CASUALTY ASSESSMENT AND THE SEVERITY OF THE ADVERSE DRUG REACTIONS (ADR) ACTIVELY DETECTED IN HOSPITAL-IN PATIENTS IN TERTIARY CARE HOSPITAL SRI LANKA: PROSPECTIVE OBSERVATIONAL SURVEY

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ABSTRACT
Adverse drug reaction is a leading cause of hospitalization in many Sri Lankan hospitals. We conducted survey on adverse reactions in all patients admitted to the tertiary care hospital in Galle Sri Lanka. A prospective observational study was conducted for actively screened ADR for causation, causality and severity using validated scales. ADR reporting cards was used from the national pharmacovigilance centre in Sri Lanka. 95 patients were analyzed for severity of ADR referring the Hartwig's Severity Assessment Scale. Casualty assessment was done using WHO scale. We found that 51% of patients had moderate ADR, severe, 36%, mild (9%) and 4.5% in fatal. Majority ADR were (27%) antibiotic related and 73% due to other drugs. Penicillins induced majority of ADR but mild. NSAIDs had caused many fatal and severe ADR. Causality assessment shows 44% of ADRs were possibly drug-related and 30% of them were probably drug related. The mean age of patients was 45 years. Skin and the nervous system and gastrointestinal system were commonly affected (31.5%, 26% and 16% respectively) and the highest number of ADR was related to the other drugs but not to antibiotics. Our study shows that most ADR detected were possibly drug related and hence they are preventable and they had contributed big financial burden to the Sri Lankan government health budget. We suggest seeking contribution form clinical pharmacists and there is an urgent need of recruiting them to government health care sector handing over this duty for reduction of government health budget.

KEY WORDS
Adverse drug reactions, Hartwigs scale, Hospital Pharmacovigilance running title - assessment of actively screened ADR in tertiary care hospital word count - 3682.

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INTRODUCTION
We defines an ADR is an undesirable effect of a drug in addition to its expected therapeutics occurring during clinical use[1]. Further WHO[2] defines an ADR as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function. Therefore ADR does not include overdose,

drug abuse, and treatment failure and drug administration errors. In many of the countries, ADRs can be seen as two types in inward patient: ADR due to admission to hospital and ADR occurs after hospital admission. The severity of the ADR had been studied by group of scientist[3-9] and found that ADRs is the 7th most common cause of death[4] and another study found that 6.5% of patient admissions National Health Service (NHS) hospitals due to ADR[10].

ADRs have a considerable negative impact on both health and healthcare costs. ADR monitoring and reporting activity is not yet completely established in Sri Lanka due to lack of active supports from the health care workers in government sector hospitals. Convincing of the huge need of all health care workers to identify and do active screening for ADRs and to prevent them to ensure the well-being of the patient in free health care services given by the government of Sri Lanka. The Ministry of Health with the help of WHO had initiated the National Pharmacovigilance Program and this need the vigorous involvement of the stake holders.

In the state health sector, over half of all hospitalized patients are treated with antimicrobial agents and their use account for 20-50% of drug expenditures in hospitals. More than 70% of ICU patients receive antibiotics for therapy or prophylaxis, with much of this use being empiric and over half of the recipients receiving multiple agents. The total costs associated with antibiotics are not only related to antibiotic use itself, but also to co-medication and adverse drug events. In some research, antibiotics accounted for 11% of iatrogenic disease. Therefore we concentrated on the previous research woks conducted on the different evaluation methods of causative factors[4-8], severity of ADR[9-12], recovery rate and the different categorical types of ADR[6] and adapted the suitable standard methods to assess the inward patients in a tertiary hospital in Galle Sri Lanka. Our study was a prospective study which further explores the types, severity and the impact.

