Comparison of efficacy and safety of intranasal Midazolam with syrup Chloral hydrate for procedural sedation of children undergoing Auditory Brainstem evoked Response audiometry – a randomized, double-blinded, placebo controlled trial

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF M.S. BRANCH – IV (OTORHINOLARYNGOLOGY) EXAMINATION OF THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY TO BE HELD IN APRIL 2014

CERTIFICATE

This is to certify that the dissertation entitled, '**Comparison of efficacy and safety of intranasal Midazolam with syrup Chloral hydrate for procedural sedation of children undergoing Auditory Brainstem evoked Response audiometry – a randomized, double-blinded, placebo controlled trial**' is a bonafide original work of **Dr. Marie Christy Sharafine S.** submitted in partial fulfilment of the rules and regulations for the MS Branch IV, Oto-rhino-laryngology examination of The Tamil Nadu Dr. M.G.R. Medical University to be held in April 2014.

Dr. John Mathew,

Professor and Head,

Department of ENT,

Christian Medical College,

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Introduction:
Hearing loss compounded by speech delay is one of the frequent and regular problems faced in the present day pediatric otorhinolaryngology clinics. The prevalence of hearing loss globally accounts for nearly 9% of the children according to recent estimates by the WHO and this represents a serious handicap to the society and the nation (1). According to Indian statistics, it is found that the incidence of hearing impairment is 8 per 1000. Children under 10 years of age account for nearly 5.4% of disabling deafness. The prevalence among urban children accounts for 1.2 % when compared to the rural side, 5.4% (2). Thus it is considered the most prevalent impairment worldwide.
Hearing impairment is the principal cause of disease burden in children and it proves to be a serious obstacle to their optimal growth and development. Besides being an impediment to their education, language skills and speech acquisition, these children gradually become disabled in multiple spheres of development including social, emotional, cognitive and personality traits, if
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Acknowledgement

The walk through the journey of thesis since its inception has been a great pleasure filled with mixed feelings. One may forget the time spent in acquiring the degree but not the effort put into bringing out this meticulous piece of compilation. And this could not have been possible without the caring effort of multitude of people involved in it.

It is my great privilege to express my heart-felt thanks to this esteemed institution for having given me an opportunity to work under the shadows and guidance of renowned people.

Foremost, I would like to express my sincere and deepest gratitude to my guide and Professor Dr. John Mathew for being a persistent inspiration and providing a continuous support besides the amiable guidance, the valuable comments, the insightful thoughts and the precious time amidst his busy schedule.

I would also like to thank Professor Dr. Ajoy Mathew Varghese, for his constant motivation, creative constructs, critical insights, extensive discussions, patient listening and for being an accelerating energy behind this work. Though lost in the wilderness of thesis, many a time, the destination could not have been reached without the needed light powered by sir.

I am extremely thankful to Professor Dr. Mary Kurien for her encouragement and support, Dr. George Mathew for his help and inciting the thought to begin this journey, Professor Dr. Manickam for his support and help, Dr. Syed Kamran Asif for his assistance in analysis.

I thank Ms. Grace Rebeccah, Biostatistics in helping me uncode the complex and perplexing information gathered along the journey thus gearing my way towards the reach.

I would also like to thank Dr. Annadurai from Pharmacy and Samarth Pharma, Mumbai who helped me with the placebos needed to carry out this double-blinded study.

I thank Dr. Achamma Balraj for her help and permitting me carry out my work in the audiology lab and Ms. Revathy for helping me during the study despite tight schedules.

I sincerely thank all the patients who participated in this study without whom this leap could not have been accomplished.

I specially remember and thank all my friends and faculty who lent me a supporting and a helping hand in compiling this work.

The entire journey has been a memorable one and could not have proceeded smoothly without the mental stability and peace ensured by my family when faced with turbulent waves many a time. I thank my mom, my brother, Britto and my husband, Raj for being a constant ray of hope and support and motivate me finish this work in the most needed times.

Last but not the least, I dedicate this work to my father and my almighty God without whom the biggest gifts of my life may not have become possible and this accomplishment is truly a fruit of His divine mercy.

CONTENTS

Introduction

Hearing loss compounded by speech delay is one of the frequent and regular problems faced in the present day paediatric otorhinolaryngology clinics. The prevalence of hearing loss globally accounts for nearly 9% of the children according to recent estimates by the WHO and this represents a serious handicap to the society and the nation.(1) According to Indian statistics, it is found that the incidence of hearing impairment is 8 per 1000. Children under 10 years of age account for nearly 5.4% of disabling deafness. The prevalence among urban children accounts for 1.2 % when compared to the rural side, 5.4%.(2) Thus it is considered the most prevalent impairment worldwide.

Hearing impairment is the principal cause of disease burden in children and it proves to be a serious obstacle to their optimal growth and development. Besides being an impediment to their education, language skills and speech acquisition, these children gradually become disabled in multiple spheres of development including social, emotional, cognitive and personality traits, if left undiagnosed and untreated. This promising age group of the community who reflect a country's economic growth and development are thus handicapped from being responsible citizens and need special attention.

Hearing development in children is seen to be a continuous process. Auditory system is fairly complete and functional at birth though the neural connections and the myelinations undergo refinement throughout childhood and adolescence, sometimes till 15 to 20 years of age. This plays a role in not just auditory perception, but in auditory speech perception. It is clear that

experience in the form of communicative interactions contribute significantly to speech and language development which becomes a functional need for the developing child.(3)

The concept of auditory linked language acquisition becomes unique in humans. Neuropsychological studies claim that the brain which is developing is 'plastic'. This implies that the developing neural system is capable of adapting and reorganizing to various insults which the mature brain cannot. The detrimental consequence is that it has only a transient capacity to plastic reorganization which can be recruited in the wake of injury. The central role of neural plasticity thus reflects the need to pick up any hearing or speech delay at the earliest as the capacity for reorganization and shaping becomes limited in the postnatal period. The age at which hearing loss is picked up is also important as earlier diagnosis amounts to the best possible rehabilitation.

While there is a wide range of tests which add to the diagnostic armamentarium, some of these tests warrant patient sedation for effective test recordings. Auditory Brainstem Evoked Response Audiometry (ABR) is one such diagnostic test to assess the brainstem responses to auditory stimuli thereby reflecting the integrity of the auditory pathway and its central connections. It has emerged out as being the standard test for hearing assessment in children undoubtedly. As it records the brainstem responses to simple auditory stimuli, it is important that the child remains immobile during the procedure to avoid any movement artefacts or false recordings. As children are poor candidates for the same, the need for paediatric procedural sedation becomes mandatory.

Paediatric procedural sedation in the recent times, in the correct setting and in the hands of the adequately trained personnel has emerged as an elegant tool in the rescue of many

difficult diagnostic tests done as office-procedures. Many medications have been tried out for the same including a vast group of Opioids, Barbiturates, induction sedative - hypnotics and chloral hydrate.

The various drugs used in the paediatric procedural sedation are not without their own merits and drawbacks. The onset and nature of sedation, the safety profile of these medications are a cause for concern. Besides, the failed efficacy of these medications in the 'difficult-to-sedate' children like the developmental delayed ones, the hyper-active group lead to further concern. Chloral hydrate is one of the earliest known sedative. In view of its sedative and hypnotic potential, it remained attractive for many years for paediatric procedural sedation although its use came to a standstill in the mid 1990's due to its narrow margin of safety. Later various other sedatives were researched into. In the recent times, the Benzodiazepines have attained popularity for procedural sedation in view of their rapid onset of action and shorter recovery rates besides a wide range of margin of safety. Midazolam is one of the benzodiazepines with enticing pharmacokinetics and safety profile besides multiple routes of administration. The nasal mode of administration in the form of spray has its own advantages and shows patient friendly profiles. The clinical application of intranasal Midazolam has been studied in various medical fields.

In our setting, it was found that nearly 20 % of the children who get referred for ABR are cancelled due to un co-operative behaviour or failed sedation with current protocol which entails syrup Triclofos (chloral hydrate) for paediatric sedation. Midazolam nasal spray has been used in a number of fields for paediatric sedation and as there was a need for an alternative drug in our setting, a pilot study was undertaken using intranasal Midazolam on

children undergoing ABR after parental consent and following favourable outcomes, the study protocol was designed

In this study, we propose to study the efficacy and safety profile of Midazolam nasal spray for paediatric procedural sedation for Auditory Brainstem evoked Response audiometry and compare it with the standard drug used for ABR, syrup Chloral hydrate.

Aim & Objectives

Aim

The aim of the study was to evaluate the efficacy and safety of intranasal Midazolam compared to syrup Chloral hydrate for procedural sedation in children undergoing Auditory Brainstem Response Audiometry (ABR).

Objectives:

The primary objective of the study was to evaluate

1. Safety, in terms of

   - Heart rate
   - Respiratory rate
   - Oxygen saturation

2. Efficacy, in terms of

   - Level of consciousness (sleep and movement)
   - Successful completion of the procedure

The secondary objectives are to measure

- Time for parental separation
- Nature of parental separation
- Time taken for onset of sedation
- Duration of procedure
- Time taken for recovery
- Post recovery behaviour
- Acceptance by parents
- Audiologists satisfaction
- Number of attempts

Review of literature

1. **Anatomy of hearing**:

Hearing is one of the four special senses humans are gifted with besides vision, olfaction and taste. Studies say, we humans hear the way we do because of at least three major forces.(4) The first is phylogeny, the evolutionary changes in the auditory system since its beginnings. The middle ear of mammals is unique, in that, it is simply not an 'improved' single-ossicle middle ear.(5) Another is embryology, the development of the system in each individual before birth.(6) Finally, there is the biologically determined auditory mechanism we are born with and our interaction with the environment in early postnatal life.(7) An insult in any of the stages of development significantly impairs the functional outcome. The complex network of hearing with diverse mechanisms thus begins very early in life.

The perception of hearing requires a complex series of structures and can be viewed briefly as those comprising peripheral auditory structures and central auditory connections. External ear, middle ear and the inner ear comprises the peripheral hearing structures that collect the sound, transforms, transduces and converts it into electrical stimuli that can be interpreted by the human brain. (Fig. 1)

Organization of the auditory system is based on the meticulous process of segregation of complex sounds into various bands of frequencies which starts at the point of the auditory sensory epithelium. Various specific frequencies get distributed along the cochlear tonotopic axis. This spatial layout of cochlear frequencies along the basilar membrane is repeated in other auditory areas of the brain. Tonotopy is a fundamental principle of organization of the

auditory system which arises from the cochlear mechanics and is evident as a linear arrangement of neurons in accordance with the characteristic or best frequency, i.e., that acoustic frequency to which a neuron is most sensitive.(8)

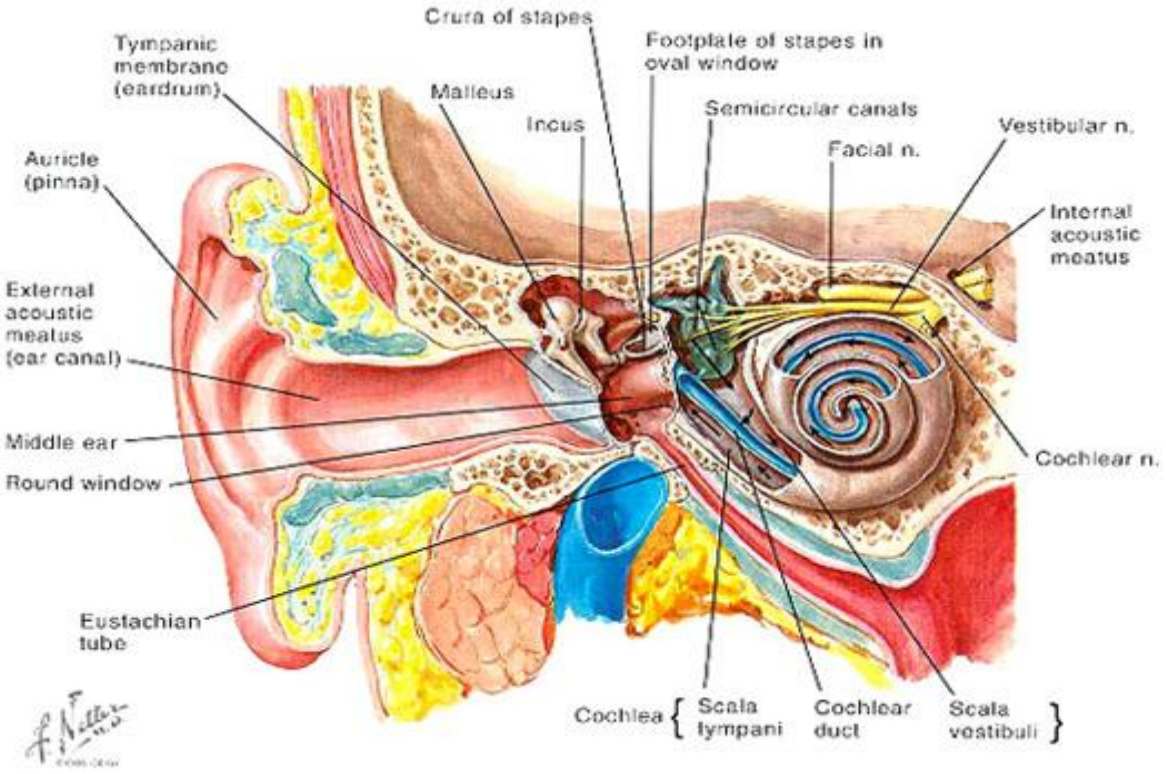


Fig.1 Anatomy of the external, middle, and inner ear (Reprinted from Netter Anatomy Illustration collection, Elsevier Inc. All Rights Reserved).

During development, physiological and structural specializations that are related to the tonotopic axis steadily evolve and expand over a prolonged time period. During early stages of auditory development, some aspects of tonotopy become evident, but mature frequency separation is characteristically not attained till hearing takes its onset.(9)

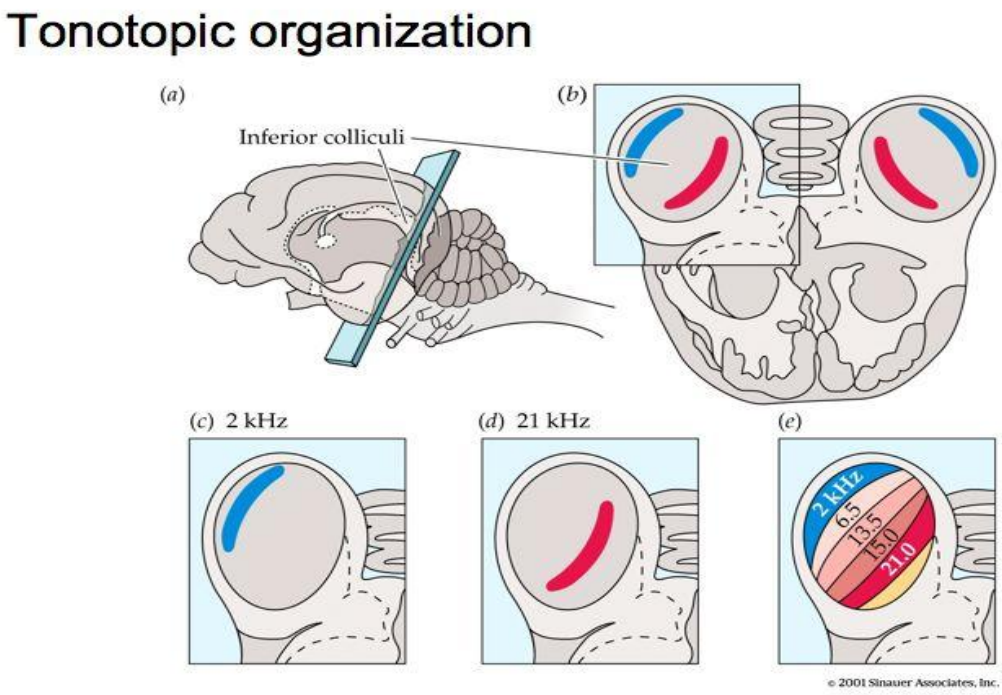


Fig.2: Auditory pathways and sound localization.

The complexity of human auditory system is characterized by a remarkably specific spectral and temporal neural code inside the auditory brain stem which is an assembly of nuclei encircling the afferent and efferent auditory neural pathways. The central auditory connections are viewed as follows: (Fig. 3)

In humans, the eighth cranial nerve, i.e., the vestibulocochlear nerve is seen to originate from 4 separate nerve branches which are the saccular nerve, the superior vestibular nerve, the posterior ampullary nerve and the cochlear nerve. The cochlear nerve is formed within the spiral ganglion by the bipolar neurons whose central processes join the vestibular nerve inside the internal auditory meatus or porus acousticus. The cochlear nerve fibres take a spiral track and show a cochleotopic organization.(10) That is, the fibres which originate

from the basal cochlear turn are located external to the deeper fibres that originate from the apical cochlear turn.

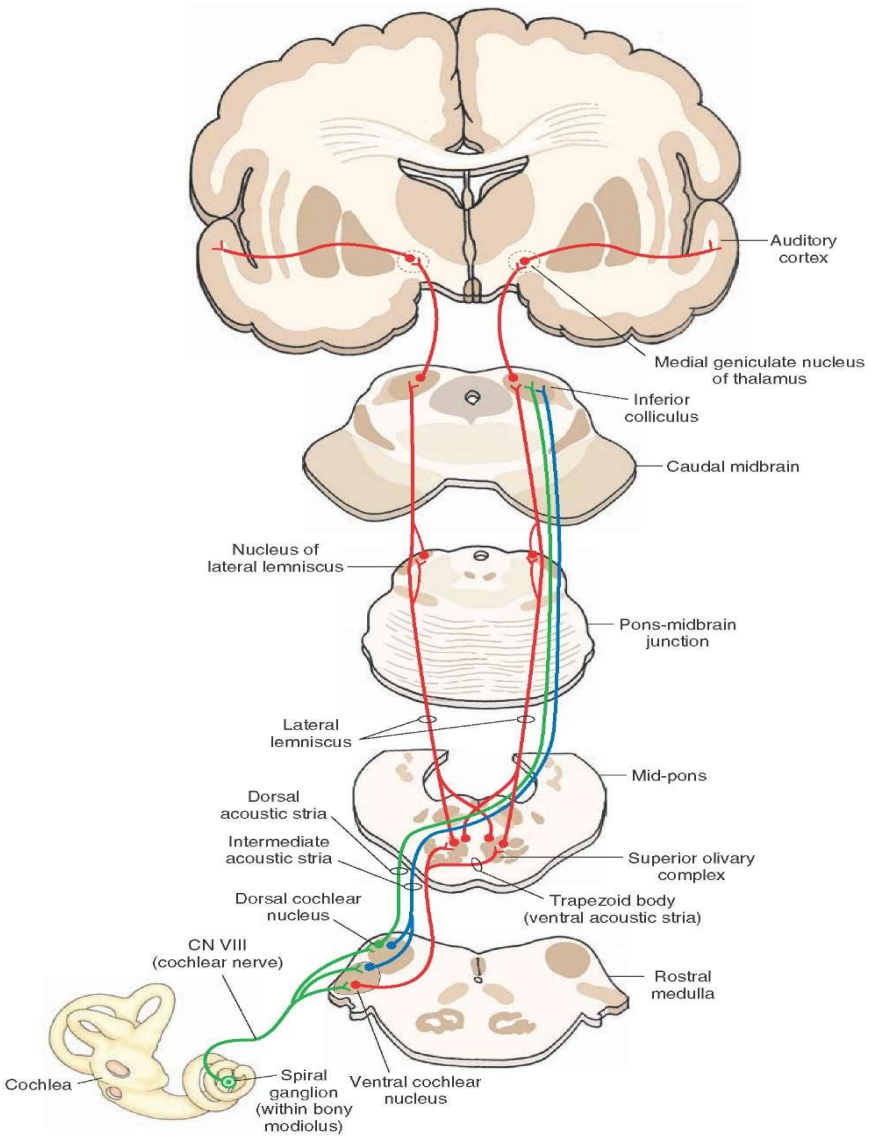


Fig.3: Auditory pathways and sound localization.

