A Contextual Approach to Managing Snake Bite in Pakistan: Snake Bite Treatment with Particular Reference to Neurotoxicity and the Ideal Hospital Snake Bite Kit

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Abstract

Although the snakebite mortality numbers for Pakistan are over estimated, snakebite remains a significant problem of rural areas. Significant improvements are possible with locally developed protocols incorporating the latest research. The use of simple reliable diagnostic tools in managing viperine envenomation and the introduction of monitoring cycles based on physiological criteria can greatly improve outcome. The acquisition by hospitals, even the most basic, of inexpensive drugs and simple readily improvisable equipment can dramatically improve patient survival in neurotoxic, particularly cobra envenomation. Basic hospitals can intervene in snakebite management and this is essential if envenomed victims are to be treated early. This paper makes recommendations as to the basic drug and equipment profile to enable all hospitals to successfully manage snakebite in Pakistan.

Introduction

Pakistan has a long history of snake bite. As early as 1854, doctors in the area were investigating the burden of snake bite and the 'deadly snakes of Sindh".[1,2] Despite this, little definitive information exists as to which species are causing the bites or the geographical range of many of the species. A prime example is the cobra family. The Asiatic cobra or 'black cobra' is probably confined to the north of Punjab and North West Frontier Province and yet the use of the Sindhi term 'Karo' or black cobra for the cobra in Sindh adds confusion as to which species are present in which area.

Much of Pakistan medical education is based on

western textbooks such as Harrison's[3] and Clark and Kumar[4] or a small number of indigenously produced textbooks.[5] In terms of snakebite these textbooks are inapplicable in the Pakistan context and can lead to anti stake venom (ASV) being given unnecessarily.[6]

There are misconceptions concerning the level of snakebite mortality in Pakistan, mainly published by international observers. Estimates are given of 20,000 snakebite deaths[7] and yet the Health Department morbidity and mortality figures from Tharparker District (Pop. 0.9 Million), with the most significant snakebite problem, in 2003 were 24.41 and 1.1 respectively, per 100,000. External estimates reflect a fundamental misunderstanding of how envenomation and snakebite is recorded in many developing countries. Without clear criteria for defining envenomation, significant overestimation occurs, as in the estimates for Pakistan, and these impact mortality figures. Whilst these numbers can be good headline grabbers they are poor guidance for policy makers who are responsible for ASV provision and procurement.

Key to the improvement of snakebite management in Pakistan is the provision of contextual protocols and data, produced within Pakistan.[8]

Patient Arrival and Investigation

When the patient arrives it is important to establish the time of the bite, the activity at the time of the bite and any first aid actions that have been taken since the bite.[9] For example, a patient bitten 18 hours ago, and not showing any symptoms, is probably a non venomous or dry bite. The longer ago a patient with symptoms was bitten, the less venom will be available to be neutralized.

The specific activity being carried out by the victim at the time of the bite can be useful in providing snakebite prevention advice. Most areas with a snakebite problem have three or four main activities e.g. grass cutting that are responsible for the majority of bites. Recording and communicating these activities to the local community can increase awareness and reduce snakebite.

The effects of first aid need to be evaluated. Victims in the region ingest ghee, chillis and other substances to combat snakebite. Abdominal pain and vomiting may not be signs of envenomation in these cases.

In parallel to the questioning and examination of the patient, the most important diagnostic test is performed. Viperine bites cause consumption coagulopathy and the best method of diagnosing this is the 20 Minute Whole Blood Clotting Test (20WBCT).[10] A few mLs of fresh venous blood is placed in a **NEW, CLEAN, DRY, GLASS** test tube and left undisturbed for 20 minutes. It is then gently tilted to 45 degrees and the blood examined. If it has remained liquid, this is evidence of consumption coagulopathy and the victim requires ASV. If the blood has clotted then no ASV is necessary at this stage.

It is important that the test is done with new, clean, dry and glass test tubes as the intention is to activate the contact clotting mechanism. The majority of current tests in Pakistan are carried out using old bottles, old drug ampoules, washed containers or plastic syringes.[11] None of these methods will give reliable results and will contribute to many false positives as the contact clotting mechanism will not be activated and the blood, containing plenty of clotting factors will remain liquid. ASV will thus be given unnecessarily to a non envenomed patient or a patient in whom the venom may have already been neutralized. This potentially wastes precious antiserum in short.

