REVIEW OF LITERATURE
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Head injuries are well known since time of evolution of man. At that time too people knew about their serious consequences.

Sushruta (1000 BC) believed that the head was the most important organ of human body for it was there that the life stayed and all the senses belonged. Later Hippocrates (460-377 BC) of Greece, who had been partly educated at school of Medicine Cnidia, where he was influenced by Indian medical thought, reaffirmed "Men ought to know that from brain only arise our pleasures, joys, laughter, jests as well as our pain, sorrow, grief and tears. That through it we think, hear, see and distinguish ugly from beautiful, the bad from good, pleasant from unpleasant. Brain makes us mad or delirious .......". Hippocrates realised that blow on one side of head occasionally is followed by convulsions or paralysis of other side of body, and he recognised the poor prognosis of patients of head injury complicated by dural lacerations. These observations made the work of Hippocrates a beacon to surgeons for over 2000 years, until the development of anaesthesia, asepsis and cerebral localization in the nineteenth century established the foundation of modern neurosurgery.
Jamieson (1976) reported that nearly all the patients sustaining head injury have persistent headaches memory difficulties and difficulties with activities of routine life, which persist for months following injury and that three months following a head injury, two thirds of the patients have still not returned to work due to sequence of brain trauma.

Rimel (1981) again documented that nearly one third of patients who had sustained minor head injuries had not returned to gainful employment after three months following head injury.

**PRIMARY BRAIN INJURY**

At the time of impact brain may experience linear or rotational acceleration or deceleration with respect to sagittal, lateral or vertical axis of the skull. This acceleration or deceleration may lead to contusion of brain, shearing of the axons, or tearing of bridging veins. These mechanisms are responsible for the damage the brain incurs in a closed head injury.

Contusions occur in regions where moving brain abruptly strikes the fixed skull or under areas of impact where skull is sufficiently bent inward to strike the underlying brain. These areas are marked by haemorrhage which frequently extends to pia, and by
swelling and necrosis of underlying tissue. If impact is severe, the pia will be lacerated and haemorrhage will spill out into the subarachnoid or subdural space. The neurological deficit that is produced coincides with region of direct brain injury e.g. contusion of motor strip will give rise to contralateral hemiparesis. And contusion is clinically silent when restricted to portions of brain not having clinically demonstrable function such as anterior temporal lobes or inferior aspect of frontal lobes, although this may become clinically significant days after initial injury as edema accumulates in areas where blood brain barrier has been destroyed.

Rotation of brain within the skull may result in tearing of axons within white matter, resulting in diffuse axonal injury. According to Ommaya and Ganesdly mild injuries damage only subcortical axons, but increases in rotational force will involve progressively deeper axons. There is little cerebral swelling and no increase in intracranial pressure with this form of injury.

A CT scan may demonstrate only small haemorrhage in corpus callosum and superolateral aspect of brain stem rest of the brain will appear normal though the patient may show severe neurological deficit.
A rise in intracranial pressure almost certainly occurs in humans after head injury. Children may show a rapid neurological deterioration. This is thought to be secondary to vasodilation with concomitant increased intracranial blood volume.

SECONDARY BRAIN DAMAGE

An evaluation of head trauma patients upon arrival in emergency showed that 35% have $P_{O_2} \leq 60$ mm H$_2$O, 15% have systolic B.P. $\leq 95$ mm Hg and 10% have a haematocrit less than 30. A head injured patient has diminution of normal protective reflexes, which may lead to obstruction of oropharynx or aspiration pneumonia. Pulmonary contusion, a flail chest or neurogenic pulmonary oedema may further compromise patients oxygenation. Hypotension is rarely a result of intracranial trauma and should alert the doctor of intra or extracorporeal haemorrhage. A positive abdominal tap is reported to occur in 17% of patients who have sustained severe head trauma.