The cochlear nerve and the vestibular nerve as they travel from the most peripheral end of the internal acoustic canal to the cerebello-pontine angle show a variable relationship. The two nerves take a 90 degrees rotation from the inner ear to the brainstem. The cochlear nerve is

antero-inferior inside the internal acoustic canal and enters the brainstem postero-lateral to the vestibular nerve. The eighth cranial nerve divides into two separate branches and at the ponto-medullary junction, it enters the brainstem. It is at the level of the rostral medulla, both branches enter the brainstem and are separated by cerebellar peduncle. The cochlear nerve fibres pass over the restiform body and enter from the ventromedial surface to reach the anteroventral cochlear nucleus. The vestibular fibres pass beneath the restiform body where they pierce the trapezoid body and advance dorsally into the brainstem.

1.1 **Cochlear nuclei:**

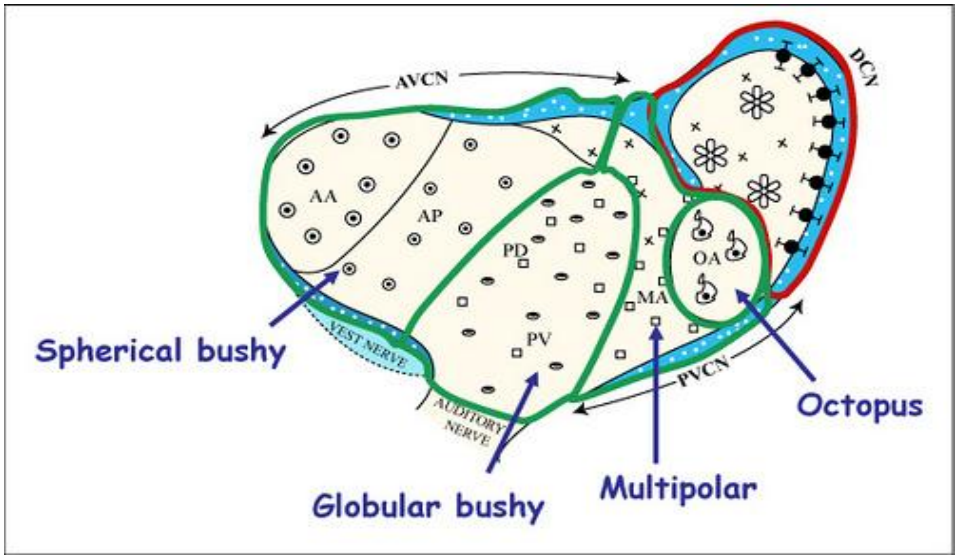


Fig.4: Cochlear nuclei.

The cochlear nuclei correspond to the foremost and obligatory relay station for all the afferent auditory nerve fibres. It is seen on either side at the ponto-medullary junction, lateral to the point where the eighth cranial nerve enters. This nuclei is divided into 2 major subdivisions which are the ventral (VCN) cochlear nuclei & dorsal (DCN) cochlear nuclei.

The VCN is further structurally sub classified into anteroventral (AVCN) and posteroventral (PVCN) cochlear nuclei. The AVCN again has 2 subdivisions: the anterior and the posterior divisions. Each of the subdivisions comprises of a distinct collection of cell types which are greatly diverse between species and obtain a comprehensive topographic representation of the auditory nerve. Based on the cell morphology, five neuronal classes are identified, which are - the bushy cells (spheric and globular), the multipolar, the pyramidal, the octopus and the granule cells. The AVCN consists of the spheric bushy cells in the anterior division and the globular bushy cells in the posterior division. The central region of the ventral cochlear nuclei is represented by the multipolar cells (stellate neurons). Octopus cells characterize the PVCN where the cells are oriented orthogonally to the incoming cochlear nerve fibres. These neurons are known to respond to repetitive acoustic stimuli. Pyramidal and granule cells compromise the DCN.

The nerve fibres distributed throughout the cochlear nuclei show a distinct and a standard cochleotopic order. Every subdivision of the cochlear nuclei displays a fairly complete and comprehensive neural depiction of the entire frequency range of the cochlea. The axonal nerve fibres from the cochlear base project most dorsally, while those from the apex project ventrally in each one of the subdivisions.

The axons of the 2^{nd} order neurons arising from the DCN (caudal medulla) shape into three principal bundles. They are the ventral acoustic stria (trapezoid body or VAS), the intermediate acoustic stria (IAS or stria of Helde) and the dorsal acoustic stria (DAS or stria of Monackow). The VAS begins from the spheric and globular bushy cells of the VCN and tracks medially and cranially across the medulla and reaches the LSO, the MSO, the MNTB

& the inferior colliculus. The IAS takes its origin primarily from the octopus cells comprising the PVCN and projects ipsilaterally, bilaterally, or contralaterally onto the trapezoid body into the ventral nucleus, besides projecting onto the lateral superior olive and the periolivary region. This forms the olivocochlear bundle. The DAS is primarily a crossed pathway through which the cells in the DCN project to the nuclei of the lateral lemniscus besides the central nucleus of the inferior colliculus.

1.2 **Superior olivary complex:**

The superior olivary complex is situated in the caudal pons directly and dorsal to the pontine gray. The large nuclear complex encompasses the lateral nucleus of the superior olive (LSO), the medial nucleus of the superior olive (MSO), the medial nucleus of Trapezoid body (MNTB) and the periolivary nuclei (PON). The MSO is characterized by bipolar neurons while the LSO by multipolar neurons. The MSO is innervated both ipsilateral and contralateral from the ventral cochlear nuclei through the VAS. The LSO receives ipsilateral inputs from the AVCN and PVCN via the trapezoid body. There is a topographic organization seen such that the dorsal and ventral PVCN project onto the extreme lateral limb and medial limb of the LSO. The tonotopic organization of the afferent cochlear nerve input to the LSO is maintained such that the axonal nerve fibres from the high-frequency regions terminate in the medial end while the lower-frequency area in the lateral limb. The contra lateral inputs arise from the caudal AVCN and rostral PVCN through the MNTB.

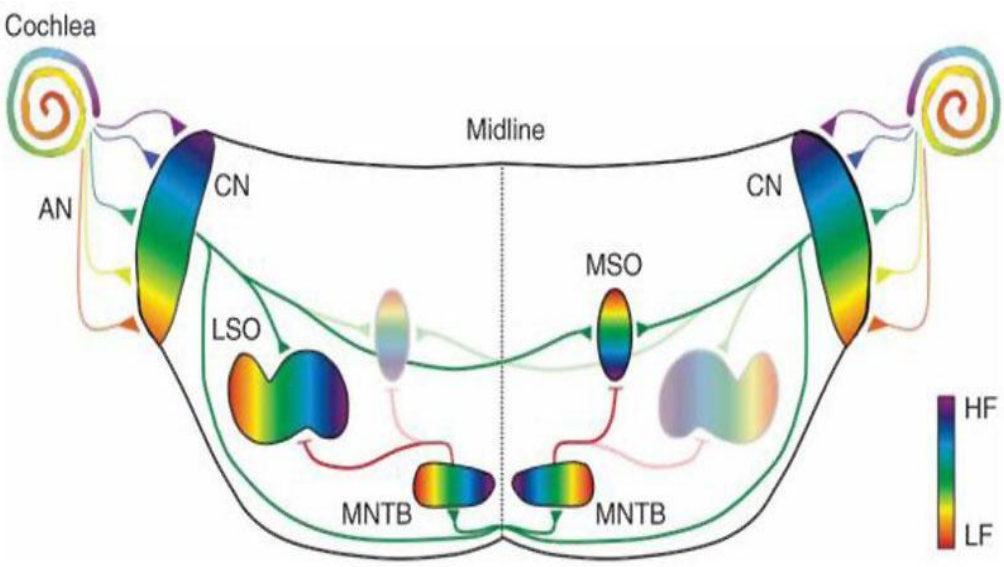


Fig.5: Superior Olivary complex.

The MNTB takes its projections from both the ipsilateral PVCN and the contra lateral AVCN via specific calyx-type endings which surrounds the MNTB cell body partially. The PONs receives afferent input from the CN.

The tonotopic organization is thus maintained in the superior olivary nuclei bilaterally and receives bilateral auditory inputs from the cochlear nuclei with lower-frequency of neurons in the MSO and high-frequency neurons in the LSO. Neurons from this nuclear complex are responsible for sound localization in acoustic space and are the first to receive binaural inputs in the entire auditory pathway. The distinct patterns of binaural convergence on MSO and LSO may play a key function in the inter-aural intensity and temporal disparities which underlie mechanisms for binaural spatial hearing.

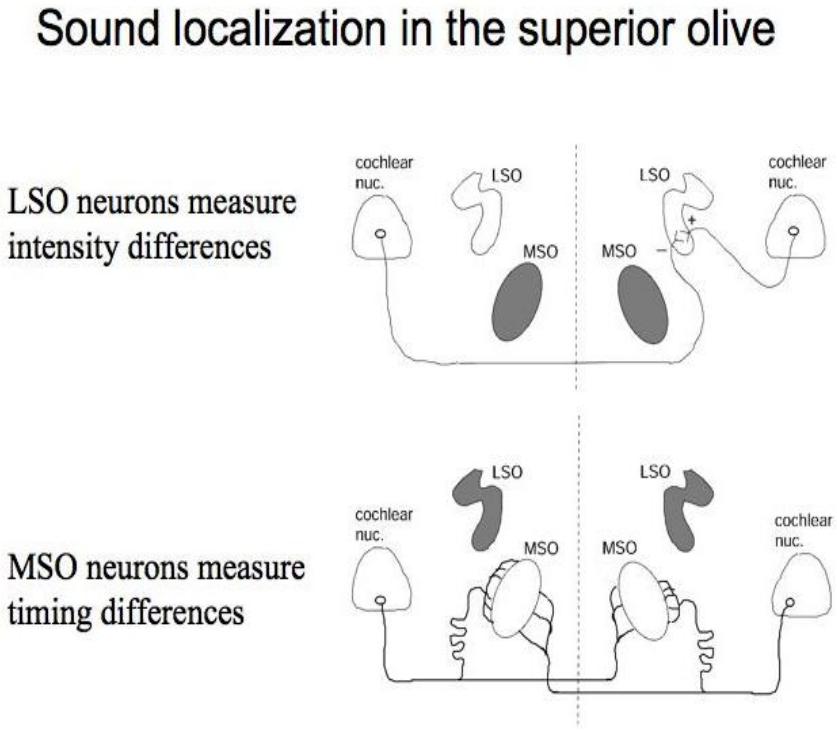


Fig. 6: Sound Localization in the Superior olive.

The fibres which ascend the superior olivary complex (SOC) reach the nuclei of the lateral lemniscus and the inferior colliculus through the lateral lemniscus. It also sends fibres which descend to the hair cells in the organ of Corti through the olivo-cochlear bundle (OCN), divided into medial and lateral parts, initially described by Rasmussen. The ipsilateral & contra lateral systems traverse peripherally such that the inferior division of the vestibular nerve joins the cochlear nerve at the vestibulo-cochlear anastomosis of Oort within the fundus of the internal acoustic meatus. These descending connections particularly the crossed fibres adjust cochlear sensitivity to the sound, probably by mediating the contractile properties of the outer hair cells.

1.3 **Lateral Lemniscus**:

The lateral lemniscus forms the chief ascending pathway and is situated cranially in the vicinity of the lateral surface of the brainstem, connecting the cochlear nucleus and superior olivary nucleus with the inferior colliculus. The nuclei of lateral lemniscus show a tonotopic organization with low frequencies projected dorsally and high frequencies situated ventrally.

The axons of the third-order neurons from the superior olivary complex (SOC) and nucleus of the trapezoid body rise up either side in the lateral lemniscus. A majority of these axons ascend in the contra lateral lemniscus and project to the nucleus of the lateral lemniscus at the level of the ponto-midbrain junction. The neurons in the nucleus of lateral lemniscus, further, project onto the inferior colliculus.

1.4 **Inferior Colliculus**:

The inferior colliculus comprises of bilateral mesencephalic structures and represent the primary relay station for all the auditory ascending pathways. It processes auditory information from the lower brainstem to the medial geniculate body and terminates onto the auditory cortex. The dorsal portion of the inferior colliculus takes projections from neurons which respond to low sound frequencies, while the ventral portion from those neurons that respond to high sound frequencies. This auditory information thus obtained is further processed and relayed by the inferior colliculus to the medial geniculate nucleus of the thalamus. There is a regular tonotopic organization seen such that the fibres are arranged in a low to high frequency order along the dorsal to ventral region with iso-frequency laminae congruent with the orientation of the dendritic laminae.

1.5 **Medial Geniculate Nucleus**:

The medial geniculate nucleus of the thalamus is seated at the caudal aspect of the thalamus, proximal to the midbrain, intercalated between the fibres of the inferior colliculus and the auditory cortex. The axons of the neurons of the inferior colliculus transmit auditory signals to the medial geniculate body of the thalamus which is tonotopically arranged and relays precise information about the frequency, intensity and binaural sound properties. These neurons through their axons, further, project to the primary auditory cortex

1.6. **Primary auditory Cortex**:

In humans, the cytoarchitectural properties, the fibre connections and the physiologic properties divide the auditory cortex into primary auditory cortex which is situated in the transverse temporal gyri (of Heschl) of the medial aspect of the superior temporal gyrus and associated auditory regions which collect auditory and other sensory inputs. Brodmann's areas 41 and 42 are known the primary auditory area, A-1 region and receive projections from the medial geniculate nucleus (geniculotemporal fibres or auditory radiations). The tonotopic organization which is observed in the auditory relay nuclei is well observed in the auditory cortex. This cytoarchitecture resembles closely the other primary cortical sensory areas.

Brodmann's areas 22 and 52 are the auditory associated areas that connect the primary auditory cortex with the frontal and temporo-parietal regions which are concerned with

speech & language, somaesthetic and vision areas. One of the secondary auditory areas include Wernicke's area, essential for the spoken word interpretation.

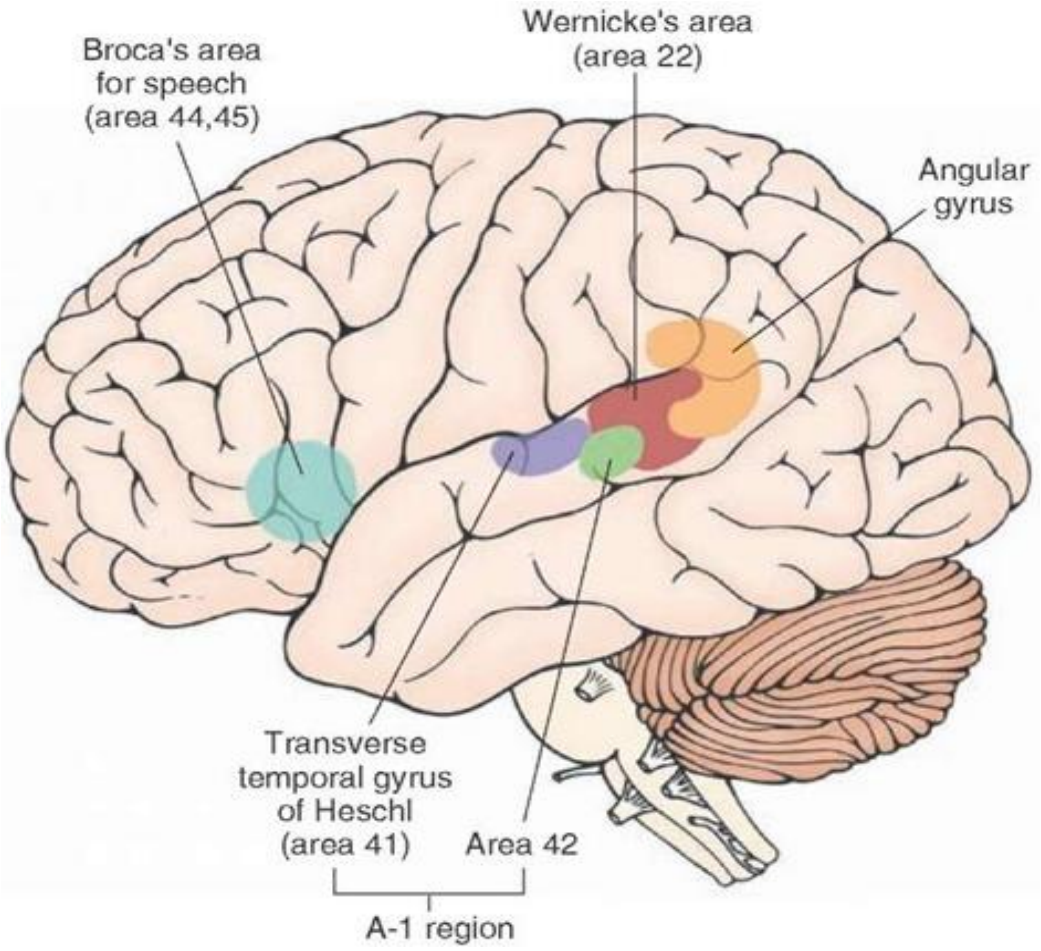


Fig. 7: Primary auditory cortex.

The sound impulses as they pass through the various levels at brainstem and the auditory cortex can be shown to elicit waveforms that can be graphically represented, thus helping in the diagnosis of the anatomical site of lesion.

2. **Physiology of hearing and speech**:

Hearing is a multifaceted special sense that co-exists with the other special senses. The concept of hearing has been viewed since 1700s. Philosophers debate if a falling tree made sound if there was no one nearby to hear the sound. Physicists viewed sound as a science of acoustics while Psychologists felt it as a personal quality of sensory perception. It was conceptualized that the human reaction to sound was hearing.

Auditory perception is defined as the interpretation of sensory evidence that is derived from sound, in terms of the object and events that caused the sound. It involves the use not only of sensory evidence, but also of contextual evidence, prior knowledge, memory, attention and processing skills.(3) Auditory speech perception is unique to humans, as the events to be perceived are those of language.

Hearing develops in-utero such that the first response to hearing has been recorded at 20-25 weeks of gestation. The auditory system is complete and functional at birth but myelinations continue for several years after birth in the auditory neural pathways. Human baby at birth is knowledged with pre-existent language specialized neural structures. These neurons only await acoustic experience with symbol based communication system. This explains how important it is for a child to attain auditory development and maturity in order to co-ordinate the co-existing special senses. This auditory linked language acquisition is unique to humans and is related to early maturational periods in the infant's life. This underlies crucial periods for biologic functions of humans.

Human developmental neuropsychological studies claim that the brain which develops is 'plastic'. That is, the immature brain has unique characteristics to reorganize and to re-shape its various neural connections which the mature brain cannot. This is why, the developing or the immature brain is much less susceptible to the detrimental damages than the more mature brain. Normal brain follows a maturational set pattern including both input from the environment and the genetic factors. Any unfavourable insult which perturbs this maturational process is circumvented effectively as the entire system responds neatly thus preventing any functional deficit. It is evident from studies that focal brain insult suffered early in life is far better than the affective and cognitive impairments manifested due to insults suffered in later life. These less devastating and differential outcomes following early insults are ascribed to the developing brain's ability for neural plasticity. This exceptional capability for reorganization, however, declines gradually with maturation.

