IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 8 Ser. 1 (August. 2019), PP 15-21
www.iosrjournals.org

A Study on Whole Blood Clotting Test Vs. International Normalized Ratio with Whole Blood Clotting Test In Management of Hemotoxic Snake Envenomation in a Tertiary Care Hospital,Guntur

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Abstract: ***Introduction:*** *Snake envenomation is injury caused by venomous snake bite. Snake bite is a neglected public health issue in many tropical and subtropical countries. For monitoring of viper bite hemotoxicity and calculating dose of antivenom, 20-min whole blood clotting test (WBCT20) is used.*
Material & Methods: *This was a prospective study done among all the patients with history of hemotoxic snake envenomation, admitted Government General Hospital, Guntur Medical College, Guntur, during 2018 to 2019 with history of snake bite. Bleeding was assessed using HEME (HEmorrhageMEasurement) bleeding assessment tool.*
Results*: Study population had a mean age of 42.58 (range: 27-66) and male to female ratio was 3.85:1. Local symptoms occurred in all the patients, systemic symptoms in 94%, bleeding manifestations in 82%, acute renal failure in 51.9%. Mean time to reach hospital was 15.80 ± 5.7 hours. In this study 106 paired tests (simultaneous WBCT and INR) were obtained. Ten times WBCT turned out to be prolonged with an INR of less than 1.5 and seventeen times WBCT turned out to be normal in spite of INR greater than 1.5.* ***Conclusions****: Monitoring of VICC using INR in addition to WBCT resulted in administering more ASV doses and a better renal outcome (oliguria duration, and lesser hemodialysis) in the subgroup of patients with SOFA> 4.*
Keywords*: snake bite, whole blood clotting test, international normalized ratio, whole blood clotting test*

Date of Submission: 19-07-2019 Date of acceptance: 05-08-2019

I. Introduction

Snake envenomation is injury caused by venomous snake bite. Snake bite is a neglected public health issue in many tropical and subtropical countries. It results in death or chronic disability of many active younger people, especially those involved in agricultural activity. The true scale of mortality and morbidity from snake-bite remains unknown due to inadequate reporting.

In March 2017, a subcommittee of the WHO Strategic Technical Advisory Group for Neglected Tropical Diseases at its 10th meeting recommended inclusion of snakebite envenoming in the WHO neglected tropical diseases portfolio as a Category A neglected tropical disease. The Director-General endorsed this recommendation in May 2017 and WHO included snakebite envenoming in the list of neglected tropical diseases in June 2017[1].

The four major species of venomous snakes ubiquitous in India known as "Big four" are considered responsible for life-threatening envenomation around the country. These include- Indian cobra (Najanaja), the common krait (Bungarus caeruleus), the Russell's viper (Daboia russelii) and the sawscaled viper (Echiscarinatus)[2].According to species of snake responsible for bite and quantity of venom injected clinical manifestations differ . Clinical manifestations range from local symptoms to generalised symptoms involving various organs.

Dry bites :Venom is not injected in 20% of pit viper bites and a greater percentage of elapid and sea snake bites. About 50–55% of all snakebites result in envenoming.

Local features :Fang marks: two puncture wounds are present in poisonous snake bite and small puncture wounds arranged in an arc in nonvenomous snake bite.

Pain: Burning, bursting or throbbing pain may occurs and spread proximally up the bitten limb. Krait and sea snake bites maybe painless.

Local swelling: Viper bites produce more intense local reaction than other snakes.

Local necrosis: In viper bites, bruising, blistering and necrosis may appear over few days following the bite. Necrosis is marked following bites of Asian pit vipers, and some rattlesnakes. Asian cobras can also cause tender local swelling and blistering. Patients spat at by spitting elapids may develop venom ophthalmia.Secondary infection: caused by Bacterial flora in the oral cavity of the snakes.
Systemic features:Clotting defects and haemolysis: Haemostatic abnormalities are characteristic of Viperidae. Sea snake venoms also cause intravascular haemolysis.
Neurotoxicity: Elapid and sea snake venoms cause neurotoxicity. Paralysis is first detectable as ptosis and external ophthalmoplegia appearing as early as 15 minutes after the bite sometimes maybe delayed for 10 hours or more. Later involves bulbar muscles.
Myotoxicity: Sea snake venom contains myotoxins that cause myalgias, myopathy and rhabdomyolysis resulting in Myoglobinuria seen 3 to 8 hours after the bite.
Cardiotoxicity: Viper and elapid venom can cause direct myocardial damage manifest as arrhythmias, bradycardia, tachycardia or hypotension
Nephrotoxicity: Renal failure is secondary to ischaemia in Viper bites.
Shock: Various of factors contribute to shock[3].

