate of adverse events in addition to relative risk, identifies multiple adverse effects, solicits information on events that may not otherwise be reported but the main limitations of CEM are its restriction to a small subset of medicinal products and relatively small fraction of the population covered. Registries containing documented exposure of medicine &/or disease related records, cross sectional survey, case control and targeted clinical investigation (done to evaluate mechanism or reason for ADRs) are other important subtypes of actively reported ADR method (11,12). An initiative named as “Sentinel” was undertaken by USFDA through the use of administrative claims, and pharmacy dispensing data. Similarly active drug safety monitoring (aDSM) in India since 2015 is used to detect, manage, and report suspected or confirmed drug toxicities of patients on treatment with new TB medicines for multidrug resistant and extremely drug resistant TB are examples of active ADR monitoring(13,14).

Passive method uses no active measures to look for adverse drug reactions. Reporting to the national authorities responsible for patient safety is entirely dependent on the initiative and Motivation of the reporters, usually health care professionals and sometimes the patients. Here both quality and quantity of adverse event reporting depend on the willingness, skill, and Experience of the reporter. Passive surveillance can further be subdivided into spontaneous reporting (most common subtype of passive ADR monitoring method, hence the term is often used interchangeably with passive method), case series (new findings or associations are detected unexpectedly),

stimulated reporting, and targeted spontaneous reporting which is preferred for newer medications (14,15,16).

Most of the countries have passive ADR reporting method, though, some developed nations have adopted an organized system for active drug monitoring. There has been a conflict regarding appropriateness of a method for pharmacovigilance. Some studies claim that active method is better as it can identify safety signals before drugs can actually do more harm and is particularly important when outcome due to ADRs are very damaging or expensive like death, damage to vital organs, increased hospital stay, requiring specific costlier treatment due to delay in adverse reaction identification and treatment (1,4,17). The projected advantages of passive ADR surveillance are that it covers a large population, is useful for hypothesis generation and for diagnosing rare ADRs.

Despite an important issue, very few studies directly compare active and passive methods for reporting ADRs. Hence this study was planned with the objective to compare active and passive ADR reporting methods in category I TB patients on DOTS. Category I TB patients were selected because tuberculosis is an important communicable and curable disease in India and as per a systematic review, the overall prevalence of ADRs with first-line anti-TB drugs is also high and it varies from 8.4% to 83.5% (18).

Materials and Methods

A prospective observational analytical study was done in directly observed therapy short-course (DOTS) and pharmacovigilance (PV) centers attached to SMS hospital, Jaipur, Rajasthan, India from 1.1.2019 to 31.12.2019 to collect ADRs after Institutional Ethical approval via letter no 4123/ MC/EC/2018 dated 9/10/18.

Sample size was calculated at 80% study power and α error 0.05 expecting ADR in 5% of patients in passive surveillance group and 15% in active surveillance group as found in pilot study. Following the above assumption, a minimum of 141 patients were required as sample size which was rounded off to 150 patients in each group as sample size for study. Hence, a total of 303 category I TB patients (means new tubercular cases) were selected and enrolled in study after inclusion and exclusion criteria. Inclusion criteria were new tubercular patients who were visiting DOTS- TB center for the first time for treatment and were willing to give consent for the study. Exclusion criteria were multi-drug resistant TB patients, concomitant immunosuppressant medication, pregnant and lactating women. These enrolled 303 patients were then randomly divided into two groups A and B.

All were started on standard isoniazid, rifampicin, pyrazinamide, ethambutol (HRZE) drugs appropriate as per their weight bands approved in National guidelines for tuberculosis 2020 (19). Group A (n=150) patients were monitored for adverse drug reactions during antitubercular therapy (ATT) for six months by active drug safety surveillance method. For it they were either interviewed personally or contacted telephonically on 1, 3,7,15,30, 90,180 days of therapy as per pre-structured and pre-validated questionnaire developed for it to actively seek ADRs.

Group B (n=153) patients registered for receiving ATT were allowed to report passively for any complaints by themselves or through their physician. For this, we planted a drop box containing slips for reporting ADR at easily accessible place in DOTs center.