Lenneberg in 1967 put forward the theory, the neurons and their connections which mediate language and other higher cognitive functions pursue a maturational outline during development. There are genetically pre-specified different brain regions that become eligible for particular cognitive functions. Under appropriate maturational calendar, these qualified regions become devoted to pre-designated functions. In most adults, functioning normally, the brain showcases such a maturational profile of organization. Yet, if the developing or the immature neural substrate confronts any insult, the brain displays alternate reorganization patterns. This neural plasticity happens as the maturing brain has not yet devoted its entire subset of resources. Thus, one region of the brain if faced with injury, there are sufficient neural structures and connections that are available to sustain the developing functions. However, there is decline in the brain plasticity as it develops such that it shows a gradual

dedication of neural resources to well defined functions maturationally with a parallel loss in the system's flexibility and capacity to reorganize .

Various authors have put forward the upper age limit for linguistic recovery following early insult. Lenneberg in 1967 was far too optimistic in postulating the upper age limits at about 12. Krashen ad colleagues in 1973 concluded that the brain plasticity does not happen after about age 5. The work in 1978, by Wood and Carey brought the limits of recovery even lesser than the first year of age. The human hearing frequency is known to range between 20 to 20,000 Hz. The output range of pitch of human speech encompasses broad range of frequencies from 500-3500 Hz which is nearly identical to the optimal hearing frequency sensitivity.

Sound is collected via the pinna, transmitted through the external auditory canal and strikes the tympanic membrane which has a larger surface area than the stapes footplate. This area mismatch provides an impedance matching between the sound wave in environmental air and inner ear fluids. Compression and rarefaction of inner ear fluids are further enhanced by the lever action of the ossicles - Malleus and Incus. Displacement of the inner ear fluids results in depolarization of the organ of Corti in the hair cells. The base of the depolarized hair cell then activates the cochlear division of the vestibulo-cochlear nerve, the eighth cranial nerve via synaptic transmission. The action potential thus generated ultimately gets processed via the auditory brainstem and cortex in the perception of sound. This way, sound is perceived as hearing. It is in the auditory cortex that the initial auditory signal once processed, the speech sounds are further processed to extract the auditory cues and phonetic information.

3. Effects of hearing impairment:

The impact of hearing impairment is seen in many domains of development in a growing child right from the child's speech, language, cognition, psycho-educational and social-emotional competence. The degree and type of hearing impairment and the age at diagnosis play an important role.

A. Functional impact:

One of the principal impacts of impaired hearing is on the individual's skill to communicate effectively with others. Language learning is key to the development of any child. As discussed earlier, the language physiology depends on the hearing maturity and thus spoken language development is often delayed in hearing impaired children. The receptive and the expressive communication skills of these children show a significant delay.

In 1978, Skinner, documented a number of detrimental 'acoustic liabilities' to a child's language learning when hearing loss exists like the following,

- There is lack of constancy of auditory clues when auditory signal fluctuates and there is an inconsistent categorization of speech sounds.

- There is confusion of acoustic parameters with rapid speech.

- There is confusion in segmentation and prosody - the child with hearing loss may miss linguistic boundaries like plurals, tenses, intonation and stress patterns. These interpretations are requisite for meaningful interpretation of speech.

- Breakdown of early ability to speech sounds - an infant begins to learn to discriminate speech sounds almost immediately after birth. Learning can be impeded if the sounds of speech are not perceived early in life.

- Breakdown in early perception of meanings - during ordinary speech, the normal listener often misses some unstressed or elided words or sounds but is often able to fill in by understanding the context of the message. However, a hearing impaired child tends to miss many of these soft or inaudible sounds and there is confusion in word naming, word order, difficulty in developing classes of objects and misunderstanding of multiple meanings.

- There is faulty abstraction of grammatical rules.

- Subtle stress pattern is missed - the emotional intent of speech, its rhythm, intonation is confused, another condition that impairs learning of speech and language.

These various parameters can handicap a child at different levels of hearing loss. This explains that one of the profound impacts of deafness is in the spoken language.

A mild hearing impaired child may miss out on the consonants, less intense speech sounds, voiceless stops and fricatives that only louder voiced speech is heard. This has a significant effect on language learning, communication and education. Most of the conventional speech sounds is missed in moderate hearing loss that these children have a significantly lower numbers of phrases and words understood besides gestures and strangers find it difficult to understand the speech of these children. A child with severe and profound hearing loss is severely handicapped that language and speech do not occur spontaneously.

Hearing loss thus affects speech and impaired speech encroaches onto the language learning which significantly hampers the communication skills. Be it understanding their own voices or the others around them, these children show a different pathway with difficulty in all areas of communications development.

The academic development of a child at various levels suffers a delay in the hearing and speech impaired children. Pre-school children suffer learning the language while in school-aged children, it manifests as poor performances in language - based tests, class tests, class participation, volunteering activities, verbal communication and interaction with peers and teachers. The grasping capabilities and the verbal memory get hampered. All these difficulties put together leads to poor academic achievement, often leading to school failure, especially in the lower grades. A child, until it reads newer information, most of classroom learning is through auditory learning.

B. <u>Emotional impact</u>:

Children especially are a source of joy to the parents and the family. Any insult to children incurs a heavy emotional burden on the part of the parents and the caregivers. The speech and hearing impaired children need special attention and additional care. Besides ensuring the best of care, parents themselves suffer an emotional letdown and stressful period many a time, and become emotionally labile. Several studies point out the lack of communication capabilities and experiences with hearing-impaired children on the part of many investigators. Besides, delays have been noted for the development of social maturity among hearing-impaired children and the parents' descriptions many a time, may reflect their own worries, if not, the emotional and behavioural functioning of the child.(11)

C. Neuropsychiatric impact:

The poor verbal communication skills results in introversion of these children and thus social isolation. These children as a result get underexposed to the worldly experiences and the repeated failures can lead to a long term impact by contributing to low self-esteem which itself may limit their opportunities and vocational choices. Increased incidences of behavioural problems have been reported to occur among the hearing impaired children. Behavioural problems may take up outward appearances such as aggression, hyperactivity, temper-tantrums, while from within, these may equate to or reflect from depression, anxiety, social seclusion, learning disabilities, negative self-image and many. Self- expression becomes difficult for many of these children and as a result become more inner-focused.

The neuropsychiatric impact of hearing impairment on children has been investigated and has been found that these children pursue various diverse developmental pathways. The measurement of various psychiatric symptoms is quite compromised as many of the evaluation procedures are highly verbal and were normalized for children with normal hearing. Accurate evaluation is thus hampered by the immature and undeveloped language displayed by many hearing-impaired children and by the hardships that may be faced in establishing rapport if the child does not comprehend the investigators verbal interactions. All these problems show that the prevalence of mental disorders among hearing-impaired children and adolescents shown in the literature differ from 15% to 60%.(11) It is also said that hearing impairment may be a pointer for brain insult in autism.(12) Various studies have explained that there is a higher degree of impulsivity exhibited by the hearing impaired children than their normal counterparts.(12)

D. Economic impact:

The economic impact caused by the hearing impairment needs special mention. It causes a heavy economic burden on not just the individual and the family, but it has an impact on the society as well. The school failure rates among the hearing impaired children is not low and the retention rate among these children and the cost of retaining such a student adds to the economic burden to the educational systems. The lifetime educational costs that these children incur add to the significant crisis. Once out of their schools, the jobs that are held by these children often carry a lesser pay.

Children who are hearing impaired or speech delayed warrant multiple clinical visits right from the time of diagnosis or even in-utero. The multiple diagnostic tests to establish the diagnosis or to rule out one are not without expensive nature these days. Many a time, these children may need to be given repeated appointments for the various procedures especially those requiring sedation thus adding to the economic burden on the family. The interventional procedures when explained to the parents are not without complications and the parents may need to be ready to face them. Parents with 'precious children' especially may not have an option and many a time do not think otherwise, rather try out the various diagnostic and interventional tests, all to bring out the best of the treatment outcome for their children. In the current day world, when both the parents are employed, may serve additional impedance to the number of hospital visits and planning schedules.

As the parents are involved in the health care of these children, their work schedule may get disturbed which reflects on their pay pattern and ultimately the family income. The entire schedule thus significantly adds to the economic crisis to the family. Not to forget is the

mental trauma the couple and the family go through, many a time needing to manage the family member as well besides the child who is impaired. This may again intensify the medical costs and add to the economic crisis in the family. It needs to be mentioned that not just the family which suffers, but, has an indirect effect on the society as well. The regular work-offs by the parents significantly adds to the decrease in productivity with higher unemployment and lower wages which serves as an impediment for the economic growth of the society.

4. Global burden and statistics:

Hearing impairment is the most common but worrisome disability in today's industrialized world. According to the American Speech language and Hearing Association, hearing impairment can be classified and defined as following:(13)(14)

Slight impairment: is defined as when pure - tone hearing threshold level, unaided, for the better ear of 16 - 25 decibels (dB), taken average of the (HL) hearing threshold levels for the frequencies - 500Hz, 1kHz and 2kHz

Mild impairment: is defined as when pure - tone hearing threshold level, unaided, for the better ear of 26 - 40 decibels (dB), taken average of the (HL) hearing threshold levels for the frequencies - 500Hz, 1kHz and 2kHz

Moderate impairment: is defined as when pure - tone hearing threshold level, unaided, for the better ear of 41 - 55 decibels (dB), taken average of the (HL) hearing threshold levels for the frequencies - 500Hz, 1kHz and 2kHz

Moderately severe impairment: is defined as when pure - tone hearing threshold level, unaided, for the better ear of 56 - 70 decibels (dB), taken average of the (HL) hearing threshold levels for the frequencies - 500Hz, 1kHz and 2kHz

Severe impairment: is defined as when pure - tone hearing threshold level, unaided, for the better ear of 71 - 90 decibels (dB), taken average of the (HL) hearing threshold levels for the frequencies - 500Hz, 1kHz and 2kHz

Profound impairment: is defined as when pure - tone hearing threshold level, unaided, for the better ear of 91 decibels (dB) or greater, taken average of the (HL) hearing threshold levels for the frequencies - 500Hz, 1 kHz and 2 kHz

Hearing loss is viewed as a hidden disability, according to the World Health Organization.

As per the study by the Global Burden of Disease in 2000 that was reported by the World Health Organization which was published in the WHO World Health Report in 2001, childhood and adult onset deafness was calculated to affect around 250 million people worldwide. According to International studies, hearing impairment was identified when an average hearing level of >= 35 decibels was noted in the better ear. Estimating the prevalence globally, in 2008, it was found nearly 1.4% children aged 5-14 years were hearing impaired, while for females >15 years of age, it was 9.4% and was 12.2% for males in the same age group.(1)(11)

Based on 42 population-based studies, the WHO, in 2012 released newer estimates on the degree and enormity of disabling hearing loss. It defined disabling hearing loss when in

adults (15 years or older), a loss > 40 dB in the better hearing ear and more than 30 dB in the better hearing ear in the paediatric age group (0 to 14 years). It has been projected that nearly 360 million people accounting for nearly 5.3% of the entire world's population suffer disabling hearing loss with 9% of these being children. The prevalence showed an unequal distribution with the greatest seen among the developing countries in Asia Pacific, South Asia and Sub-Saharan Africa. The prevalence decreased exponentially as the Gross National Income per capita increased. Also, the prevalence decreased linearly as parents literacy rate increased.

In the US, the average incidence of hearing loss was 1.1 per 1000 infants. The prevalence of mild hearing impairment or worse (>20dB) was 3.1 percent with the low income households demonstrating a higher prevalence of hearing loss compared to the higher income levels.(15)

According to Indian statistics, the National Sample Survey Organization (NSSO), Government of India, 1991 reported that among children in the age group 0 to 14 years, 2.7% in rural India and 3.0% in the urban side are known to have hearing impairment. The same survey showed the statistics as 8.3% and 8.9% in rural and urban side respectively for children with speech disability. The incidence of hearing impairment in India amounts to 8 per 1000 with 4 out of every 1000 children suffering severe to profound bilateral congenital hearing impairment.(16)(17) A recent survey conducted in one of the Indian states showed an overall hearing impairment in the rural sector to be 15.14% as opposed to the urban side, 5.9%. Children <10 years accounted for 5.4% for disabling deafness. The prevalence in urban children was 1.2 % when compared to the rural side 5.4%.(2) This underscores the need for early diagnosis and appropriate management.

5. Diagnostic audiology tests:

Hearing loss thus needs to be diagnosed early in life for adequate, appropriate and timely rehabilitation. There is a battery of objective diagnostic audiology tests done as office procedures to evaluate these condition.(18)

Behavioural test methods are available which form critical components of the comprehensive audiometric assessment battery for infants. These test methods must be developmentally appropriate for appropriate age group. There are two general categories of test approaches that are used in paediatric behavioural audiometric assessment.

1. Unconditioned test procedures:

   - Behaviour observation audiometry

2. Conditioned response procedures:

   - Visual reinforcement audiometry
   - Conditioned orienting response
   - Play audiometry

The Joint Committee of Infant Hearing (JCIH) encourages early detection and timely intervention of children with hearing loss with a goal of maximizing linguistic competence and literacy development besides functional intelligence. This is achieved by Universal neonatal hearing screening when children are discharged from hospital or within their first

month of life. Children should be referred for further expert opinion, should screen tests report 'positive'. A battery of tests is undertaken to confirm the diagnosis, this should be made by the third month of life and therapy should be started by the sixth month of life. Thus, this has significantly added to the work load of the audiologists and the speech therapists. As children cannot be expected to respond reliably to subjective hearing tests, the significance of the objective tests become underlined.(19)

The auditory electrical potentials provide the most accurate, convenient and objective method to assess the functioning and performance of the auditory system especially in children when behavioural audiometry does not help. These auditory electrical potentials are known to originate from various levels of the ascending auditory neural pathways at precise time intervals following the sound stimulus. Studies on electrophysiological work on organ of hearing was initiated since the experimental research of Luigi Galvani's discovery of electrical activity at locating the cortical hearing centre.(20) The importance of electrical potentials from cochlea and auditory nerve fibres was studied by Wever & Bray in addition to Ruben's team of Baltimore besides leading studies done by Hallowel Davis who is known as the "father of ERA studies'' which is Electric Response Audiometry. Auditory Brainstem Evoked Response (ABR) is one such objective electrophysiological test that assesses the brainstem response to simple auditory stimuli.(21)(22)

6. **Auditory Brainstem Evoked Response audiometry (ABR)** :

Auditory brainstem evoked response audiometry is an effective and a non-invasive method of evaluating the auditory pathway from the peripheral end organ through the brainstem.

Besides, evaluating for the structural lesions, it helps in determining the auditory thresholds. (23)

6.1. **History and origin**:

It was Sohmer and Feinmesser in 1967 who were the first to publish reports on ABR. Later, it was Jewett and Williston in 1971 who clearly interpreted and described the waves as those arising from the brainstem.(24) Selters & Brackman in 1977 came up with breakthrough findings on inter-peak latencies in those tumours that were greater than 1 cm being prolonged. Hecox & Galambos in 1974 explained that ABR could be used for threshold estimation in both infants and adults.(25) Starr & Achor in 1975 were the first to describe the effects of central nervous system pathology in the brainstem on ABR. Since then, ABR has become an effective and an invaluable tool with a wide array of clinical applications including universal newborn hearing screening, retro-cochlear pathology screening, frequency-specific estimation of auditory sensitivity, ICU and intra-operative monitoring especially in neurosurgical cases.

6.2. **Other names** :

It has been called as Brainstem Auditory Evoked Response (BAER), Auditory Brainstem evoked Response audiometry (ABR), Brainstem Evoked Response Audiometry (BERA), Brainstem Auditory Evoked response Potential (BAEP).

6.3. **Clinical applications**:

American academy of Otolaryngology – head and neck surgery has suggested ABR in various clinical indications. It can be used as a screening tool for hearing, besides serving as a tool in the diagnostic assessment of the degree of hearing loss in infants and in those individuals in whom a conventional hearing test cannot be performed. It is also used in the operating theatre to monitor the eighth nerve function while surgery.

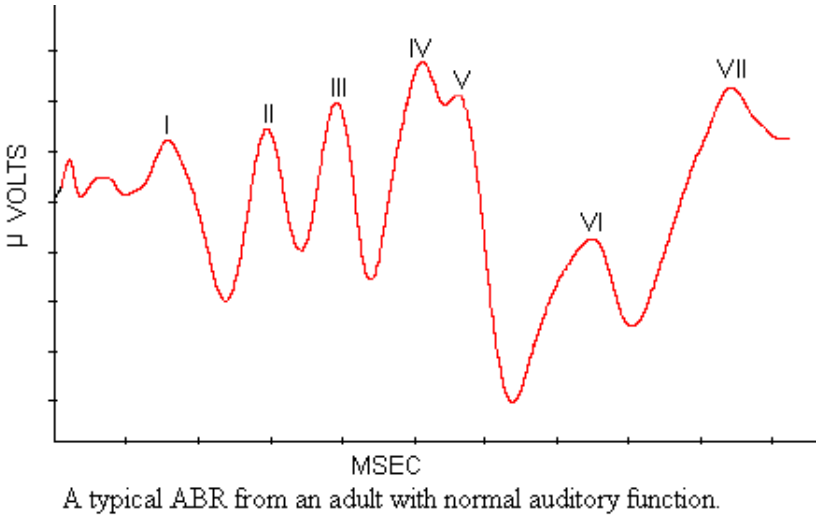
6.4. **Principle**:

ABR monitors the electrical activity of the acoustic nerve and the brainstem nuclei. It consists of evoked electrical potentials produced by the synchronous activity of the neuronal populations in the brainstem, the neural responses of which are collectively measured passively and objectively. It thus provides a tremendous means to measure auditory threshold in a clinical setting.

Studies on ABR used simple click stimuli or burst tones, to start with. Although these have been helpful in determining the basic responses, they appear to be poor estimation of the behaviourally appropriate sounds that are encountered normally outside the laboratory. There is a plethora of complex stimuli that has now been used to assess how the spectral and temporal qualities of sounds are preserved in the ABR. In 1980, Greenberg was one of the earliest to adopt complex stimuli to record ABRs. Young& Sachs in 1979, showed that speech formants are conserved in the discharge pattern of the eighth nerve, Greenberg in 1980 noted that speech-specific information / vowel formants is also programmed in the ABR faithfully.

6.5. **Waveforms in ABR**:

The surface electrodes are positioned at the vertex of the scalp and the ear lobes and the waveform response are measured and graphically represented with amplitude of the signal in micro-voltage averaged and charted against time in millisecond. The wave form peaks are marked using roman numerals I –VII, each of which are separated in latency by nearly one millisecond. Normally, these waveforms occur within a 10 millisecond time period following a click stimulus at high intensities with 70-90 dB normal hearing level. These waveforms are produced as the signal travels along the auditory pathway representing successively higher order of neuron activity at specific time intervals.(26) Various levels correspond to the specific location along the pathway. The criteria are based on the individual peak latencies and inter-peak latencies.(27) Individual latencies of waves I, III and V, amplitude ratio of wave V to wave I, inter-peak latencies of I-III, III-V and I-V are the common factors evaluated for evaluating clinically relevant abnormalities (28).



A typical ABR from an adult with normal auditory function.

Fig. 8: Waveforms in ABR.

Specific representations of the various waveforms:

Waveform I: The ABR wave I corresponds to the action potential from the distal portion of auditory nerve. This represents the afferent activity or the first order neuronal response from the eighth nerve as they exit the cochlea and enters the IAC.

