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CERBERA ODOLLAM POISONING: HISTO-PATHOLOGICAL CHANGES IN THE CONDUCTING TISSUE OF HEART

Mohandas S¹

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ABSTRACT: Cerbera odollam is a common suicidal agent in Kerala where its incidence is next to the insecticidal group of poisons. The important toxic principle is Cerberin. It is a cardiac poison and death is due to 'Heart attack' caused by the toxic principle (s) of Cerbera odollam. Moderate to massive haemorrhage was detected on histo – pathological examination, in the conducting tissue of heart, in 80% of the cases. Haemorrhage was detected in those areas of the heart with abundant vascular supply. Haemorrhage was detected in the SA node, AV node, Bundle of His and Bundle branches. Toxic principles of Cerbera odollam have a direct toxic action on the conducting tissue of heart.

KEYWORDS: Cerbera odollam Poisoning- Cause of Death-Haemorrhage in the Conducting tissue of Heart.

INTRODUCTION: Cerbera odollam / Suicide tree / Budha tree is a poisonous shrub seen all over India. Its Botanical name is Cerbera odollam Gaertn. The kernel of its fruit contains various toxic principles; the important one is Cerberin, a cardiac glycoside almost similar to digitalis in its toxicity.

It is a common suicidal, rarely homicidal agent in Kerala, more so among the females. The incidence of poisoning is next to that of insecticidal group of poisons.^(1,2,3,4) This article is on the Histo-pathological changes in the conduction tissue of heart in Cerbera odollam poisoning.

PHARMACOLOGICAL ASPECTS: Toxins identified: Cerberin (Monoacetyl neriifolin), Cerberoside, Odollin, Odollotoxin, Thevetin, Cerapain, 17-alpha neriifolin, 17-beta neriifolin, Tanghinin, Deacetyl tanghinin. Cerbera odollam is a cardiac poison similar to digitalis in action. Cerberin is more active than Cerberoside. Kernel of one fruit is lethal.^(5,6,7,8,9,10,11,12,13) Page stated that cardiac glycosides specifically inhibit the active transport of Na⁺ out of the heart muscle cells resulting in a net cellular accumulation of Na and secondarily a net cellular loss of K.⁽¹⁴⁾

Cerbera Odollam Fruit

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Narendranathan et al gave a postulate that the glycosides lead to inhibition of membrane ATPase resulting in loss of intra cellular K and increase in extra cellular K. An increase in extra cellular K concentration causes a decrease in the ratio of diastolic depolarization so that the distance between two action potential is increased leading to brady-arrhythmias and slowing of conduction. This action is secondary to its depression on the Na pump as well as its parasympathetic action.^(7,11,15,16)

GASTRO INTESTINAL:

1. Irritation of stomach mucosa.
2. Parasympathetic.

CENTRAL NERVOUS: Depression of central synaptic transmission.

CARDIO VASCULAR:

1. Through Vagus nerve.
2. Direct depressant action on the myocardium.
3. Decreasing the slope of phase 4 of action potential by inducing hyperkalemia.
4. Changes in the conducting tissue.^(17,23,24)

CYTOTOXIC: Neriifolin and Deacetyl tanghinin have cytotoxic effect- tried in Oral epidermoid Ca, hormone responsive Breast Ca, Small cell lung Ca. Anti-oxidant. Anatomy of the conducting tissue of heart: The conducting tissue of the heart comprises of SA node, AV node, AV bundle with 2 limbs & Purkinje fibres. The conducting system consists of specialized muscle fibres which connect certain pace maker regions of the heart with cardiac muscle fibres.

SA node lies at the antero-lateral region of the junction of superior vena cava and sinus intercavarum with both right atrium and auricle near the upper end of sulcus terminalis. Its anterior margin being a few mm posterior to the crest formed by the junction of the anterior margin of right atrial appendage with superior venacava; and is often in the epicardial fat just below and to the right of the summit of right atrium. From this point, the sinus node extends posterior for 10-12 mm lying just beneath the sulcus terminalis, so that its posterior margin is at the junction of atrium with sinus intercavarum instead of superior venacava.