Results

A total of 303 type I TB patients were randomly selected for study, 150 patients were in active group and 153 were in passive group. Two groups were comparable in terms of age, gender, site distribution, presenting symptoms, education, socioeconomically and associated illness. A total of 149 ADRs were attributed to anti-tubercular drugs, reported from 303 patients in our study giving total incidence of 49.2% ADRs. 126 patients reported one ADR, 10 patients reported two and maximum three ADRs were recorded by one patient. ADRs collected by two methods are shown in Table 1.

Table 1: Distribution of ADRs due to antitubercular drugs by active and passive methods along with duration of ADR presentation, measured from initiation of therapy

S. no	ADR	TOTAL	Active						TOTAL	Passive					
1	Nausea, vomiting	38	6A	20B	11C	1D	-	-	8	5A	2B	1C	-	-	-
2	GI upset	7	2A	3B	2C	-	-	-	2	2A	-	-	-	-	-
3	Abdominal pain	8	4A	3B	1C	-	-	-	1	1A		-	-	-	-
4	Jaundice	5	-	-	1C	3D	1E	-	2		-	-	D	E	-
5	Skin rash	9		4B	4C	1D	-	-	2		1B	1C	-	-	-
6	Pruritus	12	3A	2B	5C	2D	-	-	1		-	1C	-	-	-
7	Flushing	6	1A	2B	3C	-	-	-	1		-	1C	-	-	-
8	Skin peeling	1	-	-	-	1D	-	-	-		-	-	-	-	-
9	Paresthesia	4	-	-	2C	1D	1E	-	1		-	-	-	-	F
10	Numbness	6	-	-	3C	2D	1E	-	1				D		
11	Visual toxicity	3	-	-	-	-	2E	1F	2		-	-		E	F
12	Mental disturbances	6	-	-	4C	2D	-	-	1		1B	-	-	-	-
13	Loss of Diabetes control	3			2C	1D	-	-	1		1B	-	-	-	-
14	Arthritis	6		2B	1C	1D	2E	-	1		-	-	-	E	-
15	Decrease urine	1	-	--	1C	-	-	-	1		-	-	D	-	-
16	others – fever, shock, acne dyspnoea	7	2A	2B	2C	1D	-	-	2		-	C	D	-	-
	Total	122							27						

S. No. 1-4 GIT; 5-8 cutaneous; 9-12 CNS; 13-16 miscellaneous

A-F= lag period in days; A= 1-3; B= 4-7; C=8-15; D=16-30; E=31-90, F=91-180

Above data of Table 1 was used to compare ADR yield by both methods in terms of number, consistency, and organ-system affected by ADRs and yield duration (i.e. time between initiation of DOTS therapy and ADR reporting).

I. Numerically ADR yield by active method was 4.5 times higher in comparison to passive method (122 vs 27). They were reported by 72.6% and 17.6% of patients, respectively.

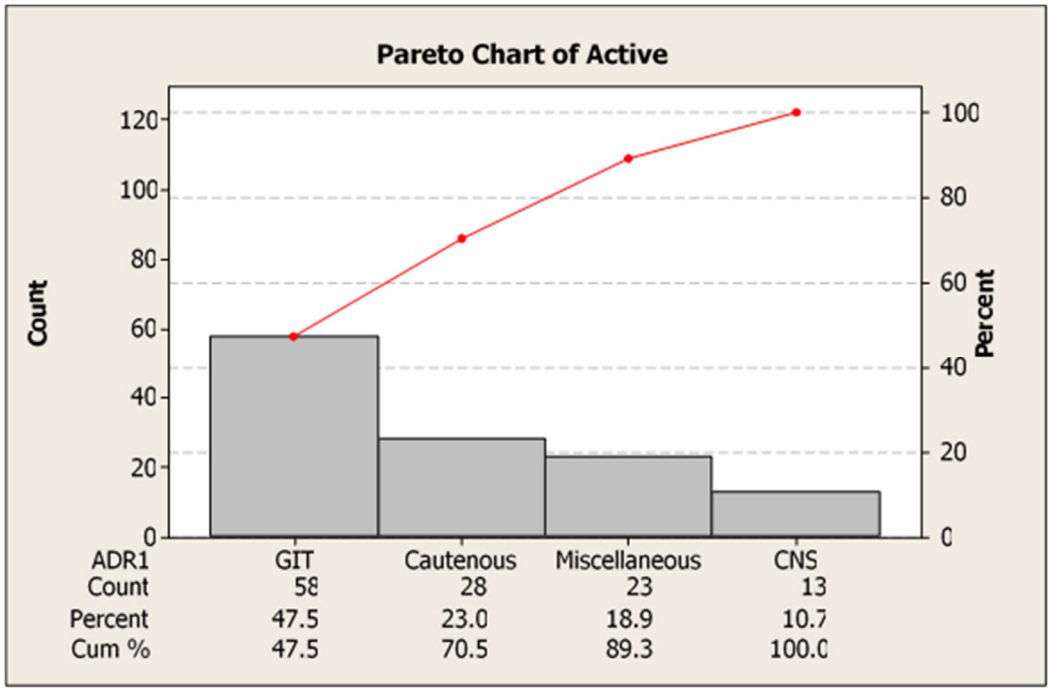
II. For consistency of yield, descriptive statistics for ADR yield by both methods were deduced and compared (Table 2).