Waveform II: The ABR wave II is produced by the proximal eighth nerve as it makes its entry into the brain stem.

Waveform III: originates beyond the eighth nerve from the second-order neuronal activity in or near the cochlear nucleus. Some studies suggest the response to be contributed in addition, from the caudal portion of the auditory pons. It is to be noted that the nearly one lakh neurons which comprises the cochlear nucleus is mostly innervated by eighth cranial nerve fibres.

Waveform IV: is seen mostly to share the same peak with wave V. It is believed to originate from the third-order neurons mostly situated in the superior olivary complex, in the pons, with additional contributions from the cochlear nuclei and the nucleus of lateral lemniscus.

Waveform V: is the wave analyzed most often in the clinical setting. It likely represents the activity arising from multiple auditory structures. Though some debate exists on the exact generation of wave V, it is believed that it originates from the vicinity of the inferior colliculus along with some additional contribution from the second-order neuron activity. The inferior colliculus is known for its complex structure, with more than 99% of the axons from lower auditory brainstem regions traversing through the lateral lemniscus to the inferior

colliculus. Due to its stability and consistency, the waveform V is prominent and considered important in the interpretation of the auditory threshold sensitivity.

It has been found that the polarity of the stimulus influences latency, waveform and amplitude of the response curves. A bifid wave form with splitting of the wave form peaks IV and V in separate peaks has been noted following rarefaction stimulation while the condensation stimulus produces a single-peaked contribution. The splitting of the wave complex IV and V may be traced to mechanical processing in the cochlea.(29)

Waveforms VI and VII: are generated from the medial geniculate body of the Thalamus, but the precise site of generation is uncertain.

Thus various waveforms can be obtained pertaining to the specific pathology and the morphology along with the above parameters help in localizing a lesion or obtaining the threshold of hearing.

6.6. **Effect of aging on ABR responses (infants and children Vs adults)**:

Aging shows a significant effect on the wave form responses. The various parameters undergo distinct maturational transformations in early life affecting both the peripheral and central auditory structure.(30) There is essentially an exponential growth with equal maturation rate for each auditory station.(31) The changes are evident even in the first hours after birth.(32) The auditory nerve maturation is seen to occur at a rate considerably faster than that for more central parts of the nervous system. The waveform morphology differs in several important ways for infants and children when compared to an adult. In infants with

normal development, peak latencies and waveform morphology approach adult values by around age, 18 to 24 months. Nevertheless, prolonged latencies may continue to persist in children beyond this age range due to sensory and conductive involvement, developmental delays, particularly at lower intensity levels. Thus, while assessing infants and young children for threshold predictions, it is essential to extend the recording or analysis window beyond the 10 ms period classically used with adults.

In preterm infants, a typical bow tie pattern is seen preceding peak III. This appears approximately 0.1 millisecond before the ipsilateral peak III and it appears to be the earliest characteristic of the developing waveform morphology in preterm infants.(33) This implies why there should be postponement of neonatal hearing screening until after 34 weeks, as the waveform characteristics in ABR will improve with age. Beyond this period, prematurity does not appear to have any effect on the maturation rate or on the time to maturity of the brainstem auditory potentials.(31) The most reliable waves during the first month of life are waves I, III, V.(34) There is a substantial reduction in amplitudes of all major ABR peaks with considerable latency shifts limited to wave forms I and III, but no influence on I-V inter-peak latencies even at high click rates. This observed absolute latency shifts in the responses can be ascribed to the changes in auditory nerve input with progressive myelinations of the auditory tract in infants.(35)

6.7. **Effect of anaesthesia on auditory brainstem responses**:

Animal studies have shown that anaesthesia is known to affect the various wave form responses. Under anaesthesia, the measurement accuracy of peak latencies, inter-peak latencies and the various thresholds decreases. Several anaesthetic agents like sevoflurane,

isoflurane, enflurane and temperature changes associated with undergoing anaesthesia are known to increase the conduction time. The wave form generated by the distal portion of VIII nerve, i.e., wave I is spared while there is an increase in central conduction time which results in delayed ABR absolute and interpeak latencies, e.g., III, V, I-III, III-V, I-V.(36) The agents studied and known are ketamine, xylazine. At physiological doses, hearing thresholds obtained with isoflurane were shown to be elevated across a broad frequency range by greater than 27 dB. On an average, isoflurane is found to dose-dependently reduce the amplitude and increase the latency of the ABR. These effects are typically seen when isoflurane is used at a concentration of 2%.(37) Thus in spite of the myogenic noise concomitant with the awake state, this is more preferable to get quality recordings though the time to recording increases.(38)

6.8. **Various stimuli used**:

6.8.1. **Click- evoked ABR**:

The click-evoked ABR, otherwise called as transient-evoked ABR is the most commonly used electrophysiological procedure used for assessing the auditory thresholds in both infants and children. When the stimulus is given in the form of an abrupt onset of click at moderate intensity levels, a major portion of the cochlea is activated which results in firing of a large network of neurons over an extended frequency range. The most constant and highly repeatable waveform is waveform V that can be detected within about 10 decibels intensity level of the average behavioural audiogram in the 1 kHz to 4 kHz frequency region in both children and adults. The main limitation of the click-evoked ABR in prediction of the threshold is its lack of frequency specificity.

6.8.2. **ABR - tone bursts**:

Tone bursts are gated sinusoids that are brief enough to produce the synchronous neural discharge which are required for a measurable ABR, still with sufficient duration, in order to retain some frequency specificity. Tone bursts may show better results in predicting peripheral sensitivity than the click-evoked responses, particularly in the cases of sloping or other unusual audiometric configurations. The waveforms, here, are seen to be longer in latency than those that are generated by click stimuli. There is a delay in the responses to low-frequency stimuli, as the time travel to reach the more apical turns of the cochlea is increased. In order to include these delayed peaks, the analysis window should be extended to 20 ms or more while recording ABRs to tone bursts, especially for tone-burst frequencies below 2000 Hz. When adequate stimulus and appropriate acquisition parameters are used, the results can be obtained at intensity levels within 10 dB of the behavioural thresholds for identical frequency stimuli, yet the correction factor may be nearer to 20 dB for 500 Hz and below.

6.8.3. **Bone conduction ABR**:

Bone-conduction ABRs can be as consistent and repeatable as air- conducted ABRs especially where signal delivery show a tight control. In young children, bone conducted ABR is mainly useful in assessing if a functioning cochlea in the presence of structural anomalies exists, like ear canal atresia. Oscillator location and coupling force seem to be prime factors in bringing out reliable bone-conduction ABRs.

6.9. **Procedure**:

The Brainstem Auditory Response estimates the electrical activity of the eighth nerve through the brainstem to the auditory cortex. Here, a sound stimulus in the form of a click is presented to one ear at a time. The electrodes placed on the scalp records the various electrical activity of this signal. The average of the responses is shown as a waveform which contains troughs and peaks that correspond to the various points along the auditory pathway. The time taken between these peaks is measured and is compared to normal data. A delayed response indicates an abnormal response. The individual peak latencies and inter-peak latencies along with the other waveform morphology are measured. Peak latencies, amplitude and morphology of the waveforms offer reliable information about the integration and maturation of the eighth nerve and lower brainstem pathways.

6.10. **Prerequisites**:

An ABR recording may become contaminated by non-physiologic artefact, particularly, 60-Hz interference that is partially phase-locked. Efforts must be made to reduce the electrode impedance asymmetries and reducing the source of artefacts. As ABR involves recording of electrical evoked potentials that are graphically represented, patient sedation is required to avoid any additional sound stimuli. Any movement artefact may interfere with the morphology of the waveform responses and thus the interpretation. It is performed satisfactorily in adults when they sleep, but becomes difficult in those who don't sleep and in children. Pharmacological sedation thus becomes mandatory.

7. Need for patient sedation in children:

Recent advances and technological breakthroughs have led to a wide increase in the spectrum of effective diagnostic procedures and therapeutic interventions in the medical field. In audiology, newer equipments and devices have come into practice providing solutions to the often faced diagnostic dilemma in many situations. This has led to a significant reduction of the burden faced by both the physicians and the patients. Not infrequently, these delicate tests require patient sedation.

Many procedures in adults can be performed under local anaesthesia and reassurance. While in infants and children, this is not the case as it may not often be possible because they may be too frightened even if the procedure itself is not painful. Hyper-active children add to further difficulty. Patient movement and agitation may lead to myogenic and movement artefacts, threshold overestimation ultimately leading to inaccurate recordings.(22)

Performance of any diagnostic or interventional procedure on children is safer and is more likely to be successful when the child does not move or when the associated anxiety, fear and stressful environment are adequately and appropriately tackled well. In addition, considerable attention to the patient's pain and anxiety is a requisite of acceptable and compassionate patient care. Very often, unlike adults, children are not candidates for reassurance or disciplined obedience. Pharmacologic and non-pharmacologic interventions as per the child's developmental status and the clinical circumstances need to be considered. Non-pharmacologic measures are not always successful. The procedure may get interrupted and providing a non-pharmacologic measure to induce sleep again may turn futile. This may interfere with the quality of the recordings and add to the time consumption. The

environment in which most of these tests are conducted warrants a calm and quieter setting with dimmer lights for effective readings. Children when they wake up in between tests to find themselves in such an unfriendly environment get frightened making it difficult for even their parents to calm them down. The chance and possibility of re-sedation in such a circumstance using non-pharmacological measure become questionable. It is not rare that these un co-operative children become candidates for General Anaesthesia for effective completion of these essential diagnostic tests.(39) This further increases the time, cost and waiting lists for operating theatre on one hand besides building up anxiety among parents on the other hand, not to forget the ill-effects of anaesthesia these children are exposed to when it could possibly be avoided if options prevail. The increased availability of newer and short-acting sedatives along with accurate non-invasive monitoring has enabled patient sedation especially paediatric sedation a possible task.(40)

There is no absolute indication for the performance of paediatric procedural sedation. It may be used for any procedure which warrants absolute movement restriction or where a child's pain and anxiety may be excessive which may impede the performance of a procedure. The need for sedation again varies with the age, developmental and behaviour status of the child. The targeted depth of sedation and the pharmacological drugs used depend on the procedure for which sedation is warranted besides the patient factors. Some of the procedures that commonly mandate procedural sedation in children include imaging by computed tomography or magnetic resonance imaging, electroencephalogram, orthopaedic procedures like fracture reduction, complex laceration repair, large abscess incision and drainage, instrumentation like endoscopies, Bronchoscopy, burn dressing change, central line

placement. In the field of oto-rhino-laryngology, ABR is one of the procedures which warrant strict movement restriction for effective completion and quality recordings.

8. Guidelines for paediatric sedation:

Procedural sedation and analgesia implies the use of a pharmacologic technique to allay patients fear and anxiety. It is seen as an effective, safe and a humane way to aid appropriate medical care. The goals for procedural sedation could be pain relief, anxiolysis or both and the desired effect could be achieved using varied cocktails of medications, besides handling safe the various adverse effects associated with them.

The trend of paediatric procedural sedation has opened new domains for managing un co-operative paediatric patients in almost all disciplines of health care.(41)(42) This has enabled safe and effective performance of diagnostic and therapeutic procedures in the outpatient setting. Coupled with the emergence of promising pharmacologic agents and non-invasive monitoring, this new and recent surge has led to a phenomenal growth in the volume and scope of safe and effective paediatric procedural sedation.(43)

For any sedation, safe implementation of practice protocols is essential. The aims of sedation during diagnostic procedures and therapeutic interventions should include allaying fear and anxiety, bringing pain control and minimizing physical discomfort and movement, the importance of each of which depends on the patient characteristics and the procedure proposed. Many sedation techniques available are studied and are being implemented but there is inadequate direction and assistance on which techniques are effective and what resources are needed to administer them safely.

There are no absolute contraindications to procedural sedation in children. Relative contraindications include anticipated difficult airway or significant medical co-morbidities. Prior to sedation, written informed consent has to be obtained from the parents after discussion about the risks, benefits, alternatives for sedation.

8.1. Classification

As a part of pre-sedation evaluation, American Society of Anaesthesiologists classification of risk stratification should be given to every patient that assesses patient appropriateness for elective procedural sedation.

ASA I - healthy normal patient

ASA II – mild systemic disease (e.g., mild asthma, controlled diabetes mellitus)

ASA III – severe systemic disease (e.g., moderate to severe asthma, un-controlled diabetes mellitus)

ASA IV –severe systemic disease which poses a constant threat to life (e.g., advanced cardiac disease)

ASA V – a moribund patient who is not expected to survive without the operation (e.g., severe trauma, septic shock)

Although the ASA classification was not specifically designed to rate sedation risk, it appears to correlate with appropriateness for sedation.

Sedation among children is regarded as a continuum and is graded as minimal, moderate and deep.(44)

According to the American Society of Anaesthesiologists and American Academy of Paediatrics, sedation is classified as follows:

Minimal sedation or anxiolysis (old terminology):

A state of consciousness which is drug induced during which patients react normally to verbal commands. The ventilatory and cardiovascular functions are undisturbed although coordination and cognitive function may be hampered.

Moderate sedation or conscious sedation or sedation/analgesia (old terminology):

A state of depressed consciousness which is drug induced during which patients react purposefully to verbal commands (e.g.: "open your eyes" either alone or along with light tactile stimulation—a light tap on the face, shoulder but not a sternal rub).

In older patients, moderate sedation may be implied by an interactive state while younger patients are expected to respond by age-appropriate behaviours (e.g. crying).

With moderate sedation, no intervention is needed to maintain a patent airway. Spontaneous ventilation is maintained. Cardiovascular function is generally maintained.(44)

Deep sedation (Deep sedation/analgesia):

A state of consciousness which is drug induced during which patients cannot be aroused easily but may respond purposefully after continuous painful or verbal stimulation (e.g. pushing away the noxious stimuli purposefully). The ability to maintain ventilatory function independently may be impaired such that patients may need support in maintaining a patent airway. Spontaneous ventilation may be inadequate, but, cardiovascular function is usually maintained. This state of deep sedation may be accompanied by partial or complete loss of protective airway reflexes.

General Anaesthesia:

A state of consciousness which is drug induced during which patients are not arousable, even to painful stimulus. The ability to maintain respiratory function independently is often impaired such that patients often require assistance in maintaining a patent airway. Positive-pressure ventilation may be required due to depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Also, cardiovascular function may be impaired.

Sedation levels and Clinical Response:

	Verbal Response	**Pain Response**	**Airway Response**	**Breathing**	**Circulation**
Anaesthesia overdose	0	0	0	0	0/+
Anaesthesia	0	0	0	0/+	2+
Deep Sedation	0	1+	1+	2+	3+
Moderate Sedation	1+	2+	2+	3+	5+
Minimal Sedation	3+	4+	4+	5+	5+
No	5+	5+	5+	5+	5+

Moderate sedation earlier called as conscious sedation is evolving as an effective way for paediatric procedural sedation. With fast evolving diagnostics and therapeutics, many Professional organizations are working towards this promising lane.(45–48) The American Society of Anaesthesiologists has updated and revised its guidelines for providing effective and safe paediatric procedural sedation and analgesia by non-Anaesthesiologists in the office-setting.(48)

8.2. Sedation by non-anaesthesiologists:

Children who belong to ASA class I and II are generally eligible for mild, moderate and deep sedation by personnel other than anaesthesiologists, outside the operating theatre. Those with ASA class III, IV, V may not be candidates for similar ways of sedation. Several studies have put forward guidelines and protocols for administering paediatric sedation by non-anaesthesiologists. Specific paediatric guidelines are established by the American Academy of Paediatrics (AAP) and the most important recommendation common to all guidelines is related to the person performing the sedation. The administering person must be adequately qualified enough to manage all potential complications ranging from airway-respiratory compromise and hemodynamic instability.

The setting must be sufficiently supported with age appropriate and adequately sized equipments and medications besides monitors while performing paediatric procedural sedation and the practitioner should be capable to rescue the child from a deeper level of sedation than that was intended. Equipments must include oxygen, suction, bag-mask ventilation device, intubation equipments. Necessary monitors to monitor saturation and heart rate should be available. Blood pressure monitoring should be available except in situations where this may itself interfere with the sedation and thus the procedure. Sedation by non-anaesthesiologists is safe if all the measures are followed.(41)(49)

8.3. Fasting status:

The duration of pre-procedural fasting guidelines is controversial. According to the ASA guidelines, the child to be sedated should be kept nil orally for 6 hours before the procedure

for infant formula or a light meal, 4 hours for breast milk and 2 hours for clear liquids. As it is not always feasible to maintain strict fasting guidelines when it comes to children, the practitioner administering the sedation should take this into consideration and be prepared to rescue the child in the unforeseen circumstances.

8.4. Discharge criteria:

After procedural sedation, children should be monitored till they are awake up to their baseline mental status and are ambulatory. The parents must be educated on the discharge instructions at discharge, emphasizing on the possible complications like respiratory distress. They should not participate in activities requiring coordination for 24 hours and should not swim unattended for 8 hours.

9. Pharmacology for paediatric procedural sedation:

There is a wide range of pharmacological drugs used for paediatric procedural sedation including Opioids, Benzodiazepines, and Barbiturates, sedative- hypnotic agents, and other induction hypnotic agents like propofol, ketamine, and nitrous oxide. The choice of drug depends on the type of procedure, patient status and age, the targeted depth of sedation, co-morbidities if any associated. Procedures which are not painful warrant only sedation and not analgesia. ABR is a non-invasive procedure which mandates procedural sedation in children.

9.1. History of sedative agents:

The evolution of sedative drugs began when the Sumerians introduced fermented beverages in 9000BC. Besides, ether and nitrous oxide, the 19th century marked the beginning of the

modern age of sedative medications with bromides and chloral hydrate. As Bromides could not be manufactured into elegant pharmaceutical products, the impurities added along resulted in much unwanted side effect profiles. It was the German chemist, Justus Von Liebig, in 1832, synthesized Chloral hydrate which denoted the first class of sedative drugs to extend longevity. It is a CNS depressant with rapid onset of action approximately 30 minutes. Soon, it was combined with alcohol to bring out the best of the cocktail preparations.

9.2. Barbiturates:

The early twentieth century popularized many of the sleeping pills, the most popular among them being the Barbiturates. Invented by the Prussian chemist, Adolf Von Beyer, Barbiturates are an excellent sedative and sleeping aid and a myriad of derivatives emerged in the 1920s and 1930s by many of the American and European pharmaceuticals. These effective sleeping pills were not without side effects, especially, their addictive behaviour, unpleasant side effects and the exaggerated CNS depressant activity when combined with the other similar drugs or with alcohol causing significant respiratory depression. This narrow safety margin prompted the budding of safer and newer sedative – hypnotic in the following decades.