It is flattened ellipse or curved fusiform or horse-shoe shaped. It is 7 to 10 mm long and 1 to 5 mm wide. On cross section, SA node is triangular with a disproportionately large central artery. Rt circumflex coronary supplies SA node in 55% & AV node in 90% of hearts. Lt Circumflex coronary supplies SA node in 45% & AV node in 10% of cases. The frame work of SA node is composed of dense collagen with few elastic fibers. Within this collagen lattice, there are interlacing bundles of fibres also. There are 3 types of cells in SA node-Principal or P cells thought to be actual pace making; typical ordinary myocardium; and transitional cells.

Three preferential path ways – upper, middle and lower / anterior, posterior and middle-connect SA node with AV node. AV node is a flat white structure smaller than SA node- 6 mm long and 5 mm wide. It is located close to and immediately above the opening of coronary sinus, directly above the insertion of the septal leaflets of tricuspid valves, below the posterior leaf of aortic valve, in the

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sub-endocardium of the median valve of Rt atrium. Towards the ventricle, the substance of the node converges abruptly to a shaft of 1 cm- Bundle of His- which divides in to right and left branches.

Internally, fibers of AV node intervene to form a mesh work. Fibres are slightly thicker and shorter than those of SA node. AV bundle, 10 mm long, is formed by the convergence of fibres at the anterior and inferior margin of AV node. It is triangular in cross section, and the two lower corners give rise to Rt & Lt bundle branches. At the level of middle or distal portion of posterior aortic cusp, AV bundle gives off fine fasciculi of the main Lt bundle branch.

At the region of the commissure between the posterior and Rt aortic cusp, Rt bundle branch is given off together with remaining portion of main Lt bundle branch. Thus the penetrating portion of AV bundle is related to the posterior commissure of mitral annulus, posterior margin of the non-coronary sinus of aorta, central fibrous body and part of the inter-ventricular portion of pars membranacea; while the branching portion is related to the pars membranacea, the summit of ventricular septum and indirectly to the base of aortic valve. Rt bundle branch runs downwards along the posterior surface of the membranous septum.

Lt Bundle branch courses forward under the endocardium of Lt Ventricle for 1-3 cm and splits in to anterior and posterior radiations. The fibers of bundle branches reach the papillary muscles and ramify sub- endocardially as a plexus of Purkinje fibers / cells. Purkinje fibers ultimately lose their specific characteristics to ordinary cardiac muscle fibers.^(17,18,19,20,21,22,23,24)

MATERIALS & METHODS: 20 cases of Cerbera odollam poisoning later confirmed by chemical analysis, autopsied in the Department of Forensic Medicine, Medical College, Trivandrum were included in this study. This group comprised of 10 males and 10 females; their age ranged from 16 to 38 years. As a control, 25 cases were selected: head injury- 3; hanging- 7; Traumatic asphyxia-1; electric shock- 1; other poisoning- 9. Heart was the important organ subjected to detailed study. The heart, after plugging wet cotton in to the superior venacava to preserve shape of the sino-atrial ring, was fixed in 20% formalin for a week, SA node, AV node with bundle of His and the bundle branches were dissected and studied by a method described by Hudson R E B.

DISSECTION OF SA NODE: The position of SA node was identified. Two vertical cuts were made from the opening of superior venacava on either side of the summit to get the entire sino-atrial ring. The bit of atrial muscle containing SA node was then cut 1 cm below the summit. If the bit was too large, it was cut in to 2 pieces by another cut parallel to cuts 1 & 2.

DISSECTION OF AV NODE AND THE BUNDLE: The walls of the heart were cut on both sides until the inter-atrial and inter-ventricular septa were reached. Location of AV node was found out. Two major blocks were taken.