METHODS

Patients and settings; the study was conducted on all the wards at the Teaching hospital Karapitiya (THK) over a six-month period. The study protocol was assessed and approved by the Ethical review Committee in the Faculty of Medicine University of Ruhuna. Known ADRs were identified on the basis of their inclusion in the British National Formulary. All the ADRs that were proved and also suspected during admission as a result of drugs initiated or continued in hospital were included. Well trained data collectors were used to collect the data from the wards and they use to visit to the wards and did the active screening. Data documentation was done in the sample form used by the national pharmacovigilance centre in Sri Lanka. Intensive care units and dialysis unit in teaching hospital were excluded. Wards include all medical surgical, psychiatric, paediatric dermatological in this hospital. Our data were collected daily from Monday to Friday by the trained pharmacology department medical staff members using the pre tested ADR reporting application issued by the national pharmacovigilance centre. Investigators visited daily to do the active screening of ADR in all wards and they collect the relevant data from bed head ticket, patients' drug charts, medical and nursing notes for evidence of an ADR. In addition to that the relevant information was taken from patient, by standers, laboratory reports. Our team of investigators were trained to communicate with the ward medical team. Clinical ward staff was informed through a document from Department of pharmacology regional pharmacovigilance centre by notification cards that were already available on the wards. Investigators use to go individual ward bed to ensure that all detected, undetected and suspected details regarding the ADR to be collected.

Casualty assessment by WHO scale

The causality relationship between suspected drug and reaction was established by using WHO. The causality of reported reactions was categorized to any one of the following categories based on the scale used: certain, probable, possible, un-

assessable/unclassifiable, unlikely, conditional/ unclassified using the WHO scale (Table No.1).

Assessment of severity

Severity of the ADRs was assessed by the Hartwig severity scale[13], which was used for many research works related to ADR[14,15]. We divided the reported ADR to mild, moderate, severe and fatal in types.

All demographic data, suspected drug, duration of treatment, other drug combination, presenting signs and symptoms, risk factors, alternative diagnosis and the results of the challenge test were recorded in data entry form. Antibiotics causing ADR analysis was conducted in detail. Type of the antibiotic causing the ADR was recorded and the results after discontinuation of the drug were also analyzed. Results were categorised whether symptoms improved, not changed, persisted, caused death or not known.

Statistical analysis

Statistical analysis was performed with the SPSS 17 statistical software program. The results are presented either as means or percentage frequencies and 95% confidence intervals, as appropriate. Statistical analysis was performed with the Mann-Whitney U test for all data and P value < 0.05 was regarded as being significant.

RESULTS

A total of 95 documented ADRs were identified all wards in teaching hospital karapitiya during the study period. The results of the age, sex and the body systems involved are documented in Table No.2.

Table No.2 shows the mean age gender distribution and the main body system involved in ADR in our study group.

All the ADR were analyzed to find out the common type of the drug group causing ADR in this hospital. Table No.3 shows the details of antibiotics and the other drug groups causing ADR in our study group. ADR caused by other drugs were mainly by NSAIDs, steroids, thyroxine, carbamazapine and immunoglobulin. Table No.2 shows the details of the antibiotics and the other drugs causing ADR in our study group. It shows penicillin causing ADR in 46% while macrolides had caused 17% of patients

out of the ADR caused by antibiotics. Out of the othe drugs, NSAIDs had caused many ADR in patients while immunoglobulin, thyroxine and carabamazapine had caused ADR in 3% of patients.

Casualty assessment by WHO scale

Figure No.1 indicates the causality assessment through WHO scale and it indicated that Highest number of ADR were possible drug related and 20% of the ADR was probably drug related. We also found 18 % of ADR is certainly related and rechallenge satisfactory. 13% of ADR was unlikely to be drug related and imporbable. We also noted 3% of conditional and more data is needed for proper diagnosis as ADR. most interestinly we found that 2% of the ADR were unclassifiable and details were contradictory.

We extended our study to do the severity analysis of ADR and found that most of the ADR were moderate (51%) severe (31%) and mild (9%) according to the scale. Further, the Figures No.2a, 2b and 2c indicate the severity of the ADR caused by the different drug groups detected in this hospital in Sri Lanka. Data represents the number of patients with mild, moderate, severe or fatal ADR seen by the different drugs groups analyzed. This analysis was done according to the hartwig's scale.

The Figures No.2a, 2b and 2c indicate the severity of the ADR caused by the different drug groups detected in this hospital in Sri Lanka. Data represents the number of patients with mild, moderate, severe or fatal ADR seen by the different drugs groups analyzed. This analysis was done according to the hartwig's scale. It shows the number of ADR reported with mild, moderate, severe, fatal and ADR with the unavailable data by different drugs as indicated in Figures No.2a, 2b and 2c.