Table 2: Descriptive statistics for ADR yield by active and passive methods

Variable	Mean	SE Mean	St. Dev	Variance	Coeff. Var	IQR
Active	7.63	2.15	8.59	73.72	112.60	4.50
Passive	1.69	0.44	1.78	3.16	105.38	1.00

While comparing for consistency, all the four measures of dispersion i.e. standard deviation, variance, coefficient of variation, and inter quartile range were considered. The values for these measures were higher for active surveillance method than for passive method, hence it was concluded that the passive method was more consistent in comparison to the active method in terms of yield.

III. To compare difference in organ-systems reporting ADRs by both methods if any, Pareto charts were drawn (Figure).



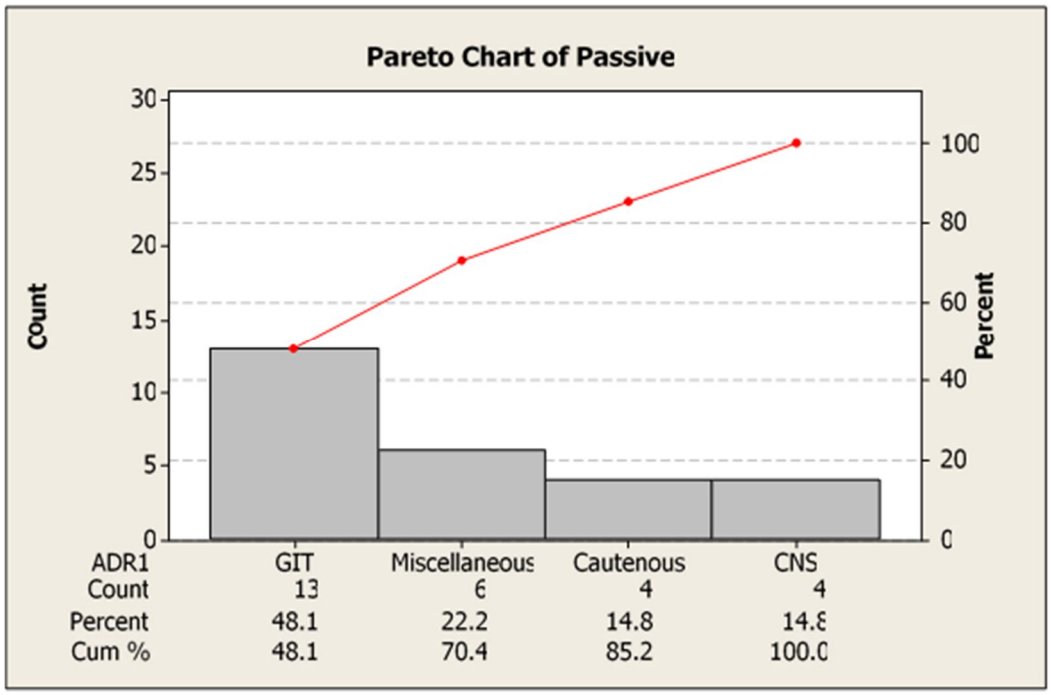
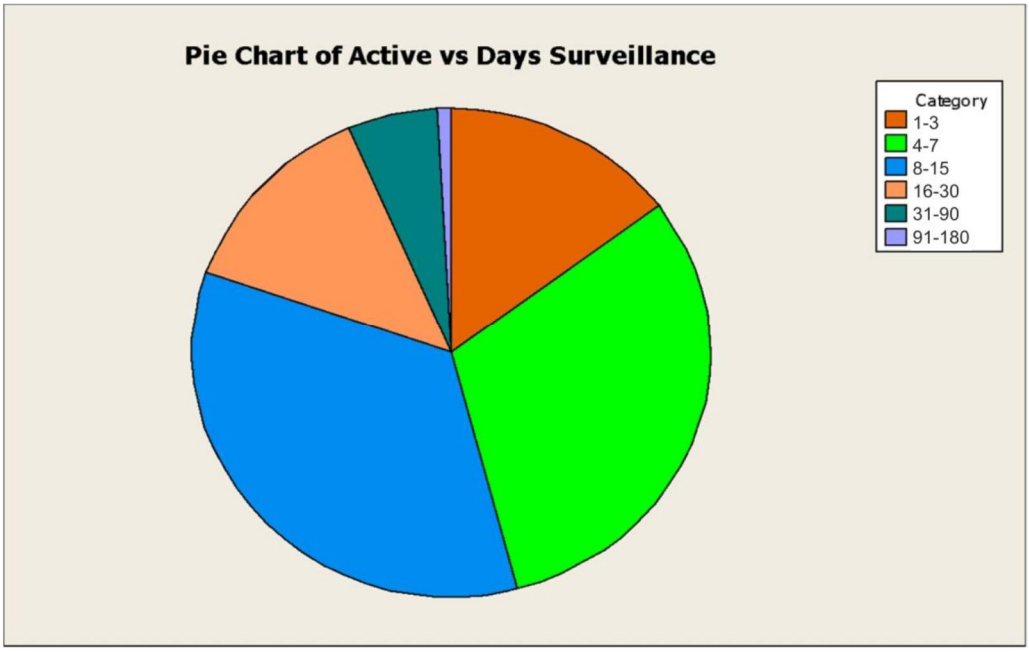


Figure 1 (a, b): Pareto charts to compare organ-systems reporting ADR (yield) by active and passive methods

Pareto chart of ADR yield by Passive Method:

Based on the findings of the above graphs, it was found that for GIT and miscellaneous ADRs, the yield in terms of percentage of patients was almost the same by both methods. However, the yield percentages for the cutaneous and CNS ADRs recorded were different in two groups. It was higher for cutaneous ADRs in the active and CNS related ADRs in the passive method.

IV. To compare the yield duration i.e. time difference between initiation of DOTS and ADRs reported by both methods, pie charts were drawn (Figure2).