Cut 1: Just behind the opening of coronary sinus.

Cut 2: Perpendicular to cut 1, made 0.5 cm above the paramembranacea.

Cut 3: Perpendicular to cut 2, made just outside paramembranacea.

Cut 4: Perpendicular to cuts 1 & 3, made 1.5 to 2 cm below the coronary sinus.

Cut 5: Parallel to cut 4, made 2 cm below it.

Two blocks were thus obtained- A & B. Block A contains AV node, AV bundle and origin of bundle branches. Block B contains peripheral portions of bundle branches.^(25,26,27,28)

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PREPARATION OF SLIDES: Processing was done in an automatic tissue processor. The processed bits were embedded in paraffin. Sections of 5 microns thickness were cut serially. One section in every 10 to 40 was taken for study. They were stained with haematoxylin and eosin; and every fourth slide was stained with Van-Gieson's elastic stain (more as a guide for the identification of the tissues).

RESULTS / OBSERVATIONS: Histo-pathological changes seen in the Conducting tissue of heart:

1. **CONGESTION:** In the SA node, congestion was marked in 9 cases, moderate in 6, minimal or absent in 5. In the AV node, congestion was marked in 7, moderate in 8, minimal or absent in 5.

IN THE CONTROL GROUP: In the SA node, congestion was marked in none, moderate in 6, minimal or absent in 19. In AV node, congestion was marked in none, moderate in 3, minimal or absent in 22.

2. **HAEMORRHAGE:**

In the SA node, haemorrhage was marked in 6, moderate in 8, absent in 6.

In the AV node, haemorrhage was marked in 7, moderate in 8, absent in 5.

In the atrial musculature, haemorrhage was present in 10, absent in 10.

In the ventricular musculature, haemorrhage was present in 11, absent in 9.

In the bundle of His, haemorrhage was present in 2, absent in 18.

In the bundle branches, haemorrhage was present in 6, absent in 14.

IN THE CONTROL GROUP:

In the SA node, few red blood cells were present in 3, absent in 22.

In the AV node, few red blood cells were present in 4, absent in 21.

In the atrial musculature, haemorrhage was detected in 5, absent in 20.

In the ventricular musculature, haemorrhage was detected in 3, absent in 22.

In the peripheral portions of conducting tissue, haemorrhage was detected in none.

3. **OEDEMA:** Absent in all the cases in the conducting tissue.

4. **SIGNS OF DEGENERATION:** Absent in all the cases in the conducting tissue.

5. **SIGNS OF INFLAMMATION:**

Mono nuclear infiltration was seen in the SA node in 2.

Polymorphic infiltration was seen throughout the conducting tissue in 1.

Polymorphic infiltration was seen in the AV bundle in 2.

Polymorphic infiltration was seen in the bundle branches in 2.

Finding	SA node	AV node	AV bundle	Bundle branch	Atrial muscle	Vent: muscle
Congestion	15	15	-	-	-	-
Haemorrhage	14	15	2	6	10	11
Mononuclear infiltration	2	-	-	-	-	-
Polymorphic infiltration	1	1	3	3	1	1

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CONTROL SERIES:

Finding	SA node	AV node	AV bundle	Bundle branch	Atrial muscle	Vent: muscle
Congestion	06	03	-	-	-	-
Haemorrhage	03	04	-	-	05	03