We further concentrated on the results of the discontinuation of the suspected drug causing ADR detected in our patients. We documented that the majority of the ADR improved with the discontinuation of the therapy. Details in Table No.4 shows an ADR by penicillin by 72% and the glibencamide reactions had improved by 60% of the patients. Most of the reactions caused by quinilone group of drugs had persisted when compared to the

other drug groups (macrolide by 25% and glibaicamide by 20%) but the reactions caused by immunoglobulin therapy had persisted 100% despite the discontinuation of the therapy. NSAIDs had caused different results after discontinuation of the therapy although 75% had improved while 8.3% of patients had ended in death. Other drug which had caused death of the patients is glibencamide in this hospital.

Table No.4 shows the relationship between drug group and the results obtained after discontinuation of the therapy in our study group. ADR due to penicillin had improved in 72% of patients while symptoms had disappeared in 27% of patients. Carbamazapine had caused ADR which are fully recovered in 60% of patients and death in one patient. Further it shows that immunoglobulin had caused ADR persisted in almost all patients in discontinuation. NSAIDs had also caused improvement of symptoms after discontinuation while causing death in one patients due to ADR.

We analyzed the patients history for the drug allergy and found that only 12% of them had positive allergy in past. We also followed the results of challenge test and found that only 5% of the patients had been faced for challenge test (Figure No.3a and 3b).

Figure No.3a shows the number of patients who had the history of drug allergy in the medication therapy in past. It indicates that only 12% of the patients had positive drug allergy or hypersensitivity and 88% of them did not give any history of allergy during past. Figure No.3b shows the results of the challenge test performed to the study group. Challenge test had been done only for 5% of patients in this hospital.

DISCUSSION

We found that most of the ADR were seen in the adult patients with mean age of 45. But Pirmohamed *et al* have shown a greater percentage of geriatric population suffering from adverse reactions which is consistent with the present results that mentioned before[12,16].

We found that there is preponderance for female patients with ADR that male patient. But researchers from India had reported that most of the ADRs in the hospital patients were more documented in males. But the sex ratio in admitted patients might be an intervening factor but does not seem to be a major determinant. Our data analysis showed that most common type of ADR seen in all the wards in this tertiary hospital was the skin rash that was commonly caused the antibiotics. This finding is in favor of the previous study[17] done in Chicago by Murphy and Frigo developed and implemented an ADR reporting program in Loyola University Medical Center, a 563-bed tertiary care teaching hospital located in the western suburbs of Chicago. Another study revealed that the most common adverse reactions were rash; and antibiotics were the most commonly implicated drug class[18]. We also found out that NSAIDs also had caused fatal and severe ADR than by the other drugs and it was the only drug which had caused death of a patient. This is comparable with other studies like one done by Classen *et al* which indicated that NSAIDs have caused extensive damage to human health[14].

Regarding the casualty assessment, we found that most of the ADR reported by our group was 44% of them were possibly drug related (44%) and 20% of them were also probably drug related (20%). Our causality assessment therefore gives an important message that the ADR which were recorded in this hospital were definitely related to the drug and almost two-thirds of reactions were potentially avoidable. Parallel to this study Sriram *et al* had also shown that their 42% of ADRs were possibly drug related, 23% of ADRs were probably drug-related, whereas 30% were classified as certainly related to drug[16]. But we could find only 18% of the ADR were certain in category. In addition to assessment by Naranjo scale had showed that 63% of ADRs were possibly drug-related, whereas 37% were classified as probably or definitely related to the drug[17].

In the analysis of severity of ADR, we found that most of the ADR reported in this hospital were moderate (51%) severe (31%) and mild (9%) according to the severity scale. Parallel to our findings, in 2002 in England there were a total of 3.8 million acute admissions, [19] suggesting that ADRs

causing hospital admission are responsible for the death of 5700 patients (3800 to 7600) every year. The true rate of death taking into account all ADRs (those causing admission, and those occurring while patients are in hospital) may therefore turn out to be greater than 10000 a year.