Determining Envenomation and Criteria for Giving Anti Snake Venom (ASV)

The criteria for establishing whether to administer ASV must be clear and unambiguous. For example, it is common practice to give ASV in Pakistan to patients who have a history of cobra bite, but no symptoms. The speed of action of neurotoxic venom is the justification for the early administration of ASV. However, as many as 50% of cobra bites inject no venom into the victim, therefore no ASV is required.[7]

In Pakistan the criteria for ASV administration are:

1. Incoagulable blood determined by the 20WBCT
2. Visible neurological signs such as ptosis or ophthalmoplegia or other evidence of descending paralysis.
3. Clear evidence of current systemic bleeding e.g. haemoptysis. It is worth remembering that when using lyophilized ASV the speed of reconstitution will almost certainly determine that primary evidence from a 20WBCT will be available before administering ASV under this category, it it therefore the 20WBCT that should be the primary measure.

Unless one or more of these signs are present, no ASV should be given and an envenomation should only be recorded if these criteria are met and ASV is required. ASV's only role is to neutralize, unbound, free flowing venom.

Pre ASV Administration

The likelihood and apprehension of adverse reactions to ASV leads to questions of prediction and prevention of such reactions. In Pakistan this frequently manifests as ASV test doses for prediction and prophylactic regimens to prevent reactions.[11-14] ASV test doses must not

be used despite the fact that they are advocated in some textbooks and ASV product inserts.[5,15] Intra dermal test doses of ASV are carried out to determine if an adverse reaction is likely. However, these tests are targeted at IgE medicated reactions whereas ASV reactions are complement activated, they are thus non predictive of anaphylactoid or late serum reactions.[7,16,17] In addition, they run the risk of pre sensitizing the patient and making a reaction more likely. Finally they waste precious time if the victim is envenomated as 20-30 minutes are required to carry out the test and are logically unsound as the envenomed victim has to receive ASV to cure the bite in any event.

Pre medications with either hydrocortisone and anti histamine or subcutaneous adrenaline are commonly used methods by doctors in Pakistan to prevent adverse reactions to ASV. These regimens cause no harm but there is no powerful statistical evidence that they do in fact prevent reactions. Both studies carried out into the effect of these strategies were too small to give conclusive statistical power.[18,19] If prophylactic regimens are used they should only be administered during the first dose of ASV. Prophylactic regimens are not required for each subsequent administration of ASV.

ASV Dosage and Mode of Administration

Two main types of ASV are available in Pakistan; the Liquid ASV produced by the National Institute of Health in Islamabad and imported lyophilized ASV mostly from India. Liquid ASV is considerably easier to administer as it requires no reconstitution but has disadvantages in areas like Sindh with a poor cold chain as it must be refrigerated. The lyophilized ASV does not require refrigeration but takes up to 1 hour to reconstitute with distilled water.

Much has been written about the initial dose of ASV to be administered, most of which, such as the advice on the ASV product insert is completely misleading or incorrect.[15]

When determining dosage levels, particularly the initial dose of ASV, it is important to consider the amount of venom injected by the snake in an average bite. Russell's viper and cobra inject approximately 60mg of venom in the average bite.[20] Kraits inject less, but the difficulty in distinguishing a krait bite from a cobra bite by clinical features necessitates that neurotoxic bites should be treated with the same initial ASV dose. Each ASV vial neutralizes 6mg of cobra (N. naja) and Russell's viper (Daboia russelii) venom and therefore the initial dose of ASV should be 8-10 vials in all cases with clear evidence of envenoming. This would be the same dose whether using NIH ASV or imported Indian ASV as the neutralizing capacity is the same.

In the case of the Pakistan saw scaled viper (Echis sochureki), known as 'Lundi' or 'Kupper', some authors have suggested its venom yield is much lower, around 15mg.[21] These venom yield studies were based on the smaller Indian saw scaled viper (Echis carinatus) and are therefore possibly unreliable for the local species in Pakistan which is much larger. Indian ASV is also not produced using the venom from the larger saw scaled viper (Echis sochureki). An initial study in India showed that the average amount of Indian ASV required in restoring coagulation, measured correctly by the 20WBCT, was 15.4 vials and the authors saw victims in Sindh that required 25+ vials.[22] Doubts also exist in India about the efficacy of Indian ASV to deal with Echis sochureki.[22]

The NIH ASV is developed using local saw scaled vipers from the Thar Desert in Sindh and therefore should be more effective against this local viper. Local doctors point out that they use smaller doses of the NIH ASV to 'cure' saw scale viper bites. Normal practice is to use much higher initial doses of Indian ASV than when using NIH ASV. However, the use of a reliable measure of coagulation is vital in determining the restoration of coagulation and many hospitals are using unreliable tests and only daily evaluation of coagulation.