SA node showing congestion & haemorrhage: H&E 100X

SA node showing haemorrhage: H&E 1000X

AV node showing congestion: H&E 100X

AV node showing haemorrhage: H&E 100X

AV node showing haemorrhage: H&E 1000X

SA node showing lymphocytic infiltration; H&E 100X

Atrial musculature near SA node showing haemorrhage: H&E 100X

Haemorrhage in Ventricular musculature: H&E 100X

SA node showing margination of lymphocytes: H&E 100X

SA node showing margination of lymphocytes: H&E 1000X

SA node showing lymphocytic infiltration: H&E 1000X

Bundle branch showing polymorphic infiltration: H&E 1000X

AV bundle showing lymphocytic infiltration: H&E 1000X

Bundle branch showing congestion & haemorrhage: H&E 100X

AV bundle showing congestion; H&E 100X

Myocardium showing infiltration by inflammatory cells: H&E 1000X

Central fibrous body showing polymorphic infiltration: H&E 1000X

Autonomous ganglion near AV node showing congestion

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DISCUSSION: *Cerbera odollam* is a poisonous plant present in the southern coastal parts of Kerala. The kernel of the fruit contains cardiac toxins like Cerberin, Cerberoside. It is a common suicidal agent in Kerala, its incidence is next to the insecticidal poisoning. *Cerbera odollam* constitutes $\frac{1}{4}$ th of the poisoning cases among the females and $\frac{1}{8}$ th among the males in Medical College, Trivandrum. Mortality rate is about 25%.

Narendranathan et al (1975), observed petechial haemorrhage, pulmonary oedema and generalized congestion of viscera in all the 9 autopsy cases studied by them in Medical College, Trivandrum; they attributed the findings to generalized asphyxia; they offered hyperkalemia as the sole explanation for cardiac arrhythmias. The toxins block the Ca ions channels in cardiac muscles. Kini & Pai(1965) had observed haemorrhage in the vicinity of AV node, sub-epicardial, sub-endocardial and sub-pericardial, in the only case reported by them; they correlated the haemorrhage in the vicinity of AV node with the cardiac arrhythmias.

Vijayaraghavan et al (1974) reported that Cerberin has action throughout the conducting tissue of heart as evidenced by ECG changes in the clinical cases; supported by animal experiments. The present study comprised of autopsies of 20 cases of laboratory proven poisoning with *Cerbera odollam* and 25 cases of death due to other causes as control. Cardiac arrhythmias were a significant finding. An attempt was made to study the structural changes, pertaining to the conducting system of the heart. The heart was examined macroscopically and microscopically the areas of SA node, AV node, AV bundle and bundle branches.

In the present study of 20 cases, moderate to massive haemorrhage was noted in 80% of cases in the conducting tissue of heart on histo-pathological examination. Haemorrhage was noted not only in the SA node, but also in the AV node, AV bundle and bundle branches. Any structural change in the SA node or AV node or the peripheral parts of conducting tissue is likely to cause alteration in the impulse production and conduction. Haemorrhage was detected in those areas of heart with abundant vascular supply. The haemorrhage may be due to toxic vasculitis resulting from structural damage of the endothelium.

This also explains the relatively few and small haemorrhage in the atrial and ventricular musculature where the density of vascular supply is less. The absence of structural changes in 20% of cases may be due to the trivial nature of structural changes which could not have been detected by the serial sectioning adopted. The possibility of structural changes being undetected under the light microscopy has also to be considered. Cellular infiltration with polymorphs in SA node, AV node and bundle branches noted in 3 cases with survival period of over 36 hours; this focal myocarditis could be an inflammatory response due to the direct toxic action of the poison.

CONCLUSION: From the present work, it can be reasonably deduced that the toxic principles of *Cerbera odollam* have a direct toxic action on the conducting tissue of heart. The presence of congestion and haemorrhage in the conducting tissue of heart in the test series and their absence in the control group suggests that the cardiac arrhythmias and conduction defects observed are due to such structural changes caused by the toxic principles of *Cerbera odollam*.

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AUTHORS:

1. Mohandas S.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Forensic Medicine, Sree Gokulam Medical College & Research, Foundation, Venjaramood, Trivandrum.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Mohandas S,
Sabarigiri, LVMRA,
31, Kunnukuzhy, Vanchiyoor
P. O, Thiruvananthapuram-695 035.
Email: mohandasdrs@gmail.com

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