As the summary finding of our work we also experienced the main problem of under-reporting of ADR in Sri Lanka as in other South Asian countries and in some Western countries although the pharmacovigilance system is well established. Limited cooperation of medical officers and the nursing staff for the reporting of ADR is seen in all these wards and some time there were many restrictions for our investigators for data collecting. We feel that this is due to the lack of active pharmacovigilance reporting centre supported by the government health department.

We have worked with our maximum effort to convince the importance of pharmacovigilance and prevent many drug induced morbidities and mortalities in Sri Lanka. Our ability to anticipate and prevent such ADRs can be facilitated by government health ministry and the all healthcare professionals including physicians, dentists, nurses and pharmacists. As the pharmacy education had made a step forward in Sri Lanka this can be easily used for the specially trained pharmacist for encouraging them through conducting educational programs on pharmacovigilance, lectures, newsletters as a main government need to reduce the country health budget by at least 30%. We also would like to take your attention about this pharmacist involvement in pharmacovigilance reporting in many countries and they mad made it more successful[20-22].

Table No.1: WHO scale

S.No	WHO Scale	Report
1	Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake, Cannot be explained by disease or other drugs, Response to withdrawal plausible (pharmacologically, pathologically), Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon), Rechallenge satisfactory, if necessary.
2	Probable/ Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake, Unlikely to be attributed to disease or other drugs, Response to withdrawal clinically reasonable, Rechallenge not required.
3	Possible	Event or laboratory test abnormality, with reasonable time, relationship to drug intake, Could also be explained by disease or other drugs, Information on drug withdrawal may be lacking or unclear.
4	Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
5	Conditional/ Unclassified	Event or laboratory test abnormality, More data for proper assessment needed, or Additional data under examination.
6	Unassessable/Unclassifiable	Report suggesting an adverse reaction, Cannot be judged because information is insufficient or Contradictory, Data cannot be supplemented or verified, All points should be reasonably complied.

Table No.2: Shows the mean age gender distribution and the main body system involved in ADR in our study group

S.No	Parameter	Value
1	Average age	45 years
2	Percentage of sex	Male 45% Female 55%
3	Body system involved	Skin -31.5% , CNS-26.3%, GIT-16.8% CVS-15.7%, Respiratory-8.43%, muscles 1%

Table No.3: Shows the details of antibiotics and the other drug groups causing ADR in our study group

S.No	ADR type	Percentage	Subgroup analysis	
1	Antibiotic related	27%	Penicillin	46%,
			Macrolides	17%
			Cotrimaxazole	4%
			Quinolones	21%
			Cephalosporin	12%
2	Other drugs	73%	NSAIDs	18%
			Steroids	8%
			Immunoglobulin	3%
			Glibencaimide	8%
			Carbamazapine	3%
			Thyroxine	3%
			Others	57%

Table No.4: The relationship between drug group and the results obtained after discontinuation of the therapy in our study group