When using NIH anti venom the guidelines should be:

1. In all cases other than a confirmed saw scale viper bite, administer 8-10 vials as the initial starting dose.
2. If using against a confirmed saw scale viper bite use an initial starting dose of 4 vials. Only give ASV following a 20WBCT with incoagulable blood taken with a new, clean, dry and glass test tube. Strictly use a 6 hour period for monitoring coagulation and repeating ASV (see below).
3. Monitor a series of patients for restoration of coagulation. If 50-60% have coagulation restored after 6 hours, 4 vials is probably the correct starting dose. If only 10-20% have restored coagulation after 6 hours (see below), then increase the initial starting dose to all patients by 1 vial and monitor results. A number of clinical trials are planned in Pakistan both to assess the effectiveness of NIH and Indian ASV and establish empirically the correct starting dose.

All anti venom should be administered over a maximum of 1 hour. The ASV can be given by intravenous injection or continuous infusion. It must not be given subcutaneously, intramuscularly (IM) or around the bite site.

Some authors have recommended a higher dose of ASV for children however the dose of ASV is the same for children and pregnant women and is not contraindicated in

pregnancy.[13]

ASV should be given only when the criteria for administration are present. If a patient presents after many days, complaining of snakebite, a 20WBCT should be carried out. In the case of incoagulable blood, ASV should be given. ASV should be given as late as the 20WBCT indicates that it is required by demonstration of incoagulable blood.[9]

Neurotoxic Snakebite: A Key Intervention

Neurotoxic envenomation by kraits and particularly cobras remains a cause of significant mortality. Both versions of the spectacled cobra (Naja naja), with a spectacle marking known as 'Gudrow', or a patternless version known as 'Karo' in the local language, cause many deaths in Sindh, Balochistan and Punjab. Cobra venom is a post synaptic neurotoxin and blocks the nicotinic receptor causing acetylcholine to be unable to bind. Krait venom is pre synaptic and damages the motor end plate inhibiting acetylcholine release.

A vital method of treatment in cobra bites, which should also be tried in all neurotoxic bites, is the use of an anti cholinesterase such as neostigmine.[23,24] Neostigmine prolongs the life of acetylcholine, by inhibiting cholinesterase, thus increasing the likelihood of the acetylcholine binding with an unblocked receptor.

In the case of a patient exhibiting neurotoxic symptoms a baseline test of neurological function such as single breath count or length of time upward gaze can be maintained should be taken and noted. Immediately following the test, 1.5mg neostigmine methylsulphate should be given IM with 0.6mg of atropine given IV. The victim is kept under observation for 1 hour. The test of neurological function is repeated every 10 minutes to assess whether there is any improvement. Neostigmine reaches peak effect after 20 minutes. If there is an objective improvement is neurological function, measured by the test, then neostigmine should be continued with 0.5mg administered IM every 30 minutes, with atropine. If there is no objective improvement after 1 hour no further neostigmine is administered.

Adverse Reactions to ASV

Once ASV therapy is commenced, the patient must be monitored very carefully for any sign of adverse reactions. Particular attention should be paid to the trunk, where the first signs of any reaction often occur. Clothing should be removed to enable a clear view as there is evidence that many anaphylactoid reactions go unnoticed.[25] There is evidence to suggest that in respect of Indian anti venoms the average time for a reaction to manifest is approximately 20 minutes from the start of ASV administration so whilst the patient should be watched throughout the first hour, this initial period is particularly important.[21]

At the first sign of any reaction e.g. itching and urticaria, the ASV should be temporarily suspended. A great many doctors in the region initiate treatment of the reaction with hydrocortisone or anti histamine. However, the drug of choice is adrenaline with 0.5mg 1:1000 being administered IM. Pulse monitoring after 3 minutes should indicate an increase, 8 minutes marks peak activity, and the symptoms should begin to improve by 12-15 minutes. If symptoms are not improving at this stage a second dose of adrenaline is given. The second dose, if required will cure virtually all patients and ASV can be resumed.