For monitoring of viper bite hemotoxicity and calculating dose of antivenom, 20-min whole blood clotting test (WBCT20) is used. This WBCT20 test was first described by Lee and White in 1903, as replacement for more than 31 other less than optimal clotting tests available[4].In this test a few milliliters of fresh venous blood is placed in a fresh, clean and dry glass vessel and kept undisturbed at room temperature for 20 minutes. Later the tube should be tilted gently to check if blood is still liquid and if so then 20WBCT is positive. Till date, there are no studies available that have validated and standardized the test.

Isbister et al showed that this 20 min whole blood clotting time has low sensitivity for detecting coagulopathy and often delays administration of anti-venom[5].

In this study we intend to compare the addition of international normalized ratio (INR) to the 20 min whole blood clotting test to identify venom induced coagulopathy and effect upon timing and cumulative dose of anti-snake venom administered.

II. Material & Methods:

This was a prospective study done among all the patients with history of hemotoxic snake envenomation, admitted Government General Hospital, Guntur Medical College, Guntur, during 2018 to 2019 with history of snake bite and satisfying following inclusion and exclusion criteria.

Inclusion Criteria:
1.History of snake bite
2.Features suggestive of hemotoxic envenomation - Rapid extension of local swelling from site of bite or early spontaneous systemic bleeding or early systemic symptoms of collapse (hypotension and shock) or passage of cola coloured urine
ORWhole blood clotting time more than 20 minutes ORINR>1.5,
3. who gave informed written consent for the study.

Exclusion criteria:
1.Pregnant females,
2.Non envenomous bites and neurotoxic snake bites,
3.Initial negative WBCT followed by negative WBCT at 6 hours after presentation,
4.Patients presenting after 72 hours of snake bite.
5.Patients with coagulopathy due to any other reasons like CLD, sepsis or bleeding diathesis – thrombocytopenia.
6.Patients receiving anti coagulants.

Study methodology:

50 patients presenting with history of snake bite and fulfilling the inclusion criteria were recruited. A detailed history with respect to timing of snake bite, time for hospital arrival, ASV administered pre hospitalization, first aid measures applied was elicited. A general physical examination was carried out along with detailed clinical systemic examination, especially focusing on any sites of bleeding. Laboratory investigations include haemoglobin, leukocyte count, differential count, packed cell volume, complete serum biochemistry namely serum electrolytes, urea, creatinine, Calcium, phosphorous, total bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, total protein, albumin, uric acid.

Radiological tests like chest X ray and if indicated a non-contrast CT head in central nervous system bleeding, ultrasound abdomen in case of retroperitoneal bleed were carried out. First dose ASV was

administered to all the patients. The initial dose of ASV administered was 8-10 vials. Each vial is 10 ml of reconstituted ASV. It was administered as intravenous infusion over one hour at constant speed and patient monitored for 2 hours following administration closely. Local cellulitis at bite site will be treated with antibiotics and sepsis along the guidelines laid out by Surviving Sepsis Campaign[6].

Patients fulfilling the inclusion criteria were randomised into two groups, Group 1 and Group 2. Group 1 were monitored by 20 min WBCT alone whereas Group 2 were monitored by 20 min WBCT and INR. ASV was administered till normalization of 20 min WBCT in Group 1 and till normalization of both 20 min WBCT and INR (to less than 1.5) in Group 2.

In both the groups, following parameters are noted:

1.Timing of first dose of ASV administration,
2.Cumulative dose of ASV administered,
3.Resolution of clinical bleeding,
4.Length of hospital stay,
5.RIFLE monitoring,
6.Need for renal replacement therapy e.g. dialytic support,[7]
7.Survival.