Cerebral oedema, an enlarging haematoma or cerebrovascular engorgement may act as supratentorial mass and causes increase in intracranial pressure which produces neurological deficit by decreasing cerebral blood flow and transtentorial herniation. Enlarging
supratentorial mass is first compensated for by displacement of intracranial venous blood and CSF out of the skull. After these buffering systems are exhausted any further increase in mass will cause marked increase in intracranial pressure.

**PATIENT EVALUATION**

In head injured patients the initial examination must be recorded in such a way that it may be compared with subsequent examinations in order to detect a deterioration in patient's condition. Head is inspected for scalp lacerations, compound skull fractures or signs of a basilar skull fracture. In the conscious patient a detailed neurological examination should be performed with special attention to abnormalities in mental status, unilateral weakness, changes in muscle tone asymmetry of deep tendon reflexes, and presence of pathologic reflex responses. In the uncooperative stuporous patient or comatose, one must rely, upon evaluation of reflexes to detect focal abnormalities in nervous system. Special attention is paid to respiratory patterns, pupillary size and light response, occulocerephalic reflex, motor response to painful stimuli and deep tendon reflexes.

An assessment of mental status is particularly difficult to record in such a way that patient's
condition can be conveyed from examiner to examiner. The Glasgow Coma scale is a standardized method of measuring the severity of patients neurological status and has a high concordance rate among different observers and should be employed in evaluating all patients of cranio-cerebral injury. The 15 point scale assesses patients neurologic responsiveness in three categories eye opening, verbal response and best motor response.

Many comatose patients after accident have sustained other major injuries. The surgeon must be aware of the presence of these injuries and their possible effect over brain injury.

Mild cranio-cerebral injuries are associated with transient vision disturbance, transient period of confusion, and a loss of memory for the moment of impact. With progressively greater degrees of brain injuries patient remains confused for proportionately longer periods of time and demonstrates a longer period of memory loss. Antegrade memory loss is loss of memory following the accident and may be the only type of memory loss in mild head injury patients. With more severe injuries the patient may demonstrate retrograde memory loss i.e. the loss of memory for events that precede the accident. With increasing degree of brain injury patient experiences the period of loss of consciousness proportional to the magnitude of injury.
The search for neurotropic drugs to reduce neurological deficits and other sequelae of craniocerebral injury still continues, and in 1952 chlorpromazine was discovered, and was the first of many drugs introduced for the management of psychiatric disorders. But it was harmful rather than useful for convalescence from craniocerebral injuries because of a number of its adverse side effects. Soon other chemicals such as magnesium pemoline, methyl phenidate and PYRITINOL were discovered. Out of them only pyritinol is being increasingly used and put to research continuously. Discovered in 1957 by E Merck of Darmstadt, F.R. Germany, Since then it is in use in various neurological disorders such as senile dementia, memory disturbances, cerebrovascular accidents organic brain syndromes and in neurosurgical disorders as sequelae of craniocerebral injuries.

Darge et al (1969) subjected pyritinol in detailed investigations and drew following conclusions:

1. Pyritinol is non toxic and side effects are rare in man.

2. Minimal lethal dose was large and varied between 800-950 mg/kg in different species of animals (mouse, rat, rabbit, cat and dog), when given orally in acute toxicity studies.
3. No clinical, laboratory, histological or pathological changes were observed during the chronic studies that were performed in rats when given 100 mg/kg orally for six months.

4. Teratological abnormality in foetal development didn’t occur after pyritinol administration to rabbits in repeated oral dosage of 1000 mg/kg and in beagle dogs given 50 mg/kg daily during the entire period of pregnancy.

5. Pyritinol hydrochloride (Pyrithioxine) was absorbed very quickly when administered orally and for the most part from stomach. These studies were performed using radioactively labelled pyritinol hydrochloride using $^{35}$S. Maximum blood level was reached not later than 40 minutes after medication and 85% of administered dose was excreted in 12 hours. After 48 hours 94% of drug had been excreted. It may be concluded that pyritinol is completely excreted and there is no retention of active substance in body.