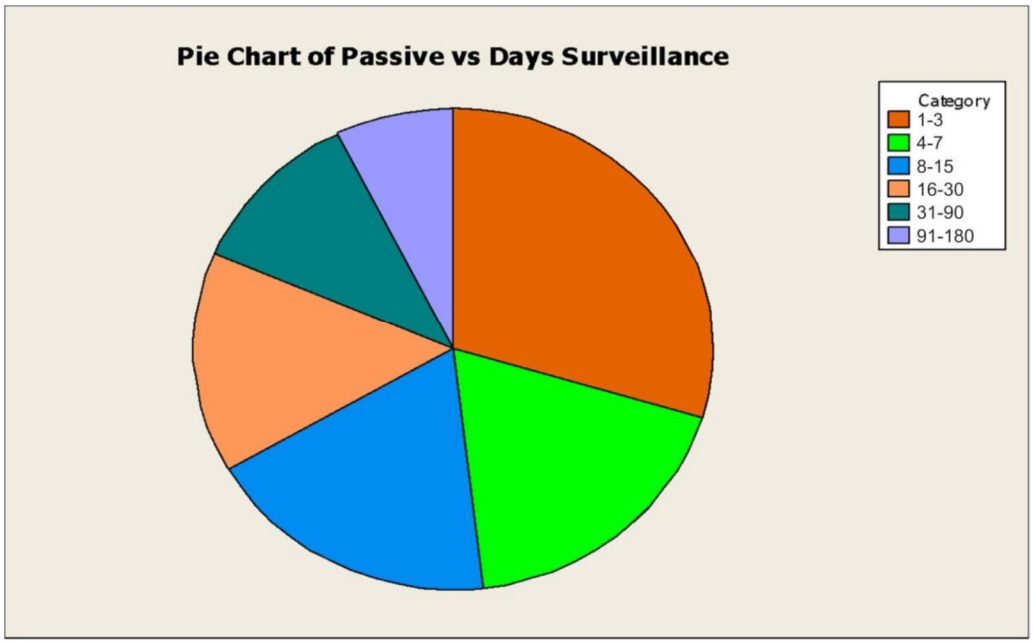
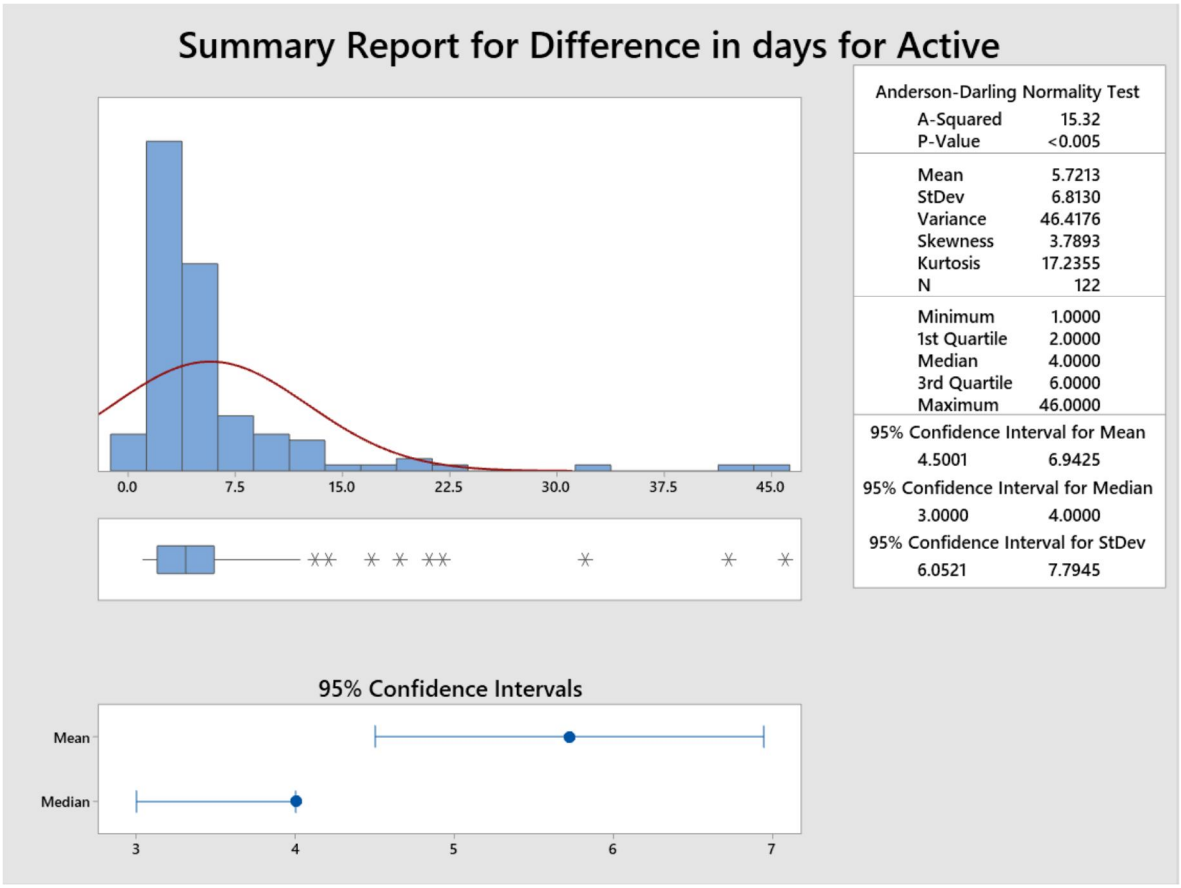


