SCOPE OF AYURVEDA IN DRUG INDUCED HEMOTOXICITY – A CONCEPTUAL STUDY

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ABSTRACT - Hemotoxicity is the condition which is characterized by the presence of hemotoxins that destroy blood cells, cause hemolysis, disrupt blood clotting and cause organ degeneration and generalized tissue damage. Hemotoxins are employed not only by venomous animals like snakes but also some therapeutic drugs, non-therapeutic chemicals and other agents. In the present scenario a wide range of medicines are causing hemotoxicites though they are used in therapeutic level such as Primaquine, Alteplase, Urokinase, Chemotherpeutic agents etc. A wide range of herbal preparations are available in the *Ayurveda* system of medicines which may be used as hemoprotective drugs. In *Agad Tantra*, branch of toxicology in Ayurveda, an array of simple medicines are being used for the management of hemotoxicities due to *maṇḍ'ali visha*, especially in traditional practices. The *maṇḍ'ali visha* deals with the management of complications due to hemotoxic snake venom, the symptoms and pathology of which are very much similar to drug induced toxicity. This study creates a new field of research for the quest for toxicity reversal drugs for many drug therapies.

KEYWORDS – Hemotoxicity, *Ayurveda*, *Agad Tantra*, *Maṇḍ'ali visha*

INTRODUCTION

The hematopoietic system ranks with liver and kidney as one of the most important considerations in the risk assessment of individual patient populations exposed to potential toxicants in the environment, work place and medicine cabinet [1]. The delivery of oxygen to tissues throughout the body, maintenance of vascular integrity and provision of the many affector and effector immune functions necessary for host defence, requires a prodigious proliferative and regenerative capacity [2]. As with intestinal mucosa and gonads, this characteristic makes hematopoietic tissue a particularly sensitive target for cytoreductive or antimitotic agents, such as those used to treat cancer, infection, immune-mediated disorders etc. This tissue is also susceptible to secondary effects of toxic agents that affect the supply of nutrients such as iron; the clearance of toxins and metabolites, such as urea; or the production of vital growth factors, such as erythropoietin and granulocyte colony stimulating factor (G-CSF). The consequences of direct or indirect damage to blood cells and their precursors are predictable and potentially life-threatening. They include hypoxia, hemorrhage, infection etc. These effects may be subclinical and slowly progressive or acute and fulminant, with dramatic clinical presentations.

Hematotoxicity may be regarded as primary, where one or more blood components are directly affected, or secondary, where the toxic effect is a consequence of other tissue injury or systemic disturbances. Primary toxicity is regarded as one among the most common serious effects of xenobiotics, particularly drugs [3]. Secondary toxicity is exceedingly common, due to the propensity of blood cells to reflect a wide range of local and systemic effects of toxicants on other tissues. Risk-versus-benefit decisions involving hematotoxicity may be controversial. Whether the effect is linked to the pharmacologic action of the agent, as with cytoreductive or thrombolytic chemicals or unrelated to its intended action, the right balance between risk and benefit is not always clear [4].

HEMOTOXICITY – AN AYURVEDIC VIEW

Ayurveda deals with many types of hemotoxic disorders. In this medical system *rakta* is considered as a *dhātu* as well as *dosha*. But hemotoxicity is not exactly similar to *rakta dusht'i* instead it is only a type of *rakta dusht'i*. There are certain diseases in *Ayurveda* with haematological disorders which are having *visha* etiology, such as *raktapitta, pāṇḍ'u, rakta atisāra, raktaja pravāhika, kushta* etc. For example, the etiological factors of *raktapitta* consist of *virudhāhāra* which in turn acts as a *visha* inside the body [5,6]. In *mr't bhakshaṇajanya pāṇḍ'u* eating of mud can be considered as a type of *gara visha* [7,8]. Among the eight branches of *Ayurveda*, the toxicology and its management is dealt by *Agad Tantra*. The *Agad Tantra* is detailing about various types of systematic toxicities of animate and inanimate origin and its management.

MAṆḌ'ALI VISHA

In *Agad Tantra*, hematological toxicities are directly dealt by *maṇḍ'ali visha*, poisoning due to hemotoxic snakes [9]. The *maṇḍ'ali visha* is getting manifested in the body in two ways – General (*samanya lakshanas*) and specific stages (*vega lakshanas*). The general symptoms of *Maṇḍ'ali visha* as told by *Ācārya Sus'ruta* are yellowishness of skin etc., desire of cold, fuming, burning sensation, thirst, narcosis, fainting, fever, hemorrhage from above and below orifices, putrefaction and falling of muscles, necrosis of bite site, vision of yellow sights, quick anger and other type of *paittika* affliction. All the symptoms described under *samanya* and *vega lakshanas* are having *paittika* predominance. As per the principle of *ās'raya-ās'rayĩ bandha*, whenever *pitta dusht'i* occurs, *rakta* will get vitiated and symptoms of *rakta dusht'i* will appear in the body. Also *visha* when enters the body will vitiates blood first. According to *Ācārya Sus'ruta maṇḍ'ali visha* aggravate *pitta*. All these suggest that *Maṇḍ'ali visha* are producing hematological toxicity in the body.