Bleeding was assessed using HEME (HEmorrhageMEasurement) bleeding assessment tool, described by Arnold et al, which was designed to describe the site, severity, duration and clinical consequences of discrete bleeding events. Bleeding severity was graded as fatal, major or minor based on the degree of physiological impairment and the anatomical site of the bleed. A bleed will be considered fatal if the patient died while bleeding; major, if it results in severe physiologic derangements, occurs at a critical site (e.g., intracranial, retroperitoneal, pericardial) or results in the need for major therapeutic intervention and minor, if bleeding doesn't meet criteria for major bleeding (e.g., epistaxis, wound-related bleeding, sub conjunctival bleeding, ecchymoses, etc)[8]. All the bleeding events in both the groups were described in terms of site, severity and duration for comparison.

Serum creatinine, urine output and electrolytes were monitored and renal replacement therapy given accordingly[9]. Renal failure was classified using GFR criteria and urine output criteria into Risk (increased s.creatinine x 1.5 or GFR decrease > 25% or urine output <5ml/kg/hr for 6 hrs), Injury (increased s.creatinine x2 or GFR decrease > 50% or urine output < 0.5 ml/kg/hr for 12 hrs), Failure (increased s.creat x3 or GFR decrease 75% or s.creat>/= 4 mg/dL with an acute rise of >/=0.5 mg/dL or urine output <0.3ml/kg/hr for 24 hrs or anuria for 12 hrs) , loss (persistent ARF with complete loss of kidney function > 4 weeks), end stage kidney disease (> 3 months) groups.

All patients were treated with 'standard of care' practices existing at our hospital. Protocol lay down by 'snake bite: Indian guidelines and protocol' was followed. Hemodynamic outcomes were studied by packed cell volume, blood pressure, pulse rate, respiratory rate, and urine output.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation and range or median and interquartile range, as appropriate. Normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of normality. The qualitative parameters were presented as number and percentage and analysed by Chi square test and Fischer exact test. Quantitative parameters were analysed applying student's t-test or Mann Whitney test.

III. Observation And Results:

Study population had a mean age of 42.58 (range: 27-66) and male to female ratio was 3.85:1. Local symptoms occurred in all the patients, systemic symptoms in 94%, bleeding manifestations in 82%, acute renal failure in 51.9%. Mean time to reach hospital was 15.80 ± 5.7 hours (range: 1-26). Median SOFA score at presentation was 8.5 (range: 6-11) and median APACHE II score was 7.50 (range: 0-16). Mean time for resolution of coagulopathy was 31.40 ± 12.18 hours (range: 8-59).

Cases were randomized into two groups, Group 1 and Group 2 based on random number table. Group 1 included 24 patients had a mean age of 39.5 (range: 26-62). Local swelling at the bite site occurred in all patients whereas systemic complaints which included nausea and vomiting in 87.5%. Dizziness after snake bite occurred in 62.5%. Bleeding manifestations were noted in 81.2%, all of which were minor in severity graded according to HEME tool. Acute renal failure noted in 50%. Mean time for reaching the hospital since snake bite was 15.80 ± 5.7 hours. Median SOFA score at admission was 8.50 (range: 1-11) and median APACHE II score was 8.50 (range: 1-16).

26 patients in Group 2 had a mean age of 39.46 (range: 21-60) and male to female ratio of 3.5:1. Local swelling and systemic complaints occurred universally in all patients whereas dizziness seen in 65.4%, bleeding manifestations were noted in 21 (84.6%) cases, 18 of which were minor in severity and 3 were major. Among

the two patients with major bleeding manifestations, one patient had trauma during transfer to hospital with a laceration on his right forearm which needed FFP transfusion and suturing whereas other patient developed anaemia to the tune of 8.2 and needed blood transfusion. Oliguria occurred in 53.8%, mean time for reaching hospital was 12.57 ± 4.5 hours, median SOFA at admission was 9.0 (range: 0-10) and median APACHE was 7.0 (range: 0-14).

Thus both the groups were comparable at presentation. In Group 2 ASV was administered till end point of normalization of both INR and WBCT in contrast to Group 1 where in ASV was administered till normalization of WBCT only.

All the 50 patients included in the study had coagulopathy with prolonged WBCT in 48 patients and a normal WBCT with INR > 1.5 in twopatients. Among them, 32 (67.6%) had persistence of coagulopathy at 6 hours after administering ten vials of ASV, 13 (23.5%) had persistence after 20 vials of ASV and 3 patients (0.05%) had persistence after 30 vials of ASV.