9.3. Chloral hydrate:

Chloral hydrate is a non-opioid, non-barbiturate sedative-hypnotic drug used since many years. Chloral hydrate, first synthesized in 1832 by Leibig is known to be one of the oldest and synthetic sedatives, brought into use since 1869 (50). Although it faced a decline from

the end of the 19th century to the middle of the 20th century, it was used principally as a paediatric sedative agent for many of the dental and diagnostic procedures in the 1990's. Though chloral hydrate is a CNS depressant, the actual mechanism of action is not known. Butler in 1948 discovered the principal active metabolite, Trichloroethanol besides the trichloroacetic acid, both of which were formed by the erythrocytes and hepatocytes. The sedative effect is attributed to chloral hydrate while the hypnotic effect to the metabolite, trichloroethanol. It is available in the oral and rectal forms. The drug was rapidly absorbed in the gastrointestinal tract with a high lipophilicity. The sedative and hypnotic effect was brought out in 20 to 60 minutes. It had a short half-life within a few minutes while the half-lives of the metabolites are longer, 8 to 12 hours for trichloroethanol and nearly 67 hours for trichloroacetic acid. It is eliminated principally by the kidneys. It shows a wide range of interactions with many drugs like, alcohol, anticoagulants, amitriptyline, and furosemide. It has been showed that Flumazenil, a GABA antagonist has been used in cases of intoxication which indicates a possible GABA mediated action. The usual dosing is between 0.5 to 2gm per day and is taken during meals to prevent gastric irritation. The chief side effects are due to its CNS depressant and arrhythmogenic potential. The adverse effects range from digestive, cardiac (risk of dysrrhythmias due to myocardial sensitization of catecholamines by trichloroethanol), dermatologic, neuropsychiatric like withdrawal reactions, delusion, hallucinations, dependence and ophthalmologic reactions. Intoxication with death occurs after absorption of doses of around 10 gm of chloral hydrate, some cases reporting even with 5gms. There are reports on genotoxicity and carcinogenicity reported in the literature. It crosses the placenta and enters breast milk. Some of the studies say that chloral hydrate can be used as a paediatric sedative only once in a lifetime.

Use is contraindicated in cases of gastric ulcers, hepatic and respiratory insufficiency, porphyria, known hypersensitivity.

9.4. Benzodiazepines:

Benzodiazepine group of drugs with its newer derivatives are the commonly used medications for sedation & anxiolysis. The core chemical structure shows a fusion of benzene ring and a diazepine ring.

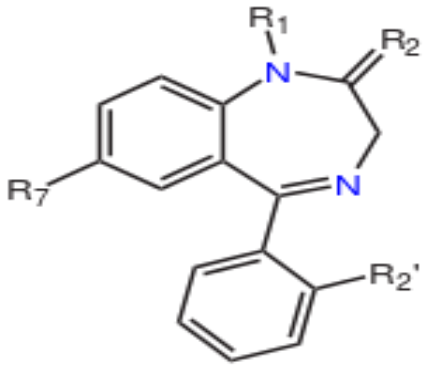


Fig.9: The core structure of Benzodiazepines.

The label "R" denotes common locations of side chains that give different benzodiazepines their unique properties.

Chlordiazepoxide, the first benzodiazepine was discovered accidentally in 1955 by Leo Stembach when working for the Hoffman-LaRoche company. Since then, it gained wide popularity and gained attraction especially for its enviable safety profile when compared to the other class of drugs. More than 15 different types of benzodiazepines exist today for various indications.

Their specific action on the central nervous system is exhibited by promoting the binding of the inhibitory neurotransmitter GABA (gamma amino butyric acid) to the Benzodiazepine receptors on the $GABA_A$ subtype of the GABA receptors. These receptors are multiple subunit complexes and are closely related with chloride gated ion channels within the neuronal cell membrane. When the receptor is activated, it causes opening of the chloride ion channel facilitating greater chloride ions influx besides a more negative (RMP) resting membrane potential that results in the neuron being less responsive to excitatory stimuli.(47) As the benzodiazepines do not cause direct opening of the chloride channels, but bind to specific BZD receptors on the $GABA_A$ complex which is separate from the actual receptor for the GABA, it only enhances the chloride ion channels response to GABA and in the absence of GABA, there is no effect produced. A benzodiazepine agonist can only cause potentiation of the body's endogenous neurotransmitter which explains the relative safety profile of benzodiazepines. The wide therapeutic index of benzodiazepines is explained. The effective-dose (ED_{50}) curve and lethal dose (LD_{50}) curve shows a very wide margin, such that the very large doses required for 'hypo-responders' are less likely to cross the brain barrier.

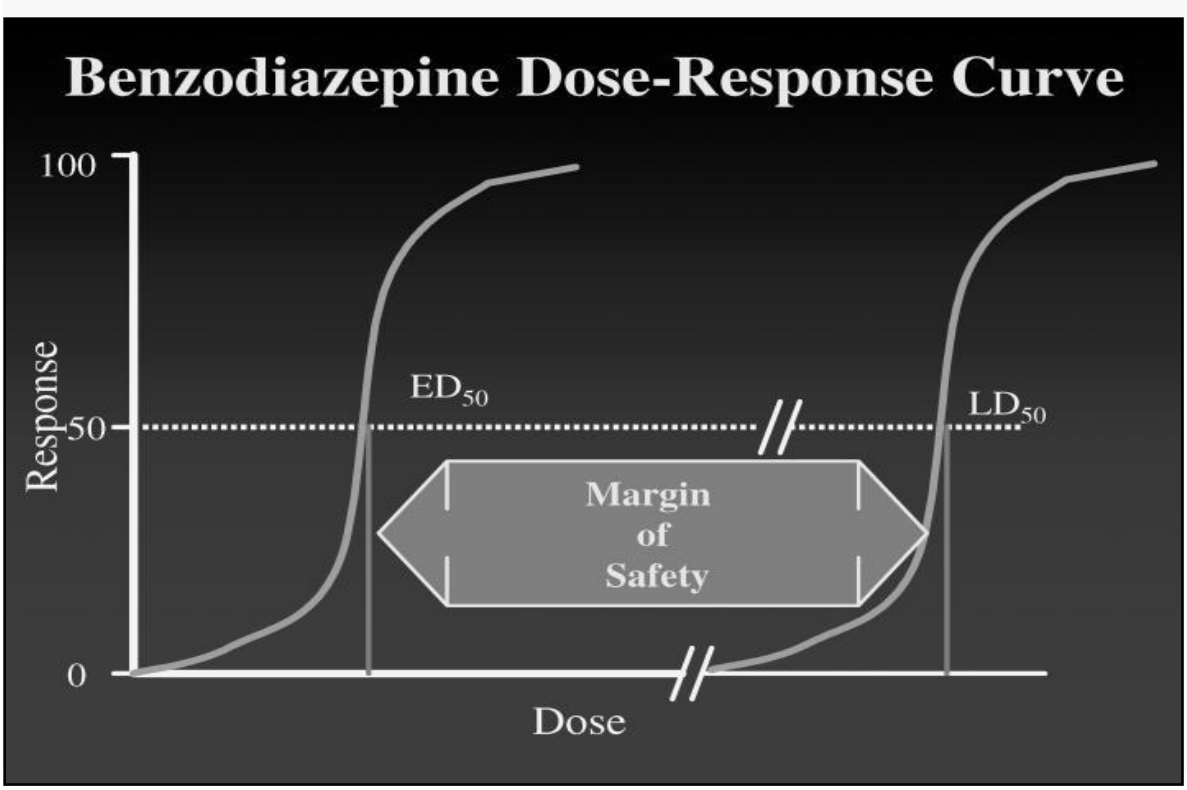


Fig. 10: Benzodiazepine dose response curve.

Almost all of the drugs belonging to this class show a similar sedative and safety profile with minor differences in the duration and onset of clinical effects among individual drugs. They are known for their various actions including sedation, hypnosis, anxiolysis, muscle – relaxant, anterograde amnesia and anticonvulsant actions.(51) Diazepam is the prototype of the benzodiazepines and Lorazepam is considered as an intermediate acting one. The next in the group is midazolam. Midazolam belongs to the short acting group and is the most common drug considered suitable for paediatric procedures in view of its rapid onset of action, short elimination half-life, its anaesthetic sparing effect and rare occurrence of serious side effects. This facilitates faster recovery process and thus preferred for ambulatory, day procedures.

9.5. Midazolam

Midazolam is a 1, 4, imido-benzodiazepine with unique chemical structure and physical properties. It was developed in the 1970s by Hoffman-La Roche and has emerged as one of the effective and rapid-onset and short-acting benzodiazepines. The salts of Midazolam are water soluble and are stable in aqueous solution. The oral bio-availability is 35 to 44 % and it has a rapid onset of action within 15 to 30 minutes to show a peak plasma levels within 20 – 50 minutes. The drug is water soluble (pH less than 4) in the commercially prepared formulation but becomes lipid soluble (pH more than 4) at physiological pH, in the form of diazepine closed ring form, when it crosses the blood brain barrier to exert its clinical effect contributing to the rapid onset of action. It is metabolized in the liver by the enzyme human cytochrome p450 (CYP3A4) system to its pharmacologically active metabolite alpha-hydroxyl midazolam and 4- hydroxyl midazolam. It is extensively protein bound and the half life ranges from 0.8 to 1.8 hours. It is excreted primarily by the kidney.(52) It is routinely dosed at 0.2 to 0.5 mg/kg.(53)

The various routes of administration have been studied extensively and include intravenous, intramuscular, sublingual, buccal, rectal, oral and intranasal.(54) Because in children of aversion to needles, oral, rectal, sublingual and nasal routes seem reasonable besides avoiding the risk of needle stick injuries.(55) The unpleasant bitter taste may not be liked by children and the extensive first pass metabolism may reduce the bioavailability of this drug when administered orally and thus may require administration of large doses which may not be without adverse effects.(56)(57) Sublingual route may be beneficial in this regard but difficulty in achieving the child's cooperation in keeping the drug under the tongue for at

least thirty seconds for desirable efficacy of the drug pose problem.(58) Rectal route may bypass this effect but may be result in unpredictable absorption rates besides adding discomfort to the child and being embarrassing especially in older children.(59) Thus disadvantages of these routes include painful injection, slow onset, unpredictable and delayed recovery. These effects can be overcome by the intranasal route of drug administration. The high nasal mucosal vasculature offers intranasal route in the faster and complete absorption of the drug into the systemic circulation. The ease of administration, avoidance of needle injuries and high predictability have made this route of administration popular.(60)

Intranasal Midazolam has been known to be in use for over a decade in providing paediatric procedural sedation in various divisions of health care. Dental procedures like tooth extractions, paediatric emergency room procedures like repair of nasal lacerations, orthopaedic reduction of fractures, oral and maxillofacial trauma, ophthalmological procedures like fundus examinations and nasolacrimal duct repair, peripheral line and central venous cannulations, diagnostic upper GI endoscopies, imaging like CT, MRI, paediatric burn patients, electroencephalogram and echocardiogram are some of the areas of its application.(61–79) The dosing ranges from 0.2 to 0.5 mg/kg for the intranasal formulation.(80) The side effect profile has been reported from common events like sneezing, lacrimation, stinging of mucosa and hiccups at the time of nasal spray.(80,81) This is mainly due to the preservative contained in the intranasal formulation of Midazolam. As with any other drug, hypersensitivity reactions are known to occur. Children sometimes exhibit paradoxical emergence reactions like disinhibitions, agitation, restlessness and hallucination. Infrequently, dose-related adverse effects are reported which include prolonged sedation, seizures, respiratory depression, hypoxia, desaturation that require

transient administration of oxygen and rarely cardio-respiratory arrest requiring mechanical ventilation.(82–84) Thus continuous monitoring becomes essential which avoids such serious mishaps that can be picked up early and managed appropriately. The antidote to overdose exists in the form of Flumazenil which reverses the effects at the receptor level.(85)(86) It has been observed from studies that Midazolam when administered alone is found safe and the mentioned serious effects are commonly found when administered in combination with Opioids.

Thus, in this regard, we propose to study the efficacy and safety profile of Midazolam nasal spray for paediatric procedural sedation for auditory brainstem evoked response audiometry and compare it with the standard drug used for ABR, syrup chloral hydrate.

Materials and methods

Design:

It was a prospective, randomized, double-blinded, placebo controlled trial.

Setting:

The study was conducted in a tertiary care hospital. It is a 2, 600 bedded hospital which caters to nearly 1, 20, 000 inpatients and 1.9 million outpatients annually with 45 births, 125 operations and nearly 25, 635 various laboratory tests carried out each day. The Department of ENT caters to nearly 35 to 40 % of the paediatric age group. Nearly 15 to 20 children per week undergo Auditory Brainstem evoked Response audiometry (ABR) in the department. The audiology room in the Department of ENT was equipped with appropriate emergency resuscitation requirements.

Recruitment of patients:

The patients for the study were recruited from the Department of ENT. Parents or care givers of patients who were referred for Auditory Brainstem evoked Response audiometry (ABR) for hearing loss were invited to participate in the study. The study was conducted from January 2012 till June 2013. 82 patients were recruited according to the statistical requirement and the inclusion, exclusion criteria.

Institutional Review board:

The study was approved by the Institutional Review board and the Ethics committee. The research funding was obtained from the fluid research grant of the institution.

Inclusion criteria:

All children in the age group of 1 to 6 years referred for ABR irrespective of their developmental maturity.

Exclusion Criteria:

1. Refusal for the procedure
2. Hypersensitivity to Midazolam
3. Nasal allergy
4. Obesity with a body mass index more than or equal to 30
5. ASA grade more than 2

Medications used:

Syrup Chloral hydrate (gold standard) is routinely used in our department to induce paediatric sedation at a dosage of 50 mg/kg. It is manufactured as syrup Triclofos sodium by the American Remedies Limited (100 mg/ml bottle, available in 5 ml and 30 ml). It is

repeated twice if the expected level of sedation is not achieved. The second dose is repeated at half the dosage and the maximum dose that can be attained is 100 mg/kg.

The interventional drug was Midazolam nasal spray (Samarth Pharma Pvt. Ltd, Mumbai), available as INSED Atomiser with 50 MD - 0.5 mg per metered dose. The number of sprays required for a dose of 0.5 mg/kg was calculated and administered. In case of second dosing, it was calculated at half the dose and administered as spray.

Placebos were prepared for both the preparation.

The Department of Pharmacy at the hospital provided the placebos for syrup Triclofos. The manufacturers of Midazolam nasal spray (INSED atomizer), the Mumbai based Samarth Pharma Pvt. Ltd. provided the placebo nasal spray. The placebo was packaged as INSED nasal spray, 0.5 mg x 1 puff x 50 md (metered doses) and was prepared in such a way that the composition and the preservative remained the same except the active drug.

The active drugs, both Midazolam nasal spray and syrup Triclofos were purchased from the pharmacy using the fluid grants fund. The Midazolam placebos were sent by the manufacturers and Chloral hydrate placebos were prepared by our pharmacy. The drugs and the placebos were packeted according to the randomization codes.

Method of randomization:

Block randomization with a block size of 2, 4 and 6 with 25%, 25% and 50% respectively was used. Computer automated generated codes were produced using SAS.9.1. A copy of the generated randomized codes was archived at the department of Biostatistics. One copy was

sent to the Department of Pharmacy to prepare identical drugs as per the randomization which was serially numbered with a marking of A and B.

Method of allocation concealment:

According to the computer generated randomized codes, opaque envelopes were prepared which were serially numbered and bound. Codes were broken after the analysis is over with the IRB permission letter.

Blinding and Masking:

Double blinding was done. Placebo was made for both Midazolam spray as well as for syrup Chloral hydrate so that every child who was randomized received both the spray and the syrup such that the chance of receiving the actual drug was one in two or fifty percent. This way, the patient and the doctor who administered the drugs were both blinded. The drugs were packeted by the pharmacist and were named drug A and B. It was made sure that the child received only one of the active ingredients at any time, either the standard practice or the interventional drug by either of the routes and the other route remained a placebo. This was done to bring out the actual efficacy and comparison between the two drugs.

Primary outcome:

1. Safety during the proposed procedure.

This is measured by assessing the below physiological parameters and intervention begins when

a. Oxygen saturation (SpO2 below 90%)

b. Respiratory rate (RR below 10)

c. Heart rate (HR below 60)

2. Efficacy during the proposed procedure.

This is measured by

- Satisfactory sedation in terms of completion of the procedure.

- Level of consciousness – sleep and movement (lack of response or purposeful movement to verbal or tactile stimuli)

Secondary outcomes:

1. Time for parental separation – the time that the child allows to be separated from the mother from the time the drug is given.

2. Nature of separation from parents – on a scale of 1 to 4

Awake and crying 1

Awake and Calm 2

Drowsy 3

Sleepy 4

3. Time taken for onset of sedation – the time of administration of the drugs to the time the child allows the electrodes to be placed.

4. Duration of procedure – time when electrodes are placed to removal of electrodes

5. Time taken for recovery – time from completion of procedure to time when child wakes up to pre-procedure level of consciousness

6. Post recovery behaviour – on a scale of 1 to 4

Irritated: awake, restless, crying 1

Normal: awake, calm 2

Inactive: tired, hardly moving 3

Sleepy: drowsy, without reaction, but arousable 4

7. Acceptance by parents – satisfied / dissatisfied

8. Audiologists satisfaction – on a scale of 1 to 3

Poor – procedure aborted	1
Fair - procedure interrupted, but completed	2
Good- procedure performed without any interruption	3

9. Number of attempts

The paediatric procedure sedation form and the scoring scales for various parameters are included in the annexure.

Target sample size and rationale:

Two means – Hypothesis testing for two means (equal variances) was used based on the primary outcome – duration of sedation. From literature, we found that the difference in means for the two different interventions was as follows,

Standard deviation in group I	= 26.8
Standard deviation in group II	= 29.4
Mean difference	= 24.1
Effect size	= 0.85
Alpha error (%)	= 1

Power (%)	= 90
Sided	= 2
Required sample size per group	= 41

Thus we proposed to recruit 41 patients in each arm to study statistically significant results which accounted for 82 patients to be studied.

Statistical analysis:

Descriptive statistics were generated for all the samples. Chi-square test was used to analyze the descriptive variables with Pearson test and Fisher's exact test to study the statistical significance. Student t-test for equality of means was used to study the difference in means of the quantitative parameters. Kaplan Myer model was used to test the association between time of onset of sedation and time to recovery and compared the effect of developmental maturity on the same. Statistical significance was based on 2-sided tests with a probability value p of 0.05. The results were computed using SPSS.

Procedure:

Parents or care givers of children referred for BERA were invited to take part in the trial. If they were willing to participate in the study and they met the inclusion and exclusion criteria they were recruited into the study. They were given the patient information sheet in their respective languages which included the need for paediatric sedation, the drugs used, and the double-blinded nature of the trial, the nature of the sedation and the procedure, the risks

associated the contact details in case of queries. They were verbally explained about the fasting status and the escort policy post procedure which was advised according to the American Society of Anaesthesiologists guidelines. They were also advised to come half an hour prior to the scheduled time of the procedure for pre-procedure evaluation.

On the day of the procedure, after discussing the risks and the benefits of the trial, if the parents were willing to allow their child to participate in the trial, an informed consent was obtained. A brief medical history and examination was done with the child seated on the mother's lap. This also included assessing the fasting status, recording the weight of the child, a brief systemic and airway examination. The vital parameters were also recorded at baseline including heart rate and oxygen saturation using a portable pulse ox meter (Model: ECPO – 250E, batch no. 012011, Easy Care group, Mumbai) attached to the child's big toe or thumb whichever the child allowed, respiratory rate by manually counting for one minute, level of consciousness – sleep and movement and developmental maturity. The Procedural sedation form was filled in as required.

After the initial pre-procedural evaluation, the child was randomized according to the computer generated allocation codes provided. The packets which were serially numbered and the opaque envelopes were opened for every child. Every packet contained one nasal spray and one syrup. The nasal spray could be Midazolam or the placebo at a dose of 0.5 mg/kg at a concentration of 100 mcg per spray divided between each nostril and the syrup could be Chloral hydrate or placebo at a dose of 50 mg/kg.

The allocation was done in such a way that at any time, the child was assured of only one of the drugs for sedation and the other route, remained a placebo. In this way, the child was not denied of the required sedation nor received both drugs together. Also, both the patient and the investigator were blinded so that the actual efficacy of the drugs brought out did not happen by chance and avoided any possible bias.