Ochs (1965) said that brain is almost as dependent on the glucose supplied to it as it is on the oxygen. Energy production in the brain is proved to occur by chain of usual glucose metabolism viz. glycolysis,
Kreb's cycle, electron transport system, amino acid metabolism and G.A.B.A. shunt pathway.

Quadbeck et al (1962) performed controlled trials on rats with $^{14}$C labelled glucose uptake with prior administration of pyritinol. It revealed a demonstrable increase in uptake of labelled glucose into brain even after a single dose of drug. The provision of 0.2% pyritinol in feed for 10 days enhanced the glucose uptake even more. It is noteworthy that increase in glucose was more marked in cerebrum than in cerebellum and brainstem. But the findings in all three areas were statistically significant. Moreover it was found that the greater increase in $^{14}$C labelled activity was located in lipid fraction of brain but it was also observed in other structural sections of brain tissue implying its incorporation into various metabolic processes.

A disturbance of cerebral glucose metabolism has been reported to exist in a majority of patients having neurological disorders, Hoyer et al (1973) investigated such human subjects using modern scientific methods for the estimation of various parameters of oxidative cerebral metabolism such as the neuronal consumption of glucose and oxygen and the output of lactate and $\text{CO}_2$ both before and after the administration of pyritinol. They
conclusively proved that pyritinol elevated glucose uptake to normal values and lowered the lactate content without any change in cerebral blood flow (CBF) or oxygen consumption.

The turnover of nucleic acid and protein synthesis rise with increasing neuronal activity. RNA molecules play an important part in storage of information and its fixation on a macromolecular substrate. Kanig (1974) studied the incorporation of radioactive phosphorus into the different RNA fractions of neurons in untreated controls and under the influence of pentobarbitone and pyritinol. He observed that rate of incorporation of labelled phosphorus into messenger RNA was increased to statistically significant extent after the administration of pyritinol. It was therefore clear that pyritinol enhanced protein synthesis and facilitated various neuronal functions such as "chemical engramming" of memory.

G.A.B.A. is an important neurotransmitter which is present in brain. It is also known to possess inhibiting properties in term of neuronal dysfunction. Mori (1970) investigated the effect of pyritinol on the uptake of $^{14}$C labelled G.A.B.A. in mice under carefully controlled experimental conditions. Uptake of GABA was shown to be augmented to statistically significant extent after pyritinol administration.
Stoica et al (1973) working in U.S.A. injected pyritinol (8 mg/kg and 2 mg/kg) intra-arterially into baboons (Papio anubis) via vertebral and carotid arteries under controlled conditions. They demonstrated that pyritinol, when injected into vertebral arteries stimulated certain vasodilator mechanisms that exist in the brainstem resulting in a 44% increase in cerebral blood flow (CBF) and a 26% increase in cerebral oxygen consumption, whereas intracarotid administration resulted in an increase in CBF of only 11% Stoica's findings are qualitatively and quantitatively similar to the changes obtained by electrical stimulation of brainstem by Meyer and associates (1971). These workers reported that the electrical stimulation of brainstem structures produced an increase in CBF of 41% and an increase of 25% in oxygen consumption.

Awareness in its wider sense depends upon integrity of brain. Werner and his colleagues (1976) conducted autoradiographic studies on distribution of $^3$H labelled Pyritinol in monkeys and mice. The experiments consistently showed, a much heavier radioactive labelling in cerebral cortex, hippocampus the brainstem nuclei and cerebellum then in white matter of corpus callosum, the internal and external capsules. Consciousness is a complex function of central nervous system and is measurable in E.E.G.. Certain E.E.G. patterns are
characteristic of various cerebral functional states. Increase in alertness is one effect of pyritinol which, apart from being experienced subjectively can also be recorded objectively in form of EEG. There is typical increase in frequency of cortical activity and reduction in amplitude (Desynchronization), which indicates that pyritinol facilitates arousal phenomenon in the cerebral cortex. Dolce (1970) having investigated the electrophysiological effects of pyritinol in cats, observed that it produced certain indisputable actions directly on cortical neurons, limbic system and mesencephalic reticular activating system.