In Group 1 coagulopathy (identified by 20 WBCT alone) was seen in 24 patients at admission, persisted in 15 patients (62.5%) after administering 10 vials of ASV at six hours, in 8 patients (25%) after 20 vials of ASV at 12 hours and in 1 patients (0.06%) after 30 vials of ASV at 18 hours after admission. In Group 2, 26 patients had coagulopathy (identified either with prolonged 20 WBCT or an INR > 1.5) at admission, with persistence in 19 patients (72.2%) at 6 hours, 6 patients (22.2%) at 12 hours and ONE patients (0.05%) at 18 hours. Among 19 patients with coagulopathy in the Group 2 at 6 hours, 8 patients (38%) had an INR of greater than 1.5 with a normal WBCT. All the 6 patients who had coagulopathy at 12 hours and one patients with coagulopathy at 18 hours also had an INR of greater than 1.5 with normal WBCT. This data shows 58% of cases with persistent coagulopathy will be missed if WBCT is monitored alone.

Mean time for administration of ASV was 19.13 ± 17.5 hours in Group 1 and 14.06 ±11.3 hours in Group 2 with a p value of 0.319. Mean dose of ASV administered in Group 1 was 20.15±7.03 vials and 17.3±6.3 vials in Group 2 with a p value of 0.13. In subgroup of patients with dizziness, mean dose administered was 19.88±7.89 vials in Group 1 and 18.26±7.05 vials in Group 2 (p=0.54).

Table 1: Analysis of mean dose* of ASV

Sub group	**Group 1 (Mean ± SD)**	**Group 2 (Mean ± SD)**	**'p' value**
Whole sample	20.15±7.03	17.3±6.3	0.13
In patients with dizziness	19.88±7.89	18.26±7.05	0.54
In pts. Presenting within 12 hours	19.93±6.2	17.37±6.2	0.66
In pt. presenting after 12 hours	20.41±6.5	17.27±6.5	0.18
In pt. presenting within 24 hours	18.50±6.3	17.3±6.3	0.380
In pts. With oliguria	19.35±7.8	18.5±7.7	0.78
In pt. with SOFA <4	20.01±6.9	15.5±2.1	0.96
In pt. with SOFA>4	20.15±7.03	17.5±6.6	0.19
In pt. with APACHE II <6	21.84±8.18	17.5±6.09	0.17

ASV: Anti snake venom; SOFA: Serial organ function assessment score; APACHE II: Acute physiology and chronic health evaluation II score; SD: standard deviation; * dose of ASV in number of vials;

In subgroup of patients who presented within 24 hours or after 24 hours of bite also no significant difference in mean dose of ASV given. In a similar way no significant difference was noted in subgroups of patients with SOFA<4, SOFA>4, APACHE II<6, APACHE II >6 and patients with oliguria. In Group 2, two patients who had major bleeding manifestations were administered 20 vials of ASV. Since the dose of ASV needed is more dependent on early presentation, patients that present early required more dose [19.92 ± 7.7 vials in patients presenting after 12 hours (n= 26); p: 0.66 VS 17.37 ± 6.2 vials in patients presenting within 12 hours (n= 24)].

Total no. of adverse reactions related to ASV administration were 33, of which 31 were minor and needed administration of inj. hydrocortisone and avil without any need for inotropic support or need for stopping further ASV administration. Two patients in Group 2 had major reaction and needed inotropic support. However the chance of occurrence of adverse reaction to ASV was same in both the groups (p=0.234). No other adverse reactions were noted in the Group 2.