Figure 2(a,b): ADRs and percentage of days surveillance in active and passive methods

As shown above, in active method, maximum (34.4%) ADRs appeared in 8-15 days of ATT and minimum (0.8%) ADRs were reported in the duration of 91-180 days. Similarly for the passive method, the maximum (29.6%) and minimum (7.4%) ADRs were found in 1-3 and 91-180 days of surveillance.

It was also seen that total maximum yield (91%) of ADR detection was in initial 30 days of treatment with 93% by active method and 81% by passive method in first month of initiating ATT.

Active and passive ADR reporting methods were also evaluated for lag period between onset or experience of ADR by patient and its information to health care facility.



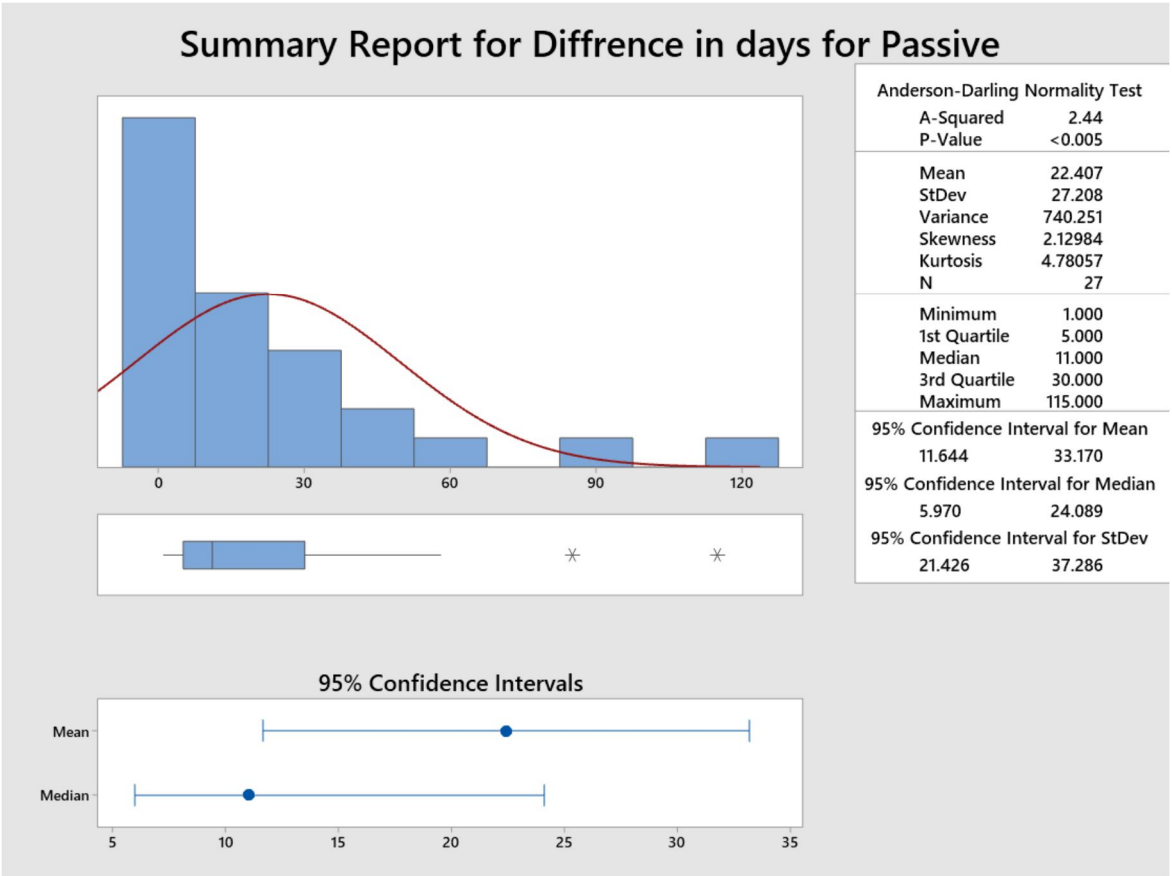


Figure 3 (a,b): Description of lag period (in days) between onset of ADRs and reporting to health system