In addition to classical literatures of *Ayurveda*, *Agad Tantra* has got a lot of traditional text books which were written by renowned traditional *visha* practitioners which were prepared based on the practical usage and availability of the medicines. Among them, widely practising text books are *Prayogasamuchaya*, *Jyotsnika (vishavaidyam)* and *Kriyākoumudi*. According to *Prayogasamuchaya*, sixteen types of *maṇ'ali visha sarpā*s have been told. In poisoning due to *pĩtanetra maṇ'ali* there will be bleeding from hair follicles. In *rakta maṇ'ali* poisoning bleeding from nose and mouth will be present [10]. Various complications of *Maṇ'ali visha* as told by *Jyotsnika (vishavaidyam)* include blood vomiting, blood spitting, bleeding from hair follicles, *rakta dusht'i* etc. [11]

The symptoms described in *maṇ'ali sarpa visha* of *Ayurveda* are very much similar to that of the snake bite poisoning due to Russell's viper. So the pathology of viper envenomation can be similar to the *maṇ'ali visha*.

VIPER ENVENOMATION

Hemotoxic venom destroys the coagulant properties of blood. This type of venom causes severe internal bleeding, as well as bleeding from mucous membrane surfaces, and the bite site. Hemotoxic venom acts as a pro-coagulant, removing fibrinogen from blood and reducing blood platelets. The venom also weakens the capillary endothelium (a thin layer of cells that line the interior walls of blood vessels) which results in internal hemorrhage. Other signs and symptoms of hemotoxic venom are bleeding from bite mark, ecchymosis, Hematemesis, epistaxis, hematuria, hypertension etc. Coagulopathy frequently occurs following bites and can result in a consumptive coagulopathy manifested by hypofibrinogenemia, prolonged prothrombin time (PT), decreased or unmeasurable activated partial thromboplastin time (A-PTT) with a platelet count of less than 20,000/mm3, or a combination of these signs. Pit viper venom alters capillary membrane permeability, resulting in loss of electrolytes, albumin, and red blood cells into the bite site, manifested clinically as edema and erythema. Altered red blood cell membrane permeability can cause hemolysis. Initially, hypoalbuminemia and hemoconcentration occur, followed by pooling of blood and fluids in the microvasculature, resulting in hypovolemic shock and acidosis; however, this process can occur concomitantly in other organs such as the lungs, myocardium, kidneys, peritoneum, and, rarely, central nervous system. Renal failure might be secondary to hypotension, hemolysis, consumptive coagulopathy, or the nephrotoxic effects of the venom components themselves [12]. Various toxic symptoms produced by such envenomation sharply simulate that which is producing by xenobiotics, particularly drugs, directly or indirectly (Vandendries and Drews, 2006).

DRUG INDUCED HEMOTOXICITY

Drug toxicity, also called as adverse drug reaction (ADR) or adverse drug event (ADE), is defined as the "manifestations of the adverse effects of drugs administered therapeutically or in the course of diagnostic techniques. It does not include accidental or intentional poisoning." The WHO defines it as: An adverse drug reaction (ADR) is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'. Very similar pathological symptoms of hemotoxicity have also been reported in several drug induced clinical situations including chemotherapy (cyclophosphamide, doxorubicin etc), immunosuppressive treatments (cyclosporine, tacrolimus, or muromonab), antiviral treatment (gangcyclovir) etc. (R. Danesia et. al., 2004). Many such drugs are common in use, despite of their toxic side effects in sake of lack of relatively cheap, less toxic or non-toxic substitutes. Hemotoxicity has got wider effects in various hematological factors such as erythrocytes, leukocytes, platelets etc. Toxicology of erythrocytes includes alteration in red cell production, alteration in respiratory function of hemoglobin and alteration in erythrocyte survival. Toxicology of leukocytes includes effects on proliferation, effects on function and toxic leukaemia and neutropenia. Toxicology of platelets and hemostasis consists of toxic effects of platelet function and blood coagulation. This tissue is also susceptible to secondary effects of toxic agents that affect the supply of nutrients such as iron; the clearance of toxins and metabolites, such as urea etc.

***MAṆD'ALI VISHA* TREATMENT**

A well-structured treatment strategy has been described for the management of *maṇ'ali visha*, classified as *samanya cikitsa* and *vega cikitsa*. An array of therapies and medications are being used as per the different conditions.

Various complications may arise after the treatment of *maṇ'ali visha*. Among them many are very much similar to the symptoms of hematological toxicity. They are hemorrhage, bleeding from mouth, eye, ear, nose, gum, hair follicles and stomach, *rakta atisāra* (malena), haematuria, *adhorakta* (anal bleeding) etc. For the management of these complications so many simple formulations as well as single drugs have been told in the traditional *visha* textbooks. These treatments include both external procedures as well as internal administrations. Some of the special medicines are given below in Table 1 [13,14].