Table 2: Comparison of Bleeding parameters

Sub group	**No. of days of bleeding manifestations (mean ± SD)**			**Platelet count on day 3 (* 10,000/mm^3) (mean ± SD)**			**Improvement time for thrombocytopenia* in days (mean ± SD)**		
	Gr 1	**Gr 2**	**'p'**	**Gr 1**	**Gr 2**	**'p'**	**Gr 1**	**Gr 2**	**'p'**
Patients with thrombocytopenia	1.2±0.6	2.7±4.4	0.10	63.9±28.2	67.1± 37.7	0.73	4±2.08	6.03±1.77	0.0005

Dizziness at presentation	1.13±0.7	3.23±2.4	0.002	64.1±27.2	64.3± 39.9	0.98	4.06±2.46	5.70±1.44	0.02
APACHE II > 6 at presentation	1.07±0.61	1.38±0.86	0.28	71.5±30.0 9	68±40.7	0.80	3.85±1.46	5.84±2.07	0.007
SOFA > 4 at presentation	1.18±0.6	2.73±4.4	0.10	65±29.2	67.15± 37.7	0.82	3.86±2.12	6.03±1.77	0.0004

Gr 1: Group 1; Gr 2: Group 2; p: 'p' value; * improvement in platelet count to greater than 1,00,000/mm^3; SD: Standard deviation;

Bleeding manifestations were analysed using following tools: no. of days of bleeding manifestations, mean platelet count on day 3 and time for improvement of platelet count to > 1,00,000/mm^3. Platelet count on day 3 was selected as a variable since around that time the effect of antivenom would occur. These variables were also analysed in subgroups of patients with dizziness at presentation, SOFA >4 at presentation and APACHE II >6 at presentation. Results summarized in the table 3 above, showed no significant difference between the groups.

The mean duration for resolution of swelling (time for circumference of the bitten limb at a fixed point from a bony prominence to become equal in comparison to other limb) was 3.19 days (range: 1-5) in Group 1 and 3.39 days (range: 2-5) in Group 2 with a 'p' value of 0.657. In similar way, the duration for normalization of leukocyte count was similar in both the groups (3.08 days vs. 3.47 days; p 0.784). Antibiotics and tetanus toxoid injections were given to all the patients irrespective of initial leukocyte count.

Renal outcomes were analysed using the following variables : maximum level of serum creatinine reached, number of hemodialysis sessions required, number of days for normalization of urine output (>500 ml/24hrs) and category of kidney injury according to RIFLE criteria. Subgroup analysis was also done in patients with Oliguria, in patients presenting within 24 hrs of snake bite, in patients with dizziness, in patients with thrombocytopenia at presentation, in patients with APACHE >6, in patients with SOFA >4.

This analysis showed that certain subgroups of patients with hemotoxic snake bite had better renal outcomes in Group 2 as compared to Group 1. Across the three parameters studied in all cases of hemotoxic snake envenomation, those with oliguria duration of > 24 hours, thrombocytopenia, APACHE II > 6 the renal outcomes were better but did not have a statistical difference when Group 1 was compared to Group 2. However when patients with SOFA >4 were analysed there was a statistical difference in two of these parameters (number of hemodialysisrequired and number of days for normalization of urine output). Categorization into risk, injury, failure, loss and ESRD groups showed no differences in both the groups.

Mean duration of hospital stay in Group 1 was 12.04 days and 8.57 days in Group 2. Using tests of normality, p value was 0.833 and hence no statistical significance. Since longer duration of stay was mainly due to renal failure, mean duration of hospital stay in subgroups of patients without (3.5 vs. 3.5; p 1.00) and with (16.16 vs. 8.85; p 0.292) oliguria were calculated and they were also not statistically significant. These results are shown in table 6. The duration of stay rather related to severity of envenomation which was evident by statistical significance between patients with and without dizziness at the time of snake bite (4.9 vs. 11.14; p 0.05). There was no mortality in the study.

In this study 106 paired tests (simultaneous WBCT and INR) were obtained. Ten times WBCT turned out to be prolonged with an INR of less than 1.5 and seventeen times WBCT turned out to be normal in spite of INR greater than 1.5.

Table 3: INR Vs.20 WBCT

	INR < 1.5	**INR > 1.5**	**Total**
20 WBCT negative	35	17	52
20 WBCT positive	10	44	54
Total	45	61	106

IV. Discussion

India is a country known to the western population as a country of snake charmers and snakes over centuries. Despite generation after generations some families in our country who play with snakes(snake charmers), we fail to protect the community from snake bite.