Statistical analysis and interpretation:

According to the statistical analysis, it was seen that the mean lag period for the passive method was high as compared to the active method (22.41 vs 5.72 days). Also it was found that the coefficient of variation for both the methods was almost same (119.08 and 121.42 respectively) but was very high indicating that distribution of lag period for both the method was also not consistent.

Discussion

Adverse drug reactions can be collected and reported with active and passive reporting methods. Passive method provides opportunity to confidentially and voluntarily report ADRs(14).While active method proactively and systematically monitors patients to seek detailed information about ADRs encountered during treatment (10,13). The primary outcome of both methods in terms of yield, and time lag may differ in different diseases and settings.

In terms of yield, our study revealed that a total of 149 ADRs were reported from 303 category 1 TB patients;122 ADRs from active group and 27 from passive group. It means that numerically yield by active method was approximately 4.5 times higher than passive method. Our study also found that the majority of patients suffered from GIT, cutaneous, and CNS related ADRs. Though the incidence of GIT adverse effects was similar in both groups (48%), comparatively more cutaneous and CNS related ADRs were detected by active and passive drug surveillance methods, respectively. It could be because the mild rashes and flushing are not recognized easily by patients. Similarly because of the social stigma associated with the disease, patients become stressed on diagnosis and complaints like anxiety, stress, and worries were reported more by patients via passive method. Yun IS et al. found ADRs with gastrointestinal manifestations were most frequently reported by spontaneous (passive) surveillance method while they reported that active surveillance was more reliable to identify adverse reactions associated with changes in laboratory values, such as hepatobiliary toxicity, hematologic manifestations, and renal manifestations (20).

When compared in terms of consistency of yield by two methods, passive method was found to be more consistent for reporting ADR. This is because spontaneous reporting method found substantial ADRs throughout the study while in active method approx. 93% concentrated in initial one month of therapy. Since it is a new study, we failed to find exactly similar study comparing active and passive methods in terms of consistency. However, some studies have reported nearly parallel findings that maximum yield benefit of ADR by active monitoring is in first four weeks of treatment and active surveillance method for ADRs was accepted with high compliance rates and significant data collection (21,22). According to the studies conducted by Fei C.M. et al. and Yang M et al. also most of the ADRs of anti-TB drugs occurred during first two to three weeks of initiation of treatment(23,24).

As far as yield duration was concerned, maximum percentage of ADRs (34.4%) were recorded between 8-15 days in active and 29.6% ADRs were recorded in 1-3 days in passive surveillance method in our study. As the tubercular patients were followed for 180 days, it was observed that passive method reported ADR in the later half (91-180 days) of therapy. Our findings are different when compared to those by Palanisamy S et al. who found more ADRs with lag period of 28 days followed by 15 days in tubercular patients since that study was limited to 7 weeks only (25).

Mean lag period between onset and reporting of ADRs by active and passive methods were 5.72 and 22.4 days, respectively. Statistical analysis revealed that distribution of lag period for both the methods was also not consistent. No similar study could be traced to compare with.

Conclusion -ADRs are inevitable part of drug administration. Our study compared active and passive methods of ADR monitoring and revealed that active method can be used additionally to support but not replace passive method as it was most fruitful at the initiation of long term therapy while for steady reporting

in long term therapy passive method was more rewarding. Hence an integrated approach will be more beneficial and in the interest of patients without stressing health system for resources. Managing the ADRs earliest in tubercular patients will also ensure compliance of treatment, reduce suffering of patients, help in plummeting spread of infection, and drug resistance.

Future scope- Further, cost effective analysis of the two methods in various diseases and on a larger scale will help in better understanding of the suitability of different methods of drug safety monitoring in diverse diseases.

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Conflicts of interest

The authors declare no conflicts of interest.

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