The child and the mother were taken to a 'quiet' room equivalent to a recovery room. The dose of the syrup was calculated according to the weight of the child and was given to the mother to administer to the child. Once the child swallowed the syrup, he / she were made to sit straight again on the mother's lap. The nasal spray was opened and after shaking, the first two sprays were pushed out in the air. Following this, it was introduced into the nasal vestibule of the child and the required calculated number of nasal sprays as per the weight of the child was sprayed equally between both the nostrils. Any agitated movement by the child during the spray was controlled by the mother and the drug administrator. Following this, the child was left with the mother and was monitored for the parameters. Once the child showed signs of parental separation, he / she were taken to the procedure room next to the recovery room and were placed on the procedure bed. If the child allowed placement of the electrodes on the scalp and the ear, the time was noted for onset of sedation. Throughout the entire procedure, the mother was made to sit inside the procedure room and the Doctor monitored the child for the vital parameters as mentioned and the behaviour of the child every 5 minutes as the audiologists carried on with the procedure in the standard way. Those children who did not sleep with the first dose of drugs were re-administered the drugs with half the original dose and again observed. If they did not sleep for almost one hour after the second dose, they were tagged, failed sedation. All children were evaluated till they attained the pre-drug administration vital signs and behaviour status.

During the procedure, any child whose oxygen saturation dropped below 90% was given a mild chin lift and a pillow under the shoulder if needed. Any movement interrupting the procedure or if the child woke up in between the procedure were noted down.

The child was observed throughout the procedure using non-invasive monitoring at regular intervals of 15 minutes till onset of sedation and every 5 minutes then on.

After completion of the procedure, the child was awakened and monitored in the recovery waiting area with the parents till he/she was back to pre-procedure level of normalcy. Once the child recovered, the parents were educated about the dietary advice, escort policy and the child was discharged as per discharge guidelines. Emergency resuscitation measures were available if required. The parents were provided with contact numbers to approach for medical help in case of adverse events after discharge.

Results

The study was completed with 41 children recruited in each arm. The results were analyzed using appropriate statistical methods and results tabulated.

All children in both arms were between the age group of 1 to 6 years with a mean age of 2 years. The mean weight in kilograms was 11.9 among those who received Midazolam and 12.4 in children who received chloral hydrate. Independent student t-test for equality of means was used which did not show any significant difference between the two groups and thus both arms were comparable.

Of the 82 children who participated in the study, 55 (67%) were males and 27 (33%) were females. Of the male children, 68.3% received Midazolam and 65.9% received chloral hydrate. While 31.7% and 34.1% were females among those who received midazolam and chloral hydrate. 58% and 65% of children were developmentally normal among those who received Chloral hydrate and Midazolam respectively as against 41% and 34 % of the developmentally delayed ones. Children for whom ABR was indicated were grouped primarily into 3 categories as hearing impaired, speech delayed and those who suffered both. Nearly 20% of children were hearing impaired in both the arms. 53% of children who received Chloral hydrate and 56 % of children who received Midazolam were speech delayed, while 26% and 24% respectively suffered both. Chi-square tests were used with Pearson test which did not show any statistical difference between the groups as can be seen from tables 1.1 and 1.2.

Comparable characteristics between the two groups:

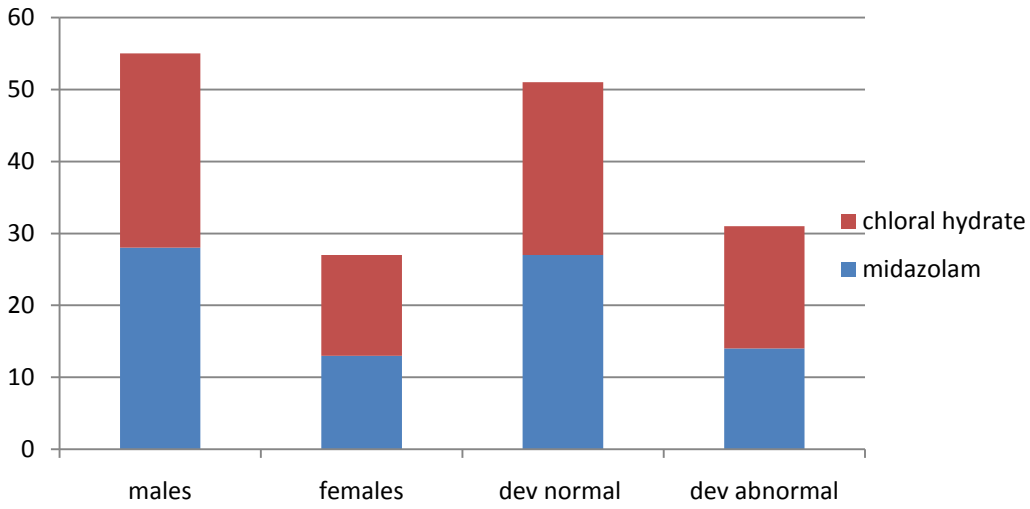
Table 1.1

Parameters		Midazolam (n = 41)		Chloral hydrate (n = 41)		p value
		Mean	SD	Mean	SD	
Age (in years)		2.66	1.527	2.78	1.33	0.701
Weight (in Kgs)		11.95	3.500	12.41	3.62	0.557
Baseline	Heart rate (in mins)	110.78	11.13	110.65	9.45	0.952
	Respiratory rate	25.95	3.01	25.71	2.54	0.698
	Oxygen saturation %	98.23	0.85	98.29	1.01	0.791

Table 1.2

Parameters	Midazolam (n = 41)		Chloral hydrate (n = 41)		Total (n=82)		p value
	n	%	n	%	n	%	
Males Females	28 13	68.3 31.7	27 14	65.9 34.1	55 27	67.1 32.9	0.814
Development Normal Abnormal	27 14	65.9 34.1	24 17	58.5 41.5	51 31	62.2 37.8	0.494
Hearing impaired Speech delay Hearing & speech impaired	08 23 10	19.5 56.1 24.4	08 22 11	19.5 53.7 26.8	16 45 21	19.5 54.9 25.6	0.966

Fig. 1: Graph - comparing the baseline characteristics.



1. Primary outcome – a. safety:

The primary outcome being safety was measured in terms of the physiological parameters such as heart rate, respiratory rate and oxygen saturation and both groups did not show any statistically significant difference. Heart rate less than 60 beats per minute, respiratory rate below 10 and oxygen saturation below 90% were considered not safe. There were no significant adverse effects noted. Both drugs were observed to be safe at all time intervals pre-sedation and post- sedation till recovery.

At baseline, both the groups had comparable readings of these parameters as shown in table 2.1. The mean and standard deviation of these parameters pre-sedation and post sedation for individual drug groups and comparative statistics are tabulated. Both were found safe.

Table 2.1

Pre - sedation	Midazolam group (Mean ± SD)		Chloral hydrate group (Mean ± SD)		p value
Heart rate (bpm)	110.78	11.125	110.65	9.453	0.952
Respiratory rate	25.95	3.006	25.71	2.538	0.698
Oxygen saturation %	98.23	0.848	98.29	1.009	0.791

Table 2.2

Post - sedation	Midazolam group		Chloral hydrate group		p value
	Mean	**SD**	**Mean**	**SD**	
Heart rate (bpm)	102.18	9.83	102.98	8.60	0.748
Respiratory rate	23.93	1.85	24.71	2.49	0.218
Oxygen saturation %	97.47	1.31	97.31	1.27	0.655

The parameters were checked pre-sedation at intervals of 15 minutes and at 5 minutes intervals post sedation. There were two episodes in the same child who had a transient oxygen de-saturation to 89% which improved promptly with mild chin lift and position adjustment of the child. This did not require any airway manipulation or invasive methods.

The child belonged to the Midazolam group (1 of 39 children who slept, i.e., 2.6%) and this effect was seen at 10 minutes and 25 minutes post sedation. p value was found to be 1.00 and thus was not significant. The remaining parameters were found to be within normal limits throughout the procedure and till recovery. Thus both the drug groups were found to be safe at all levels.

1. Primary outcome – b. efficacy:

The other primary outcome is efficacy which is measured in terms of

- Satisfactory completion of the procedure and
- Level of consciousness in terms of sleep and lack of movement during the procedure.

Table 3

Overall outcome	Midazolam		Chloral hydrate		Total		p value
	n	%	n	%	n	%	
Successful sedation	21	51.21	38	95.12	59	72.0	< 0.01
Failed	20	48.8	03	04.9	23	28.0	
Total	41	100	41	100	82	100	

The numbers of children who were successfully sedated overall and lead to the completion of the procedure in the Midazolam group were 21 and in the Chloral hydrate group were 38.

This was found to be statistically significant.

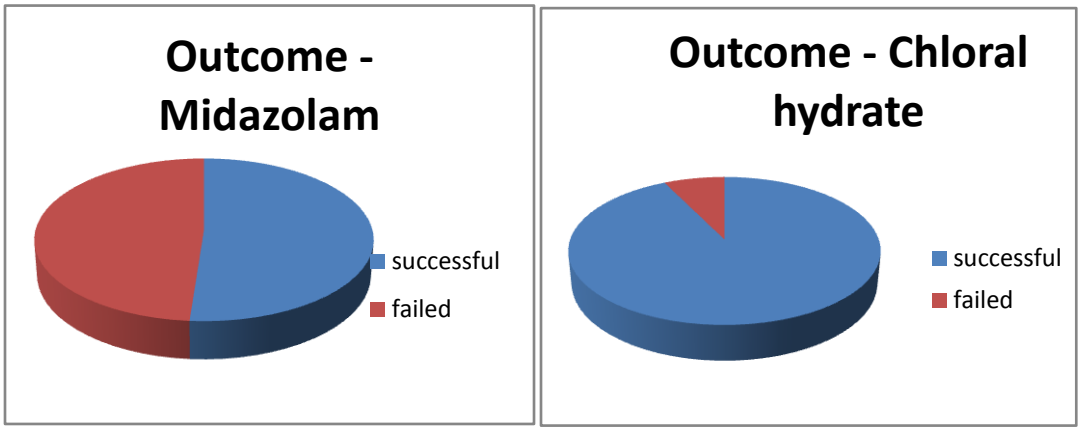


Fig. 2: Diagram comparing the outcome between Midazolam and Choral hydrate

Following the onset of sedation, it was observed that children in both the arms slept throughout the procedure and there was no statistically significant difference in terms of interrupted sleep to abort the procedure.

While considering movement, the first 3 categories in the scoring scale were combined as 'movement' and the score 4 remained as 'no movement'. It was observed that, following onset of sedation, in both the groups, children achieved a score of 4 during intra-procedure and did not show any lesser scores to interrupt with the procedure.

2. Secondary outcomes:

2a. Onset of sedation:

Among those children (41 in each arm) who were given the drugs, at the end of 30 minutes, it was observed that 7 children among the Midazolam group and 26 children among the Chloral hydrate group had slept. This was statistically significant

In other words, 7 (33.3%) children among those who were sedated in the Midazolam group and 26 (63.41%) of those in the Chloral hydrate group showed onset of sedation at 30 minutes or earlier.

Table 4.1

Onset of sedation	**Midazolam n (%)**	**Chloral hydrate n (%)**	**p value**
<= 30minutes **>30minutes**	07 (33.3) 14 (66.7)	26 (66.7) 12 (33.3)	0.017
Total sedated	21 / 41 (51.21)	38 / 41 (95.12)	

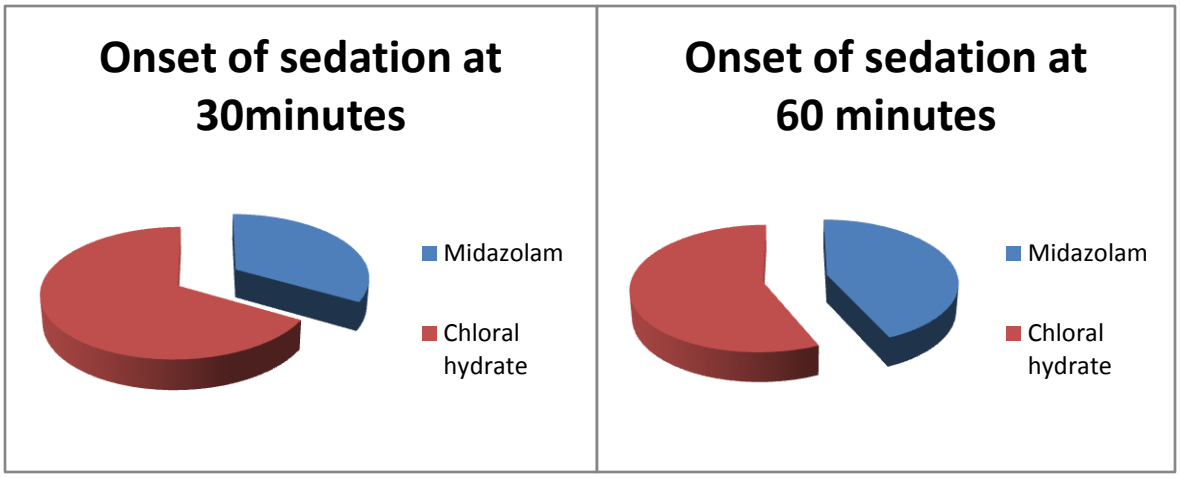


Fig. 3: Comparison between Midazolam and Chloral hydrate for onset of sedation at 30 and 60 minutes.

14 (66.7 %) children out of the 21 who slept overall among the Midazolam group and 34 (87.2 %) children out of the 38 who slept among the CH group had onset of sedation at 60 minutes. But statistically, this did not show any significance as shown in table 4.2.

Table 4.2

Onset of sedation	Midazolam n (%)	Chloral hydrate n (%)	p value
<= 60minutes **>60minutes**	14 (66.7) 07 (33.3)	34 (87.2) 04 (12.8)	0.09
Total	21 / 41 (51.21)	38 / 41 (95.12)	

At the end of 60 minutes, there was no statistical significance between the groups. It was noted that 33% among the Midazolam group and 12.8% among the chloral hydrate group had delayed onset of sedation later than 60 minutes as shown in table 4.2.

The figure below shows the results graphed by Kaplan Meyer's cumulative survival comparing onset of sedation between the two groups. It was found that children in drug group B, i.e., Chloral hydrate showed earlier onset of sedation than those in group A with Midazolam.

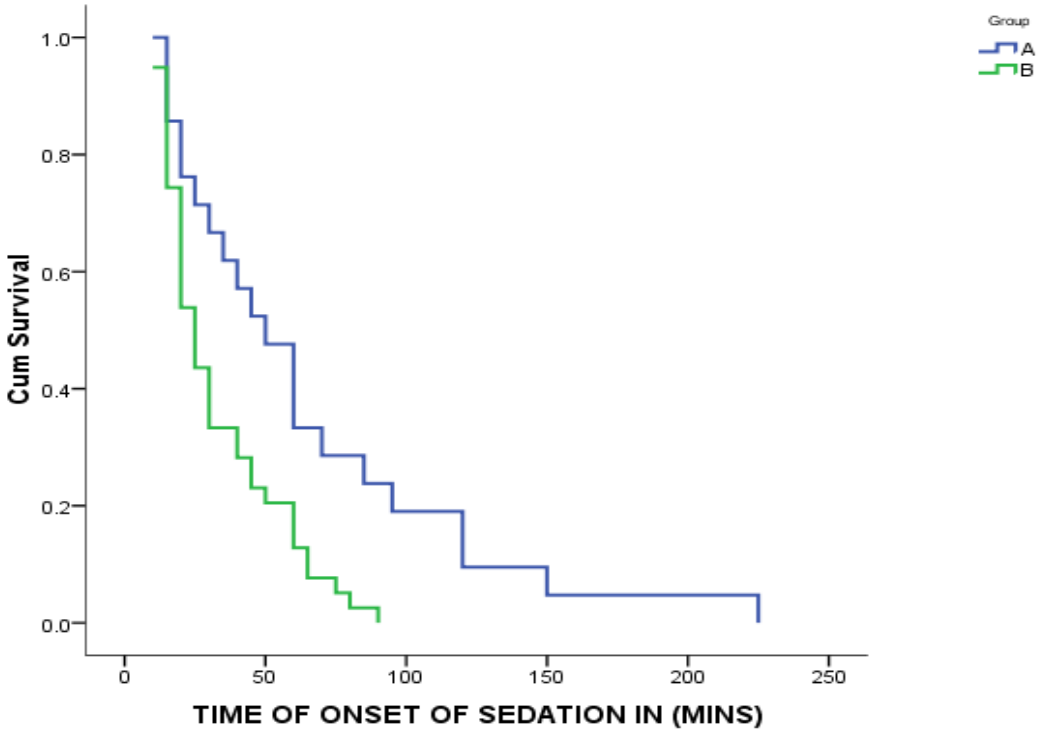


Fig. 4: Kaplan Meyer graph comparing Midazolam (A) and Chloral hydrate (B) for onset of sedation.

2a.1. Effect of developmental maturity on sedation:

Among the children who had slept, i.e., in 21 of 41 among the midazolam group and 38 of 41 among the chloral hydrate group, the developmental maturity was compared as an affecting factor.

Table 5.1

Developmental maturity	Midazolam		Chloral hydrate		Total recruited		p value
	n	%	n	%	n	%	
Normal Abnormal	27 14	65.9 34.1	24 17	58.5 41.5	51 31	62.2 37.8	0.494
Total recruited	41		41		82		

It was seen that among children who received sedation with both the regimes, more than half were developmentally normal. Among those children who slept, a significant difference was found between developmentally normal and the delayed children between the two groups.

Table 5.2

Developmental maturity	Midazolam n (%)	Chloral hydrate n (%)	Total	p value
Normal **Abnormal**	12 (57.14) 09 (42.85)	22 (53.65) 17 (41.46)	34 26	0.006
Total sedated	21 / 41 (51.21)	39 / 41 (95.12)	60 / 82	

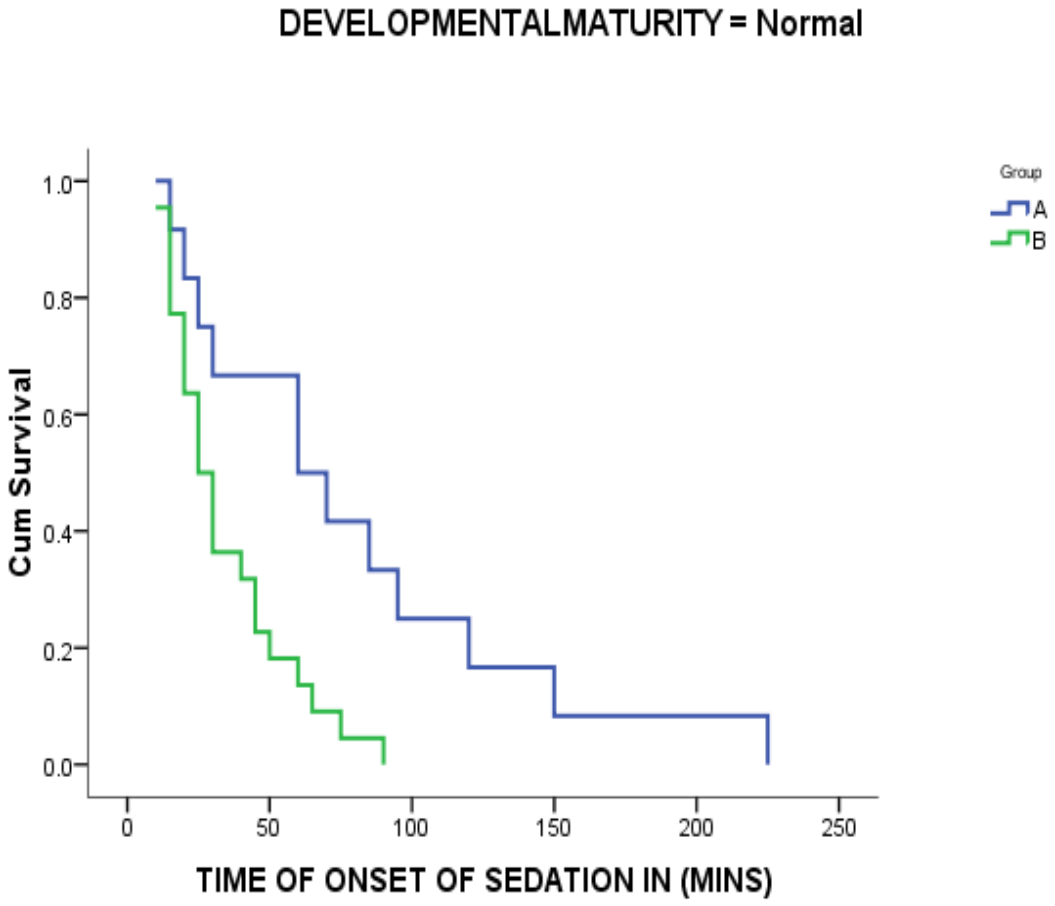


Fig.5: Kaplan Meyer graph comparing Midazolam (A) and Chloral hydrate(B) among developmental normal children for onset of sedation.