The mean age in our study was 42.58 years (range: 27-66 years) with a male to female ratio was 3.85:1. In the study from Anuradhapura, Sri Lanka (n=336 of viperine envenomation), most of the patients were around age of 40 years and a male to female ratio was 5:1. A definite male predominance is noted almost all the studies in literature (4:1 by Myint et al; 2.9:1 by Paul et al; 1.9:1 by Cherian et al;).[10-12] In our study the most common activity at the time of snake bite was walking through irrigated fields (82%) and most common part bitten were the lower limbs (94%). This fact is in accordance to other studies of viperine envenomation also. [13,14]

In this study, local symptoms in form of pain and swelling at the bitten site was evident in all the patients and mean duration for this swelling to resolve was 3.29±1.5 days (range: 1-5 days). This observation is similar to the Anuradhapura study which showed that swelling occurs in 92% of patients and lasts 4-7 days.[15]

Sharma et al showed neuroparalytic features in 60.6% of cases, which are hallmark of cobra and krait bites and hemostatic abnormalities attributable to viperine bites in 36.6% cases. Sharma et al studied snake envenomation and showed that most of the cases were young rural men, during the months of May to October because of flooding of habitat of snakes and their prey. It showed that most of the bites were among young rural men during sleep. It also showed a median time for arrival in hospital after bite to be nine hours and median stay in hospital to be 8 days. Among the patients presenting with haemostatic abnormalities, viperine bites most frequently resulted in bleeding, followed by intravascular hemolysis and hematuria. In this study, the mean dose of antivenom for neuroparalytic snake bite was 51.2 vials and 32 vials for viper bites.[16]

VICC induced spontaneous systemic bleeding occurred in 82% patients in our study, 46% in the Burmese study, 59% in the study by Philips et al and 77% in the Anuradhapura study. The occurrence of thrombocytopenia in 88% of our patients was much more when compared to the study from Burma (25%).[10] These differences are due to the inclusion criteria. For instance, the Burmese study included the patients bringing along the dead snake even though no features of systemic envenomation were present.

The time elapsed since snake bite to the time VICC was identified varied from one hour to 36 hours in our study. Most of this delay occurred due to patient behavior related factors in seeking appropriate medical advice. This delay has also seen in other studies to range from 12 hours to 24 hours.[10,15] Most of the envenomed patients arrived late to the health care facility causing a considerable delay in identifying VICC. In our study, the time taken for VICC to resolve ranged from 8 hours to 59 hours (mean = 31.40 ±12.18 hours). In Anuradhapura study, this ranged up to 48 hours.[15]Suchithra et al from Kerala showed that time taken for resolution of VICC using PT, INR and aPTT) was higher (71.8 hours) when compared to monitoring by WBCT only (37.25 hours).[17] Furthermore, in this study, the authors used only WBCT for administering further doses of ASV. This apparent difference in time for resolution of VICC in our study compared to that of Suchithra et al may be attributed to a different species of viperine envenomation seen (Russell's) as compared to that in our study (saw-scaled vipers) or due to different INR cutoff values for VICC in the two studies. In our study, an INR <1.5 was normal as compared to a value of INR < 1 as seen by Suchithra et al. In the study from Kerala, Suchithra et al also showed a higher rate of bleeding complications that correlated to an INR> 1.8.[17] In our study, despite 28 patients presenting with minor bleeds, only four patients had an INR > 1.3, of which one patient had acute renal failure. The remaining 2 patients of VICC presenting as major bleeding complications had INR values of 1.8 and 3.63 respectively.

The limitations of this study include small sample size, heterogenicity in cases regarding time of ED presentation after snake bite, prior treatment received and greater proportion of complicated cases being a tertiary referral centre. There is thus a dire need for a study recruiting a large number of patients before recommendations can be made to add on/replace crude 20WBCT by INR in managing VICC.

V. Conclusions

In conclusion, this study has shown that monitoring of VICC using INR in addition to WBCT resulted in administering more ASV doses and a better renal outcome (oliguria duration, and lesser hemodialysis) in the subgroup of patients with SOFA> 4. Thus, wherever facilities exist, INR can be used as a non-inferior and add-on tool to WBCT for complicated cases of VICC. INR testing is not readily available in all centers. Also INR testing is not cost effective and not affordable.Further work is required to develop such a test that performs to an acceptable standard in the field, and delays to antivenom are minimized. To do this, it may be worth exploring a range of methodologies, an ideal test would be able to provide a result more rapidly than after 20 min.

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