S.No	Drug type	Improved	Disappeared	Persisted	Death	Not known
1	Quinolones	40%	0	40%	0	0
2	Cephalosporin	33%	33%	0	0	33.33%
3	Penicillin	72.72%	27.27%	0	0	0
4	Macrolides	50%	25%	25%	0%	0%
5	Glibenclamide	60%	0	20%	20%	0%
6	Steroids	20.00%	20.00%	20.00%	0.00%	40.00%
7	Thyroxine	0	0	0	0	100%
8	Carbamazapine	100%	0	0	0	0
9	Immunoglobulin	0	0	100%	0	0
10	NSAID	75%	8.33%	8.33%	8.33%	0.00%
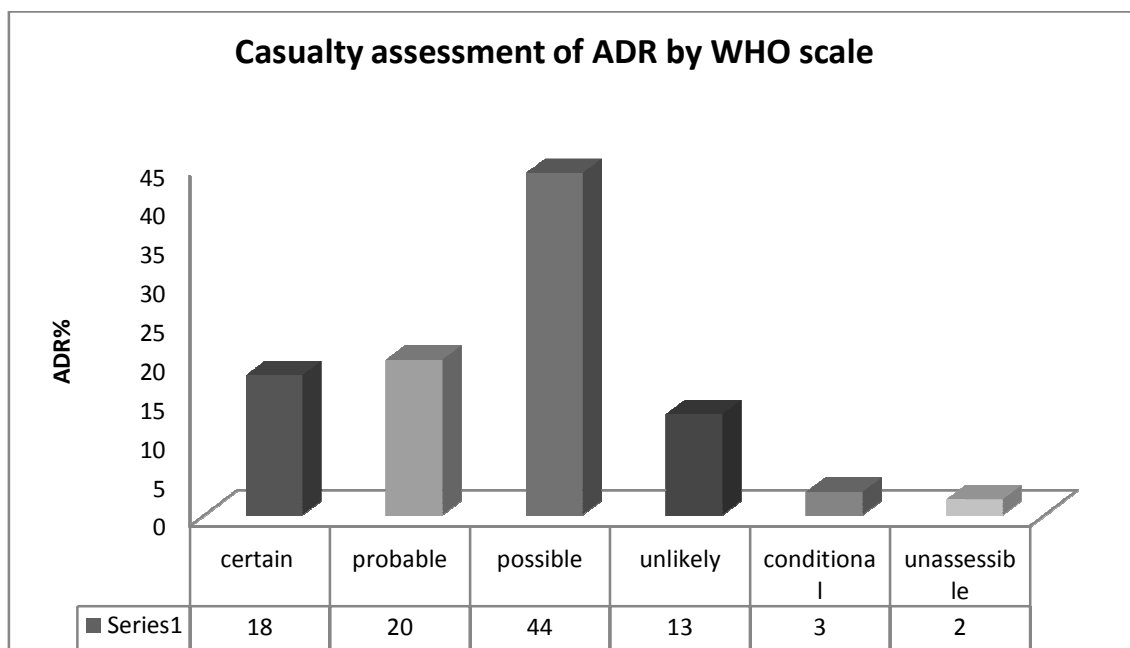
Figure No.1: Casualty assessment of ADR by WHO scale
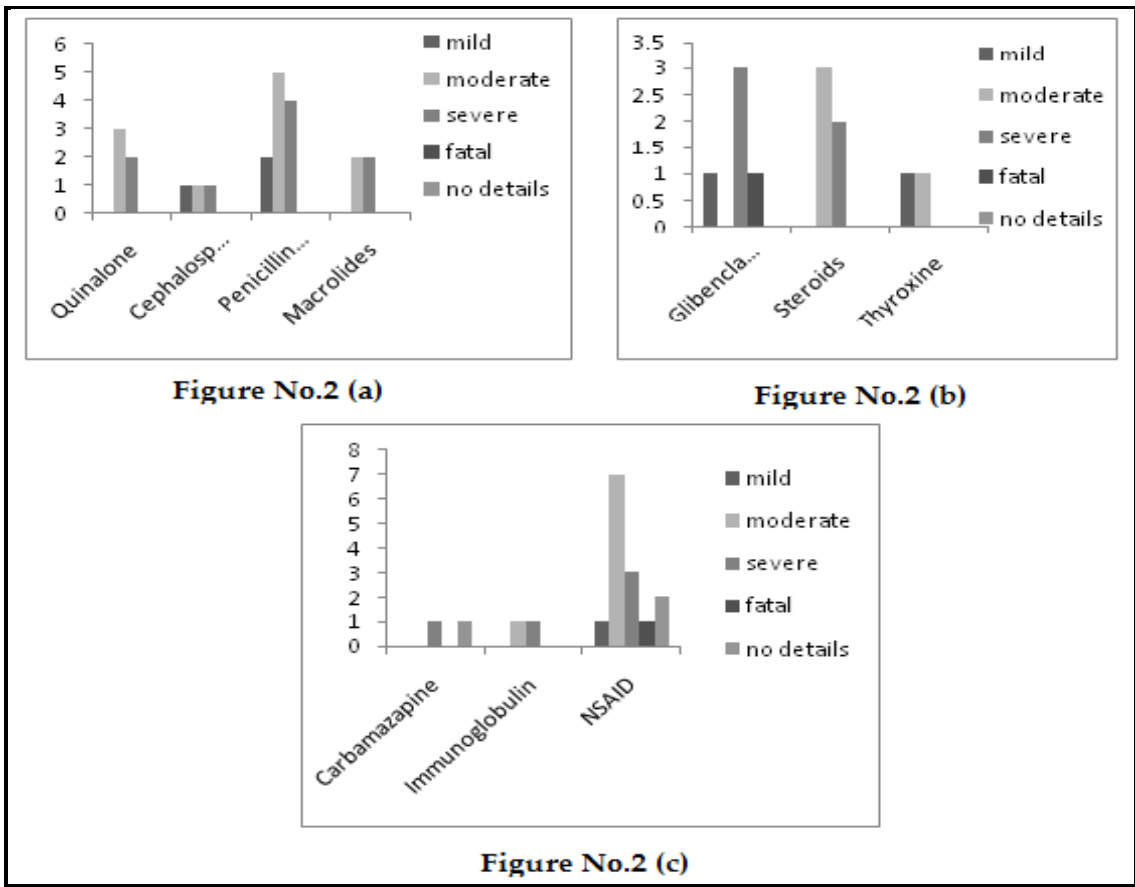
Figure No.2 (a)