Children in Midazolam group (A in figure) and who were developmentally normal still took a longer time for onset of sedation when compared to similar children in the CH (B in figure) group. Likewise, similar results were obtained between the two groups among developmentally delayed children. p value was found to be 0.012.

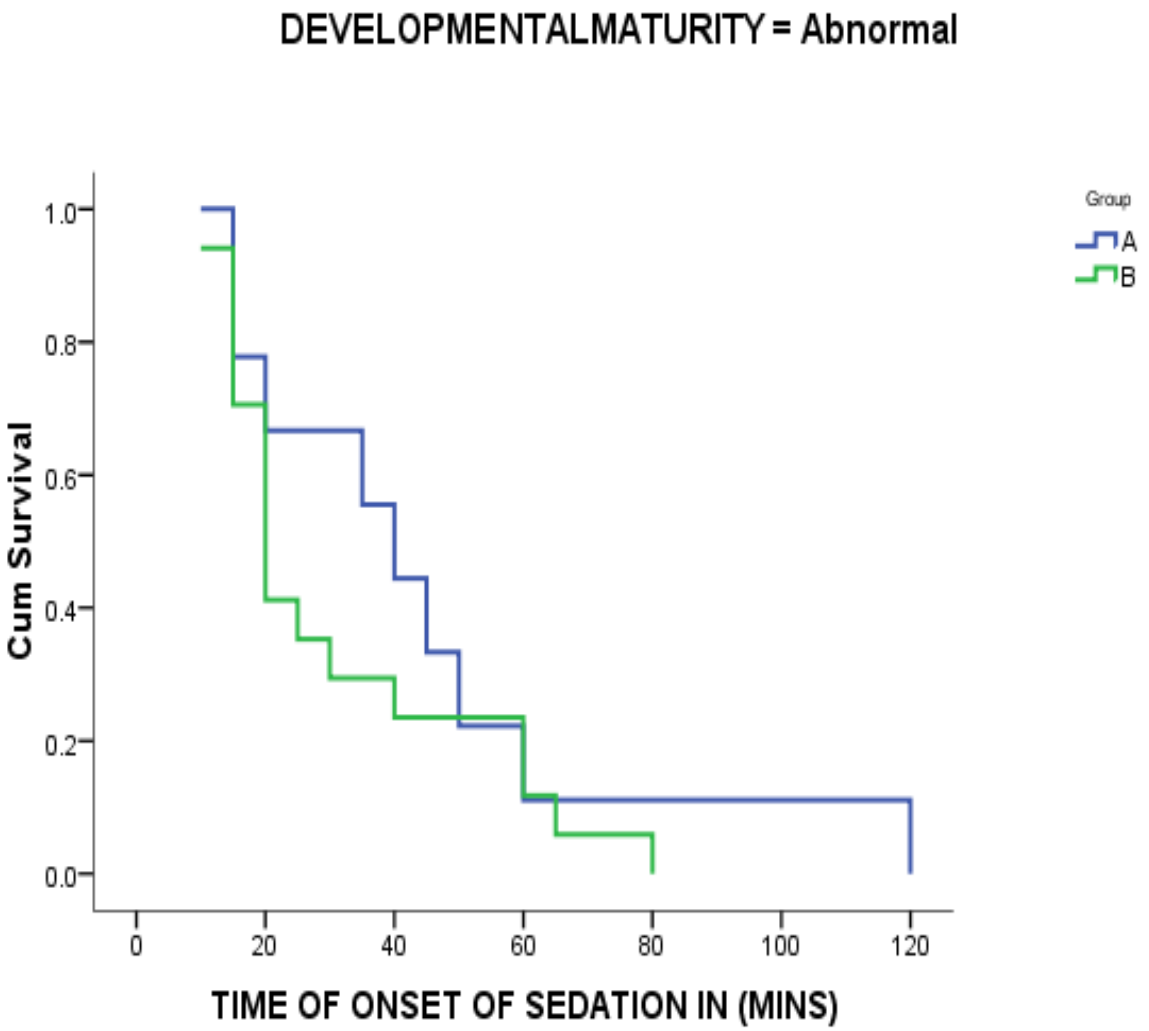


Fig.6: Kaplan Meyer graph comparing Midazolam (A) and Chloral hydrate (B) among developmentally abnormal for onset of sedation.

Table 5.3

Developmental maturity	Median for time to onset of sedation in minutes		p value
	Estimate	Standard error	
Normal	30.00	8.731	0.116
Abnormal	20.00	4.780	

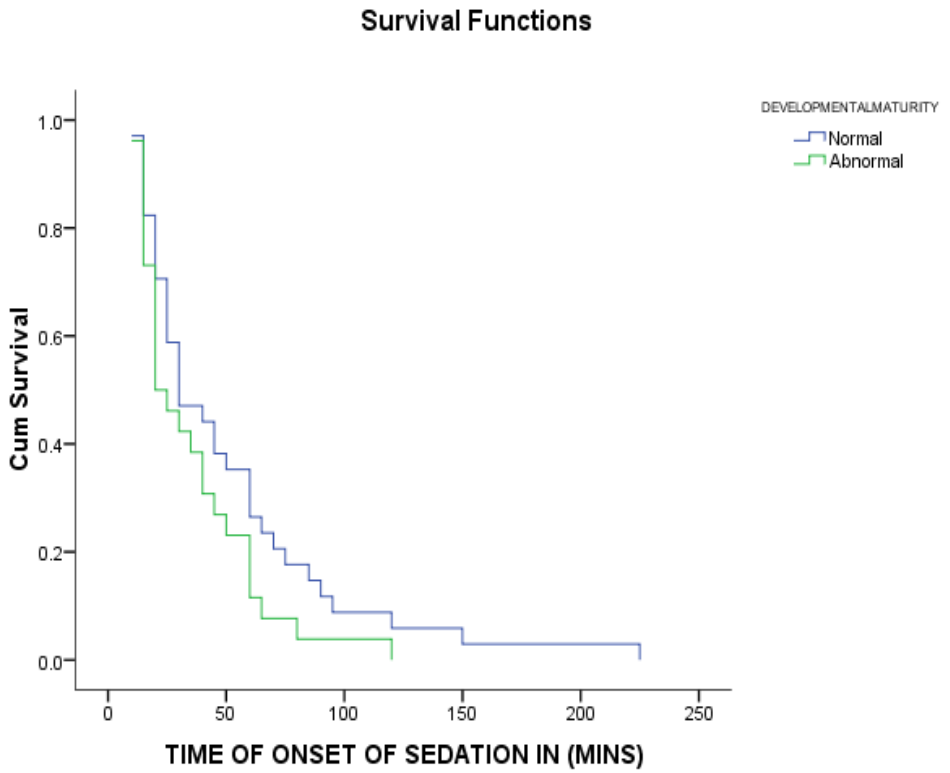


Fig.7: Kaplan Meyer graph comparing developmental normal (A) and developmental abnormal (B) children for onset of sedation.

On the whole, developmental delayed children showed an earlier time to onset of sedation when compared to developmental normal children, but the difference was not statistically significant.

2b. Time for parental separation:

Time taken for children to be separated from their parents following drug administration was found to be significantly different at the end of 30 minutes between the groups.

Table 8

Time for parental separation	Midazolam n (%)	Chloral hydrate n (%)	p value
<= 30minutes **>30minutes**	12 (52.2) 11 (47.8)	30 (71.4) 09 (23.1)	0.05
Total	23 / 41 (56.09%)	39 / 41 (95.12%)	

23 and 39 children in each arm allowed parental separation of which 71 % of the children among the Chloral hydrate group allowed themselves to be separated from their parents while only 52 % among the Midazolam group could be separated at the end of 30 minutes.

Thus, on the whole, children who received Chloral hydrate showed earlier parental separation with onset of sedation compared to those who received Midazolam which was statistically significant.

Table 9

	Midazolam Median(IQR)	Chloral hydrate Median(IQR)	p value
Time of parental Separation (minutes)	0.30(0.15,0.60)	0.20(0.15,0.30)	0.009
Time of onset of sedation (minutes)	0.50(0.23,1.30)	0.25(0.15,0.45)	0.013

The results for the above table were computed using Mann-Whitney test and the percentiles calculated as above. Children in Midazolam group took 30 minutes and 50 minutes as against 20 minutes and 25 minutes in chloral hydrate for parental separation and onset of sedation respectively.

2c. <u>Nature of parental separation:</u>

The nature of parental separation was scored on a scale of 1 to 4. The first 3 were clubbed together as one group versus the last score 4 kept as 'sleepy' group. There was no statistically significant difference in the nature of parental separation among these children between the two groups.

2d. <u>Time to recovery</u>:

There was significant difference in the time to recovery with children in the Midazolam group showing delayed recovery than their counterparts. The effect of developmental maturity on time to recovery was also studied.

<u>Table 10:</u>

Time to recovery n (%)		**p value**
Normal **Delayed**	34 (57.14) 26 (42.85)	0.112
Total sedated	60 (51.21) / 82	

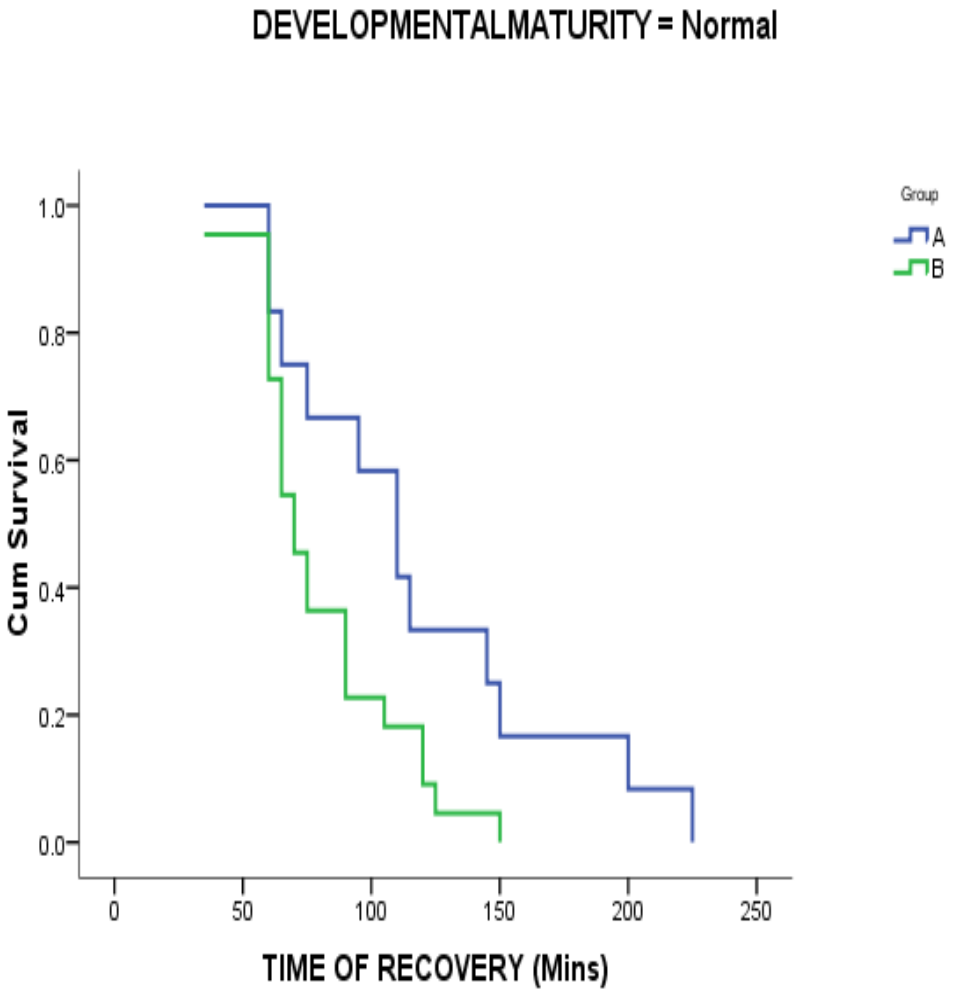


Fig.8: Kaplan Meyer graph comparing Midazolam (A) with Chloral hydrate (B) among developmentally normal children for time of recovery.

Children with normal development who received chloral hydrate recovered earlier than those who received Midazolam.

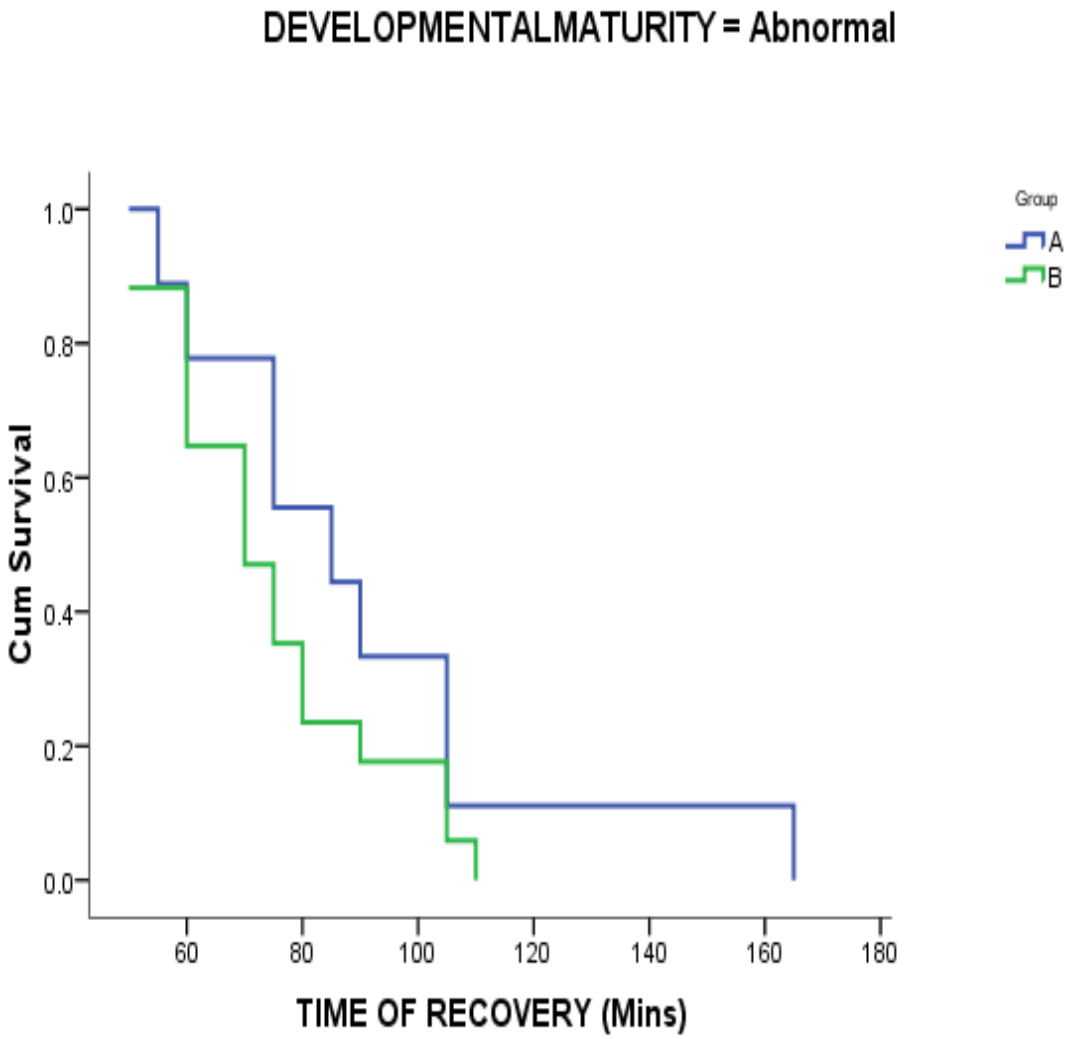


Fig.9: Kaplan Meyer graph comparing Midazolam (A) with Chloral hydrate (B) among developmentally abnormal children for time of recovery.

It was also seen that in general, children who were developmentally abnormal required lesser time to recover than developmentally normal children as shown in the graph below:

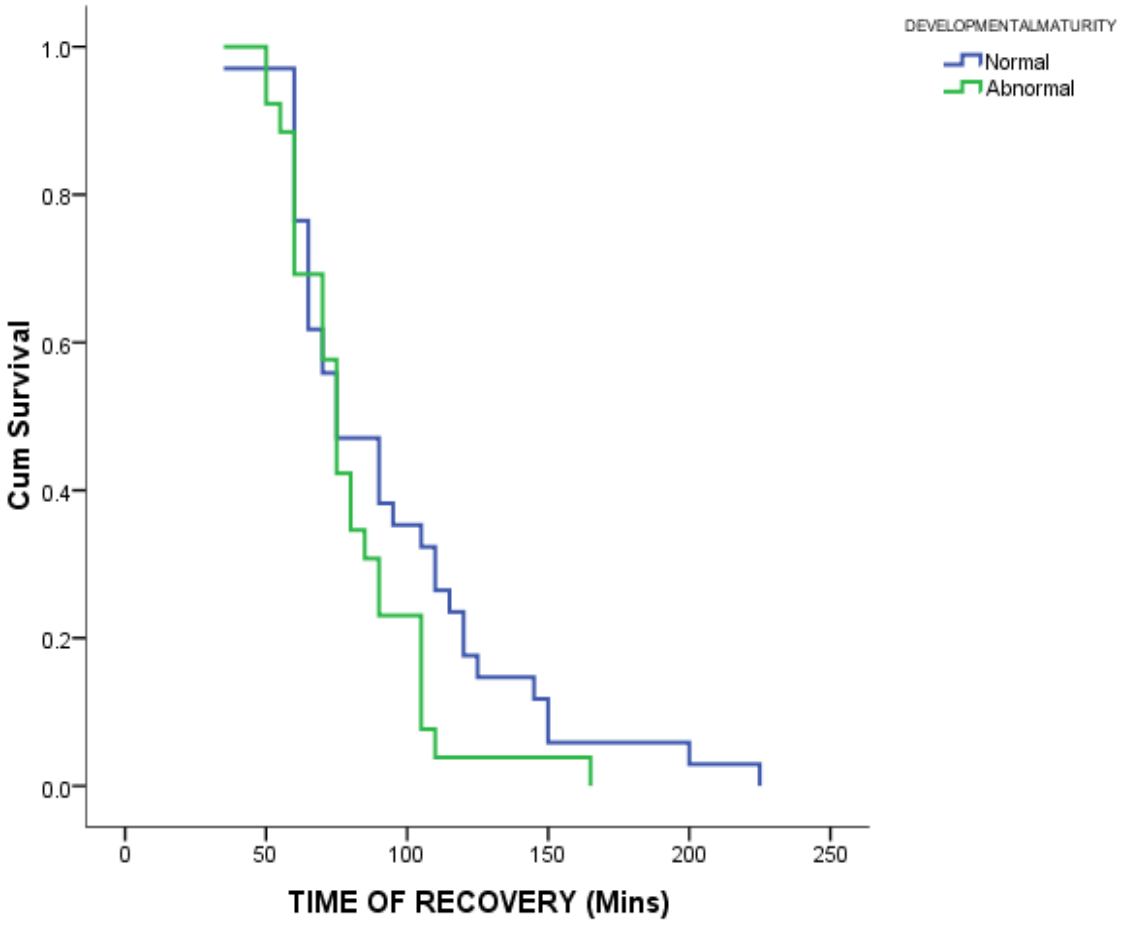


Fig.10: Kaplan Meyer graph comparing developmental normal and developmental abnormal children for time of recovery.