The reticular activating system is of decisive importance in maintaining alertness. Consciousness is possible only if the cerebral cortex is continuously stimulated by impulses from reticular formation. This effect of reticular formation over cortex is known as Arousal and is reflected in a typical increase in frequency and reduction in amplitude of activity in EEG. The increase in alertness after pyritinol administration is seen as a distinct improvement of arousal tracings (Sierra et al, 1963).

An increase in the spontaneous electrical activity of limbic system induced by pyritinol has been observed in animals trials conducted by various
researchers such as Offenloch and Vossius (1970) who observed in cats that the spontaneous activity of neurons in the limbic system (Nucleus amygdalae) increased after infusion of PYRITINOL.

Deusinger et al (1972) showed that pyritinol improved short as well as long term memory. A four weeks double blind trial was carried out in 80 volunteers who were daily given 300 mg of pyritinol orally or a placebo. All of them underwent 7 memory tests before as well as 2 and 4 weeks after beginning of medication. Results provided statistically significant improvement in performance confirming that pyritinol improved short term memory and immediate retention. A particularly interesting finding was marked improvement in performance between the second and fourth weeks which demonstrates the beneficial effects of prolonged medication with pyritinol.

Martin (1985) reported that pyritinol increases the release of acetylcholine in cerebral tissues at the synaptic level and thus improves cholinergic transmission and thus rehabilitation of cerebral function.

Learning process can be tested experimentally by conditioning animals to perform certain reflex actions. This makes it possible, for example, to measure by how much the learning time is shortened by a pharmacological
compound in question. The effect of pyritinol was tested by the following method: Rats were placed in a cage divided into two halves. Five seconds after an acoustic signal, an electric shock was applied to the half of the cage in which the rats were sitting. The test sequence was repeated at intervals of 30-50 seconds. The times required by two groups of rats (one treated with pyritinol and one control group) to develop flight reflexes to the shock free half of cage were measured. In pyritinol group more rats developed a flight conditioned reflex to unpleasant stimuli more quickly than in control group (Ogawa, 1968 and Kawasaki et al, 1968).

Rossignol et al (1972) investigated the action of pyritinol, Hydergine (Codergocrine) and Vincamine in experimentally produced acute cerebral ischaemia. These workers found that pyritinol markedly accelerated the return of evoked cortical activity and distinctly counteracted the post anoxic increase in amplitude of thalamic evoked potentials induced by ischaemia. Similar effects but of lesser degree were observed with hydergine and Vincamine. These workers also reported that recovery after experimentally induced cerebral ischaemia was accelerated because of a protective effect of pyritinol against cerebral ischaemia.

Herrschaft (1975-78) studied the effectiveness of some 24 vasoactive drugs on cerebral blood flow (CBF)
of over 500 patients and found that the vast majority of
drugs either reduced the blood flow or had no effect over
it. Piracetam (1978a) and pyritinol (1978b) increased
CBF of total cerebral grey matter as well as of the
ischaemic grey matter. But in order to achieve this
efficacy, piracetam had to be administered in a large
dose of 6-10 gm intravenously as opposed to Pyritinol
which was infused in a dose of 400 mg.

Kiesewetter (1984) also concluded that Drug
demonstrably increased erythrocyte flexibility and blood
flow. Thus microcirculation in brain is normalized and
oxygen and glucose supplies are increased.

Lesney and Co-workers (1974) who were particu-
larly active in study of clumsy children, reported their
experience that hypotonia and other neurological and
psychological findings in children aged 3 months to 14
years, improved after administration of encephalotropic
drug i.e. pyritinol.