The IM route is preferred over subcutaneous due to the speed of reaching peak levels in the blood. Adrenaline administered IM reaches peak levels in 8 minutes whereas administered subcutaneously the peak time is 34 minutes.[25] Time is of critical importance as the ASV has been suspended. The priority is for the victim to receive the ASV as quickly as possible in order to neutralize the venom. As a consequence we need the adverse reaction to be reversed as soon as possible. All available evidence suggests that anaphylactoid reactions can be dealt with easily and speedily if IM adrenaline is used early and without delay.[26]

In addition, to provide longer term protection against anaphylactoid reactions, 100mg of hydrocortisone and an H1 antihistamine, such as Phenimarine maleate can be used at 22.5mg IV or Promethazine HCl can be used at 25mg IM, or 10mg chlorphenimarine maleate if available, will be administered IV.

Repeat Doses of ASV

In the case of a viperine bite, once the initial dose of ASV has been administered, six hours after the completion of the ASV, a further 20WBCT is carried out. The six hour time period reflects the time required by the liver to restore clotting factors.[7] Further 20WBCTs taken before 6 hours will simply reconfirm the first test, they will not provide any useful data. If the 20WBCT after 6 hours is incoagulable, a repeat dose is given, a further 6 hours elapse, an additional 20WBCT is carried out and ASV is again given if required, until coagulation is restored. Viperine bites should be managed on a 6 hour cycle. Many doctors in Pakistan use a daily cycle. A blood test is taken in the morning; if coagulation disturbance is detected, ASV is given. The next day a further blood test is taken and more ASV given if required. There are two major flaws in this approach:

1. If, following 6 hours after ASV is administered, there is still unbound venom in the system; 18 hours will

elapse before a second neutralizing dose is given. The unbound venom will be unopposed during this time and will be able to inflict more damage.

2. Patients will occupy beds for greater periods. Under this approach a patient requiring three doses of ASV will be in hospital for 4 days; three days to administer ASV and the fourth day to confirm resumption of coagulation. Under the 6 hour cycle, the patient will be discharged after 18-24 hours, unless there are complications such as necrosis or renal failure.

In the case of neurotoxic envenomations, once the initial dose of ASV is given the patient is reviewed after 1 hour. If the symptoms have worsened i.e. the paralysis has descended further, a second dose of ASV is given over 1 hour. If the symptoms have not worsened a further review is carried out after 2 hours.[9] If after 2 hours the symptoms have not improved, a second dose of ASV is given. Once the patient has received 2 doses of ASV, sufficient neutralizing anti venom has been given and ASV should be stopped. The patient will now either recover or require mechanical ventilation. There is no role for very large doses of ASV in neurotoxic bites.

Use of Blood or Blood Products in Viper Bites and other Drugs

The use of whole blood in dealing with viper bites is common in Pakistan. Some doctors expressed a view that after 24 hours, ASV had no role and blood products should be used instead. However, the primary means of restoring clotting factors to normal levels is by the use of ASV. Once the venom has been adequately neutralized with anti venom the liver will begin to restore factors to normal levels. Blood or blood products are only required in exceptional circumstances such as severe bleeding and should not in any eventuality be given until coagulation has been restored.[27] Giving blood while un-neutralised venom is present in the system fulfills no useful function.

Heparin and coagulant drugs have no place in the treatment of viper bites. Pain management should be dealt with using paracetamol but not aspirin, due to its impact on coagulation. Routine tetanus medication is probably required but antibiotics are not required routinely, they should be used if there is necrosis or if the victim has used cutting as a first aid measure.

Referral Criteria to Better Equipped Hospitals

There are three major consequences of snakebite in Pakistan that require specialized treatment which is likely to be unavailable in most hospitals. These are:

1. Occult systemic bleeding and renal failure which require access to blood testing such as platelet count, packed cell volume and blood creatinine to establish presence
2. Neurotoxic cases requiring longer term mechanical ventilation
3. Surgical cases requiring debridement of necrotic tissue.

It is useful to consider hospitals that cannot perform these functions as hospitals capable of 'Initial care' and hospitals that can perform these functions as capable of 'Ultimate Care'. In snake bite terms this distinction is clearer and removes the reliance on terms such as primary and secondary hospitals. Many secondary hospitals cannot perform the three additional treatments and thus have the same status as the 'initial care' hospitals in snake bite terms.

Both 'initial care' and 'ultimate care' hospitals can treat snake bite and it is essential that both perform their role, with the support of clear criteria as to when a victim should be referred from 'initial' to 'ultimate' care.