Table-1 : Simple medications using for *Maṇ'ali visha cikitsa* in traditional practices

General Hemorrhage	*Dhāra* with *bakula bĩja* and *hingu*
	Kvātha of *s'āriba, candana* and *madhuka* taken along with honey and sugar
	Ghr`ta prepared with *candana kvātha*, *s'atāvari svarasa* and *yasht'i kalka*
	External application of leaves of *nirguṇ'i* grinded with *kānjika*
	Root powder of wild variety of *bimbi* taken along with ghee
	Manjisht'a powder, *s'āriba* decoction, honey and leaves of *lakshmaṇa* along with butter applied on vertex as tala
Bleeding from eyes	*Sphot'ika svarasa* and tender coconut water mixed together and grinded with *kataka, anjana*
	Ghr`ta prepared with *jĩvanti svarasa* and applied as *tala* on vertex

Bleeding from ears	Butter grinded with *vilvapatra svarasa* and applied as *tala* on vertex
	Butter grinded with *vilvapatra svarasa* for instilling into ears
Bleeding from nose	Butter grinded with *pat'olapatra svarasa* and applied as *tala* on vertex
	Nasya with *kr'shṇa jĩraka* grinded with breast milk
Bleeding from gums	Chewing cooked *kooshmāṇd'a* pieces
Bleeding from hair follicles	Fried and powdered *s'igru* root with ghee internally and externally
Rakta atisāra	*Kvātha* of root bark of *kut'aja*
	Karanja bark or *kadamba* bark grinded with water
Hematuria	Pills made of *hastapādi* taken in *hastapādi svarasa*
Bleeding per rectum	*Kvātha* of *s'atāvari* tuber taken along with honey
Bleeding from mouth	A mixture of *mālatĩpatra svarasa* and *tila taila* internally
	The root of wild variety of *pāt'ala* or *nimba* bark or leaves grinded with milk

CONCLUSION

The consequences of Hemotoxicity include direct or indirect damage to blood cells and their precursors are predictable and potentially life-threatening. They include hypoxia, hemorrhage, infection etc. These effects may be subclinical and slowly progressive or acute and fulminant, with dramatic clinical presentations (John C. Bloom and John T. Brandt; 2008). At present a single medicine to reverse the hemotoxicity is not available in the conventional system of medicine.

An unrevealed treasure of herbal medicines for hemotoxicity are available in *Ayurveda*, especially *Maṇd'ali visha cikitsa* explained in traditional textbooks which are yet to be evaluated scientifically, though most of them are widely practising clinically. This insight creates a wide scope for research to find a best medicine for the reversal of such kind of toxicities.

REFERENCES

1. Kauhansky K, Blood: New designs for a new millennium, Blood 95: 2000, pg- 1-6
2. Kauhansky K, Lineage-specific hematopoietic growth factors, N Engl J Med 354, 2006, p-2034-2045
3. Vandendries ER, Drews RE, Drug-associated disease, Hematologic dysfunction, Crit Care Clin 22, 2006, p-347-355
4. Bloom JC, Introduction to hematotoxicology, In Sipes IG, Mc Queen CA, Gandolfi AJ (eds.), Comprehensive Toxicology Oxford, UK, Pergamon press, 1997, pp 1-10
5. Susruta, Susrutasamhita, Dalhana & Gayadasa (comm.), Trikamji J & Ram N (edi.), Chaukhamba Sanskrit Sansthan, Varanasi, Reprint, 2010, Uttarasthana 45/3, p 735.
6. Vagbhata, Ashtangahrdaya, Arunadatta & Hemadri (comm.), Kunte AM & Navre KRS (annot.), Paradakara HSS (edi.), Chaukhamba Sanskrit Sansthan, Varanasi, Reprint 2011, Sutrasthana, 8/13,14, p 150.
7. Vagbhata, Ashtangahrdaya, Arunadatta & Hemadri (comm.), Kunte AM & Navre KRS (annot.), Paradakara HSS (edi.), Chaukhamba Sanskrit Sansthan, Varanasi, Reprint 2011, Uttarasthana, 35/49, p 905.
8. Caraka, Caraka Samhita, Cakrapanidatta (comm.), Sharma R & Dash B (trans.), Chaukhambha Sanskrit Series Office , Reprint 2008, Cikitsasthana, 16/30, p 89.
9. Susruta, Susrutasamhita, Dalhana & Gayadasa (comm.), Trikamji J & Ram N (edi.), Chaukhamba Sanskrit Sansthan, Varanasi, Reprint, 2010, Uttarasthana 40/138,139, p 573.
10. Thampuran K, Prayogasamuchayam (vishavaidyam), Sulabha books, Thrissur, 1st edition 1999, chap 3, p 60,62.
11. Jyotsnika (vishavaidyam), Mahadevasasthrikal K (editor), Sree Vanchsethulakshmi Grandhavali 9; 1958:chap-6, p- 27-37
12. Handbook of Venoms and Toxins of Reptiles, edited by Mackessy SP, CRC Press USA; 2010: chap-24, p-496-498.
13. Thampuran K, Prayogasamuchayam (vishavaidyam), Sulabha books, Thrissur, 1st edition 1999, chap 3, p 64-89.
14. Kuttikrishnamenon VM, Kriyakoumudi (bhashavishavaidyam), Sahitya Pravarthaka Co-operative Society Ltd. Kottayam,1986; p 142-176.