Declerck (1969) was one of the first to report
on the use of pyritinol in successful treatment of
patients with cerebral trauma. He treated 123 patients
suffering from various sequele following cerebral trauma
due to head injuries, with pyritinol in doses varying
between 300-600 mg daily and over periods ranging from
5 to 12 weeks. He reported that symptoms such as headache, impairment of memory and concentration, mental irritability, vertigo and other such disorders were completely relieved in 85% of patients, and that 90% were able to resume gainful employment. In the control group, however, who were not treated with pyritinol, only 40% of the patients improved satisfactorily.

Gerstenbrand and his co-workers (1969) from Austria examined in detail 92 individuals who had suffered from severe head injuries. These were treated with pyritinol in daily doses ranging between 400-800 mg for periods of 2-4 weeks without any side effects being observed. As various neurological syndromes were not comparable, these workers subjected 30 patients to detailed study in three groups of 10 patients each, who were submitted to a battery of psychological tests. About one third patients in each group suffered from traumatic Apallic syndrome. The ages of all patients from group were comparable.

First group consisted of patients who had suffered from a recent brain injury and were in process of recovery.

Second group consisted of patients in whom the sequele of head injury had become stabilized. The third
group contained individuals whose symptomatology had also stabilized. The last group served as a control for the patients in the first two groups, who received PYRITINOL (500 mg) daily via oral route for four weeks. At the conclusion of study it was observed that with pyritinol there was a definite improvement in memory, concentration, visual learning ability, performance and fine motor functions. It was also reported that the drug was also effective in treating patients with frontal akinesia.

Soo Young Oh (1975) working in Switzerland, reported on 42 patients of coma who had suffered head injuries immediately prior to admission to hospital. Encephabol (PYRITINOL) was administered in doses up to 2000 mg per day. In view of nature of cerebral injury, and the condition of patients, only Encephabol was administered intravenously with I/V fluid until consciousness was regained. In the opinion of author the infusion of Encephabol produced a more rapid recovery of consciousness and reduced the time of regression of various neurological symptoms i.e. sequele of head injury.

Wild and Dolce (1976) reviewed progress in the intensive treatment of patients with severe brain damage leading to the apallic syndrome (prolonged unconsciousness akinetic mutism, coma, vigile, coma prolonge). They, studied in particular, 5 adult patients for a period of
8 weeks, commencing some 6-11 weeks after the occurrence of head injury. During this total period, these subjects received Encephabol 600 mg daily, apart from other intravenous infusions and had their EEGs recorded at regular intervals. During the later recordings, Encephabol 600 mg daily was infused intravenously. Wild and Dolce concluded intensive therapy permitted recovery which was dependent on the duration of the apallic syndrome. These workers observed that oral administration of Encephabol over a long period accelerated clinical recovery in the group of patients studied.

Bystricky et al (1977) observed the effect of Encephabol after parenteral administration in 40 patients. With cerebral trauma and compared than with a control group of 40 patients. The EEG, neurological and psychological findings together with all the biochemical investigations were regularly performed in all subjects. Initially the allocation of patients to the two groups was done at random. But during latter part of study, the more severe individuals were treated with pyritinol. Initially while the patients were unconscious Encephabol was administered intravenously in doses of 600 mg daily but on recovery of consciousness the dosage decreased to 300 mg daily orally. This was continued on an average for 26 days.
According to the authors, their observations permitted the following conclusions:

1. Encephabol significantly improved the quantitative disturbance of consciousness caused by contusion.
2. It has an accelerating effect on regression of neurological symptoms.
3. Drug had a significant effect with respect to the normalization of pathological EEG findings.
4. It has a favourable effect on the restoration of intellectual function as well as on the subjective psychic condition.
5. Preparation didn't produce any untoward side effects.

Kitamura et al (1980) reported on an intensive double blind controlled multicentre study undertaken in 270 patients who had suffered from head injuries resulting in cerebral trauma. These subjects were administered, over a period of six weeks, either Encephabol (Brand of pyritinol) 600 mg daily or a placebo of identical appearance from their findings, the authors concluded that Encephabol was significantly effective in treatment of patients recovering from sequele of cerebral trauma.