Figure No.2 (b)

Figure No.2 (c)

Figures No.2 (a), 2 (b) and 2 (c): Indicate the severity of the ADR caused by the different drug groups detected in this hospital in Sri Lanka
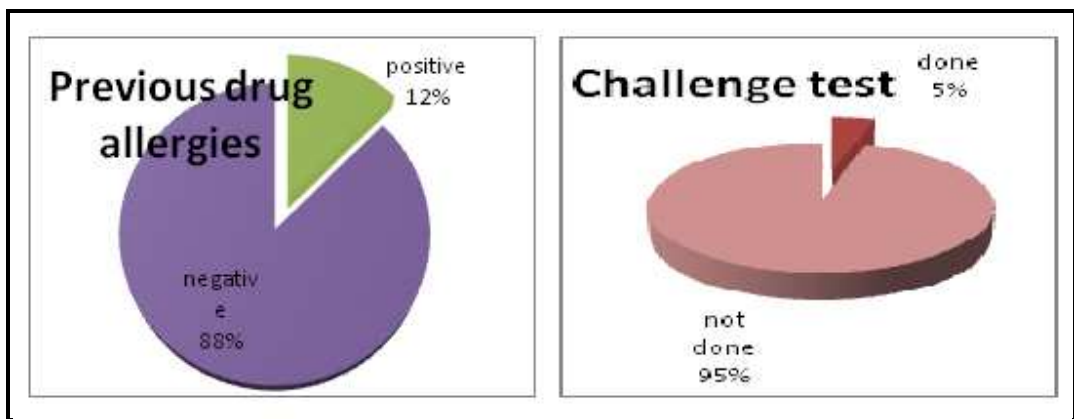

Figure No.3 (a): shows the number of patients who had the history of drug allergy in the medication therapy in past and Figure No.3 (b): shows the results of the challenge test performed to the study group

CONCLUSION

We hereby conclude that many of the ADR reported in this teaching hospital in Sri Lanka were possible and drug related and preventable if we do the prescription and dispensing carefully and precisely. In Sri Lanka the government hospitals are burden with large number of patients, medical officers and nursing officers are restricted for dedicated pharmcovigilance activity. But now the universities are producing many hospital/clinical pharmacists to our country government should plant to recruit them for area of pharmacovigilance to strengthen the national pharmacovigilance program. In addition to that either central or local governments should plan for the feasibility of developing and maintaining electronic documentation of patients' medical records may serve as a valuable tool to detect early signals of potential ADR with intranet facilities.

We could not detect the relationship between the reason for admission to the incidence of ADR as with any other study of this nature. There is another limitation of this study was that we could not categorize the ADR according to the type of the ward: eg medical surgical etc. We could not calculate the average staying days in hospital due to ADR. If we could calculate it we would have extrapolated the burden of ADR on bed occupancy and the cost for the Sri Lankan government.

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ETHICAL CLEARANCE

This proposal was reviewed by the Faculty ethical review committee in the Faculty of Medicine, University of Ruhuna, Sri Lanka.

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