In the case of viperine envenomations, on arrival at the initial care hospital the victim will be diagnosed, if envenomated, by the 20WBCT. The initial dose of ASV should be given and any adverse reaction dealt with by the use of IM adrenaline and hydrocortisone and anti histamine. Once the initial dose of ASV is complete, a 6 hour window is available to transport the victim to an ultimate care hospital. The 6 hour window until the next 20WBCT provides ample time to safely move the victim.[9]

In the case of neurotoxic envenomation, the victim will be diagnosed by visible neurological signs such as ptosis. The victim will be given the initial dose of ASV, neostigmine and atropine and any adverse reaction will be handled by IM adrenaline. The key consideration in treating the neurotoxic victim is respiratory failure and the need to provide mechanical ventilatory support. As long as respiratory failure is not imminent the victim can be treated entirely within an initial care hospital, particularly with a positive response to the neostigmine test. The two doses of ASV can be given and the patient can be discharged on recovery.

The determination of respiratory failure is a key referral criteria and the use of a neck lift provides the key test.[9] As long as the victim can perform a neck lift, imminent respiratory failure is not likely. The patient should be frequently tested on their ability to perform a neck lift. As long as the ability continues the patient can be treated in the initial care hospital.

If the patient is unable to perform the neck lift then referral and transportation becomes the key consideration. Most victims of neurotoxic envenomation die during

transport due to inadequate measures to preserve respiration. A key feature of good transportation is the use of a resuscitation bag. However, flaccid paralysis, the tongue falling back into the airway and the operation of the bag by an untrained bystander frequently renders the use of the bag inadequate.

To greatly improve effectiveness, and thus patient survival, nasopharyngeal tubes (NPA) should be inserted into the nostrils. These devices sit behind the tongue; do not trigger the gagging reflex and therefore can be used in conscious or unconscious patients. If nasopharyngeal tubes are not available they can be improvised with 2 size 5-0 rubber endotracheal tubes cut down to the correct length. Proper length is best estimated by measuring the distance between the external naris and the tragus of the ear. The tubes should be lubricated and inserted before referral and the individuals who are accompanying the victim told to commence the use of the resuscitation bag if the victim stops breathing on the journey.

In the case of unconscious patients, and if available, the use of bridging airway devices such as laryngeal mask airways should be used. They are more effective but also more expensive. The use of improvised NPAs give very effective support, are inexpensive and readily available. The early use of ASV in the correct dosage and timing, neostigmine and effective airway support will dramatically reduce neurotoxic deaths, particularly in the case of cobra bites.

The Ideal Snake Bite Kit in the Pakistan Context

In order to effectively treat snakebite in either an initial care or ultimate care setting a basic equipment and drug profile should be available. Ideally these should be kept on a snakebite tray ready for immediate deployment when the victim arrives. The equipment on the tray should include:

1. Anti snake venom. If the cold chain is adequate NIH liquid ASV is best, otherwise lyophilized Indian ASV. In areas where envenomations occur, determined under the two main criteria of 20WBCT incoagulable blood or visible neurological signs, the number of vials is recommended to be number of victims in one month, multiplied by 20 vials, multiplied by the time in months required to replenish supply. For example, if 3 victims are envenomed per month and ASV is replenished every month then 60 vials would be required at minimum.
2. Test tubes, new, clean, dry and glass for 20WBCT. 24 vials are required for all patients. For example if 20 patients come with snakebite in one month 480 test tubes are required. Not all will be used in the three envenomations from the previous example but they will be required to confirm that other patients are non-envenomed.
3. Neostigmine and atropine. 20 ampoules of 0.5mg neostigmine should be obtained for the average number of victims who present visible neurological signs per month. Three will be used in the initial neostigmine test and others will be required for continuing treatment. The actual number held will vary by location as some districts such as Mirpurkhas have higher levels of neurotoxic envenomation than others.
4. Adverse reaction drugs. Adrenaline (1:1000) is priority and 10 vials of 1mg should be kept on the snakebite tray. 5 vials of 100mg hydrocortisone and 5 vials of 22.5mg Phenimarine maleate should be available for longer term protection and support.
5. Pain medication. Paracetamol tablets 500mg are the preferred pain medication, and not aspirin.
6. Resuscitation bag. This is vital in dealing with neurotoxic bites and most hospitals have access, even in the remote desert areas.
7. Airway support Kit. The tray should also contain the improvised nasopharyngeal airway constructed from ET tubes. If possible a laryngeal mask airway should also be available.

If such a tray is made available in each hospital, including Basic Health Units (BHU) and Rural Health Centers (RHC), snakebite mortality will be dramatically reduced. All levels of health care will be equipped with the drugs and equipment to treat snakebite in an initial care role. This will ensure that envenomed patients receive ASV at the earliest and are transferred under optimal conditions when required.

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