But this was not found to be statistically significant.

2e. Duration of procedure

The duration of procedure was almost similar between the two groups.

Table 11

	Midazolam **Mean±SD**	**Chloral hydrate** **Mean±SD**	**p value**
Duration of procedure	0.27±0.07	0.30±0.08	0.210
Time to recovery	105.95±47.11	78.08±24.11	0.004

There was no statistically significant difference seen in the total duration the procedure was carried once children had attained sedation irrespective of whether they receiver Midazolam or Chloral hydrate.

2f. Audiologist satisfaction:

There was a statistically significant difference noted among the audiologist satisfaction. There was a 3 scale scoring system with poor /fair / good. The first two were grouped into one as ‘not satisfied’ versus ‘good’ as satisfied.

Table 12:

Audiologist satisfaction	**Midazolam n (%)**	**Chloral hydrate n (%)**
Satisfied **Not satisfied**	12 (29.3) 29 (70.7)	31 (75.6) 10 (24.4)
Total	41	41

It was found that audiologists were satisfied overall in 75 % of children who received Chloral hydrate as against only 29 % of children who received Midazolam as the remaining children either did not sleep or had interrupted movement.

2f. Parental satisfaction:

Similarly, 95% of those parents whose children received Chloral hydrate were satisfied compared to only 49 % of parents whose children were in the other group. This was found statistically significant.

Table 13:

Parental satisfaction	**Midazolam** n (%)	**Chloral hydrate** n (%)	**p value**
Satisfied Not satisfied	20 (48.8) 21 (51.2)	39 (95.1) 02 (4.9)	<0.01
Total	41	41	

2g. Number of attempts:

The number of attempts tried at drug administration was studied.

Table 14:

Number of attempts	**Midazolam** n (%)	**Chloral hydrate** n (%)	**p value**
1	15 (36.6)	33 (80.5)	<0.01
2	26 (76.5)	08 (23.5)	
Total	41	41	

It was found that 26 of 41 children (76.5 %) required a second dose of the drug among the Midazolam group while 33 of 41 children (80%) in the Chloral hydrate group slept with only a single dosing. It was a statistically significant difference.

Thus, Chloral hydrate, in our study was found more efficacious in terms of earlier onset of sedation and quicker recovery though Midazolam was found equally safe.

Discussion:

With the advent of scientific advancements each day, the numbers of diagnostic tests have gone up. Paediatric procedural sedation has become widespread in every field across the medical world such that many office procedures are easily carried out without the need for an anaesthesiologist.(47,87,88) Auditory Brainstem Response audiometry (ABR) and its application in various fields warrant procedural sedation as a routine office procedure. Among the various pharmacological agents, Chloral hydrate and Midazolam are known to enhance cooperation among children. Adverse effects are known to occur with all classes of drugs and with all routes of administration. The once dreaded complications like neurologic damage and death, probably due to drug interactions, overdose and administration pathways are rarely heard of today. These may be because of the enticing pharmacokinetic properties shown by the newer drugs.(89) Many authors have pointed out the guidelines for safe sedation.(90)(91) Thus, careful selection of drugs in appropriate patients with vigilant monitoring and adequate resuscitation skills have made procedural sedation safe and effective.(92)

NICE guidelines recommend both Chloral hydrate and Midazolam for paediatric painless procedural sedation, provided the candidates are assessed thoroughly on an individual basis and receive meticulous monitoring with appropriate and adequate resuscitative backup.(93) Our study showed both drugs to be safe within the normal therapeutic dosage that was administered to achieve adequate sedation for the procedure.

In this study, we prospectively compared the efficacy and safety of paediatric sedation with oral Chloral hydrate and intranasal Midazolam for ABR. Both Chloral hydrate and

Midazolam were found to be safe for procedural sedation. However, oral Chloral hydrate is more effective than intranasal Midazolam for ABR.

The safety was measured in terms of the various physiological parameters in both the groups. Heart rate, respiratory rate and oxygen saturation were found to be within normal limits safe at all intervals, except in one patient in whom Midazolam caused a transient hypoxia, which was promptly corrected with appropriate head positioning. There was no need for any interventional resuscitative efforts. There were no other major adverse effects seen among children in both the groups. A similar result was reported by other studies.(94–97) Rarer reported complications like paradoxical reaction, oxygen desaturation, respiratory depression, dysrrhythmias and prolonged sedation in varying frequencies have been reported by other studies for Chloral hydrate.(98–100) There were no major adverse reactions seen in either of the two groups in our study. Studies have shown worrisome adverse effects with both the medications in the past. High doses were hypothesized to be responsible for these effects even when guidelines and protocols were followed. Cote et al., in 2000 reported 13 of 20 Chloral hydrate patients and 12 of 26 Midazolam patients had died or sustained permanent neurologic injury.(101) Leelataweedwud at al. in 2001 reported, besides 3% of vomiting, prolonged sedation, desaturation and apnoea in patients with Chloral hydrate.(102) Martinez at al. in 2006 found that children having received combination regimen with Chloral hydrate showed prolonged sleepiness compared with those treated with Midazolam.(103) Unlike these studies, we did not find any significant differences in the physiological parameters between the two groups. This was similar to the study by Dallman et al. reported in 2001.(95)

Minor side effects in the Midazolam group were sneezing, hiccups, stinging or burning sensation, crying and increased nasal discharge. The incidence of hiccups was found to be 22% in the study done by Marhofer et al, who showed that the occurrence of hiccups was age–dependant, with younger age group more prone. Hiccups were also found to be dose independent.(104) In our study, children in the younger age group had hiccups. Sneezing was noted among some children similar to Wood et al.(61) Sneezing could be due to the drug being used as a spray formulation, which children sometimes find unacceptable. The intranasal stinging effect or burning could be due to the effect of the preservative added to the intranasal formulation of Midazolam to maintain its stability.(105) It could sometimes be perceived as pain, as reported by Antonio et al. who used a score to rate the same.(106) Studies have shown that this effect can be ameliorated by adding lignocaine to the same formulation or by spraying a separate intranasal lignocaine formulation prior to the Midazolam spray.(106–108) In our study, children cried at the time of administering the nasal spray, probably due to the atomized aerosol effect or due to the stinging effect in the nasal mucosa.(105)(109) Midazolam is also known to cause a bitter taste as it trickles down the oropharynx, which has been reported by Isik et al.(110) However, was not seen in our study. Other minor adverse effects reported by various studies like nausea, emesis were not shown by children in our study.(111)(112)

Chloral hydrate, administered at therapeutic doses, has not been reported to cause significant adverse effects. Various studies have reported common adverse effects like nausea, vomiting with frequencies 3%. (99) In our study, we did not find any of the mentioned side effects.

Chloral hydrate is a sedative hypnotic with apparent safety and efficacy demonstrated at oral doses of 25 to 50 mg/kg, up to 80 to 100 mg/kg with a maximum dose of 1 gm.(113)

According to the study done by Malis and Burton, Chloral hydrate is the most frequently used sedative for outpatient procedures in children 5 years or younger at an initial minimum dose of 61.0 mg/kg.(99)(114) In our study, we sedated children younger than 6 years at an initial dose of 50 mg/kg of Chloral hydrate and sedation was achieved in 80% of children with the first attempt and overall sedation was achieved in 95% of children.

Similarly, the safe and effective sedative dose of Midazolam for children from 6 months to 5 years of age is 0.05 to 0.1 mg/kg to a maximum dose of 0.6 mg/kg titrated gradually to achieve adequate sedation in those difficult to sedate children. While for older children 6 to 12 years of age, the initial dose recommended is 0.025 to 0.05 mg/kg till a maximum of 0.4mg/kg to achieve the desired sedation.(115) In our study, children were sprayed Midazolam at an initial dose of 0.5 mg/kg (100mcg delivered per spray) divided between both nostrils and sedation was achieved in 36% of children with the first attempt. Those children who required the second dosing received a further half of the initial dosing and overall sedation was achieved in 51% of children.

Chloral hydrate and Midazolam have been recommended for procedural sedation. Studies done by Layangool et al., Mc. Carver et al., and Reeves et al., showed an almost equal efficacy by both the drugs for sedation.(96,116,117) However, Fallah et al. showed only 40% success for sedation with Midazolam as against 76% with oral Chloral hydrate for CT imaging.(97) Similarly, Dallman et al., showed Chloral hydrate to be more effective than Midazolam.(95) In our study, Chloral hydrate was more effective than Midazolam for procedural sedation. Sedation was achieved among 95% of children with Chloral hydrate when compared to only 51% among the Midazolam group.

Following oral administration, Chloral hydrate is rapidly and completely absorbed from the gastrointestinal tract and plasma concentration peaks within 30 minutes.(114) Similarly, Midazolam administered intranasally has a good absorption rate due to the highly vascularized nasal mucosa.(117)(118) Layangool et al., found that intranasal Midazolam has a shorter onset of action while Wheeler et al. noted no differences in the onset of sedation between both the groups.(119)(120) However, in our study, Chloral hydrate had a faster onset of action compared to Midazolam.

There was no difference in the duration of procedure between the two groups in our study, which was similar to the study by D'Agostino et al. and Reeves et al.(94)(116) Layangool et al. showed that though there was no difference in the procedure time between the two groups, although the total study time was significantly shorter in the Midazolam group.(119)

Once sedation was achieved, both the drugs were efficacious in maintaining sleep when the procedure was being carried out without any intra-procedural interruption. However, Dallman et al. and Layangool et al. showed that patients who received Midazolam slept less and had a lesser depth in the level of consciousness than their Chloral hydrate counterparts.(95)(119) Laryngool et al. concluded saying the lesser depth in sedation level with Midazolam may be advantageous in those high risk patients in whom deep sedation may need to be avoided.(119)

The time taken for parental separation was compared and was found that Chloral hydrate helped in earlier parental separation than Midazolam. However, there was no significant difference in the nature of parental separation between the two groups. Cote et al. compared

three doses of oral Midazolam and showed 88% of satisfactory anxiety rating for parental separation.(112)

Different studies have reported conflicting results in the time to recovery of the sedated patients. D'Agostino et al., Wheeler et al. and Dallman et al. found faster recovery in the Midazolam group while Bae et al., and Maeda et al., noted faster recovery in the Chloral hydrate group.(94,95,120–122) In our study, children who received Chloral hydrate recovered earlier (78 minutes) than the Midazolam group (105 minutes), which was significant ($p = 0.004$).

Wood et al., in their study using intranasal Midazolam, found that the rating was 8.3 out of 10 for parental satisfaction.(61) However, in our study, the parental satisfaction was found to be better with satisfaction in 95% of children on Chloral hydrate. ($p = 0.001$). Similarly, audiologists were more satisfied with Chloral hydrate group (75%) than when Midazolam (29%).

In our study, we found that intranasal Midazolam was quite safe and efficacious. When compared to Chloral hydrate, it was not superior in 'time taken for onset of sedation' and 'time taken for recovery from sedation'.

The possible reasons for the comparative lower effectiveness of intranasal Midazolam in our study could have been due to the following reasons - some children started crying when the drug was sprayed into their nose, even when they were seated on their mother's lap. This increased nasal secretion, may have diluted the Midazolam spray. Secondly, some children sneezed after being sprayed, reducing the efficacy of the medication. Thirdly, older children required multiple sprays as the concentration was only 0.5%. This required the children to be

restrained for longer periods of time which made them uncooperative. Older children may have benefited from higher concentration of Midazolam in the nasal spray.

Similarly in the Chloral hydrate group, some children spat out the syrup, which might have resulted in lesser dose of the drug administered.

In our study, intranasal Midazolam and oral Chloral hydrate were found to be safe and effective for procedural sedation for Auditory Brain Stem Evoked Audiometry. Neither of the drugs was found to have any significant side effects. Both parents (95% versus 49%) and audiologists (75% versus 29%) were more satisfied with Chloral hydrate than with Midazolam. Higher percentage of patients (66%) achieved adequate sedation within the first 30 minutes with Chloral hydrate than with Midazolam. Both Midazolam and Chloral Hydrate are effective in providing sedation for the duration of the procedure. Significant number of children achieved sedation with the first attempt of Chloral hydrate than with Midazolam ($p = 0.01$). Successful completion of the procedure with adequate level of sedation was achieved in 95% of children with Chloral hydrate, when compared to only 51% among the Midazolam group ($p < 0.01$).

Conclusion

In conclusion, Chloral hydrate and Midazolam were both found to be safe. There were no major adverse effects noted with either of the drugs. The observed minor side effects were not significant.

Chloral hydrate, when compared to Midazolam, showed a faster onset of sedation and an earlier recovery. However, both Chloral hydrate and Midazolam caused adequate sedation for the required duration of procedure.

Parents and audiologists were more satisfied with Chloral hydrate than with Midazolam. Significant number of children achieved sedation with the first attempt of Chloral hydrate than with Midazolam ($p = 0.01$).

Successful completion of the procedure with adequate level of sedation was achieved in 95% of children with Chloral hydrate, when compared to only 51% among the Midazolam group ($p < 0.01$).

Overall, both syrup Chloral hydrate and intranasal Midazolam are safe for paediatric sedation. However, syrup Choral hydrate was more efficacious than intranasal Midazolam for procedural sedation of children undergoing Auditory Brainstem evoked Response audiometry.

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Patient information sheet

Your child has been referred for a hearing assessment test called Auditory Brainstem evoked Response audiometry (ABR). The duration of the procedure is around 45 minutes to one hour during which your child is required to be calm and motionless so that the test can be performed effectively. As children are playful and especially it is difficult to put hyper attentive children to sleep, in our Department, currently, we administer syrup called Pedicloryl to make the child sleep. But, not all children sleep with the dose administered and sometimes we may have to cancel the procedure as they are not maintained motionless which interrupts the completion of the procedure. Again at re-appointments, it is not assured that the child sleeps at the first attempt.

It is for this purpose that a trial is being conducted in our Department. It is to administer a drug called Midazolam sprayed through the nose that puts the child to sleep. Midazolam belongs to a group of drugs called Sedatives and Hypnotics. It is not a new drug and it has been in use since 10 years. It has been found safe among children to cause short term sleepiness and faster wake up after the procedure.

The side effects include sneezing, crying at initial sprays into the nose and hiccups. At times children may sleep longer. There may be a remote chance of allergic reactions and airway obstruction like any other sedative drug. It is for this purpose that they are monitored continuously during the entire procedure by a Doctor till they wake up.

The trial is conducted in such a way that Midazolam spray is compared with Pedicloryl syrup. Your child will receive one of the two drugs to sleep either Midazolam spray or Pedicloryl syrup and one other dummy preparation during the trial. Neither you nor your Doctor will know which drug is administered to the child. But at any time, your child is ensured of one of the drugs to sleep. This is done to compare the effectiveness of both the drugs in the best possible way. Otherwise there is no change in the usual performance of the procedure.

At the completion of the trial if the drug tested, Midazolam is found more effective than Pedicloryl, then this may in future help other children referred for ABR. If you are interested to know which drug was administered for your child during the procedure, it may be intimated to you on request at the end of the entire study period (nearly 15 months). We propose to include around 81 patients for the trial.

To take part in the trial, your child should be from 1 to 6 years of age completed irrespective of developmental maturity. Your child should not take part if he / she is allergic to Midazolam, if you are not willing for the procedure, if he / she is obese with BMI more than 30, has nasal allergy or has any other illnesses involving major organs like heart, lungs, liver and kidney.

You are requested to volunteer your child to take part in the trial. Taking part in the trial does not incur any extra expenses. If you are not willing your child to take part in the trial, this will by no means compromise the usual routine care provided to your child for the procedure.

The results of the study will be published in a medical journal but your child will not be identified by name in any publications or presentation of results. However, his / her medical notes may be reviewed by people associated with the study without your additional permission, should you decide your child to participate in this study.

For further queries, you can contact

Dr. Sharafine Stephen, **sharafine@gmail.com** 9894542681, Dept. of ENT.

Dr. John Mathew, **jmathew@cmcvellore.ac.in** 9994516016, Dept of ENT -2.

Informed consent

I----------

mother / father / guardian of ----------

declare that I have read the information sheet provided to me regarding this study and have clarified any doubts that I had and I also understand that my child's participation in this study is entirely voluntary and that I am free to withdraw permission to let continue my child to participate at any time without affecting his/her usual treatment or legal rights. I also understand that neither I, nor my doctors will have any choice or knowledge of which active ingredient my child will receive or the identical looking dummy drug. I also understand that apart from the cost for the procedure, no extra expenditure will be incurred as part of the trial and that my child will receive free treatment for any study related adverse event but will not receive any other financial compensation. I understand that the study staff and institutional ethics committee members will not need my permission to look at the health records of my child. I agree to this access. I understand that the identity of my child will not be revealed in any information released to third parties or published. I voluntarily agree to let my child take part in this study

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Date:

PEDIATRIC PROCEDURAL SEDATION FORM

Name Date -

Hospital no. Sample no. -

Age & sex Study arm -

Weight Place

Developmental maturity - normal / abnormal

Indication – (Both – 3, speech delay – 2, Hearing impairment – 1)

Dose calculated - Oral syrup - 50mg/kg = -- mg = --- ml

Nasal spray - 0.5 mg/kg = --- mg, ----sprays per nostril (100mcg/spray)

Parameters - Pre sedation		Baseline	15min	30 min	45min
Heart rate (bpm)					
Respiratory rate (per min)					
Oxygen saturation (%)					
Level of Consciousness (scoring)	Sleep (1 to 3)				
	Movement (1 to 4)				

Parameters – post sedation (min)		5	10	15	20	25	30	35	40	45	50	55	60	65	70
Heart rate (bpm)															
Respiratory rate (per min)															
Oxygen saturation (%)															
Level of Consciousness (scoring)	Sleep (1 to 3)														
	Movement (1 to 4)														

Time drugs administered:

Time for parental separation:

Nature of parental separation (scoring 1 to 4)

Time of onset of sedation:

Duration of procedure ---------- Time started ----------; Time ended ----------

Time of recovery:

Nature of recovery (scoring 1 to 4)

Acceptance by parents: satisfied / not satisfied

Audiologist's satisfaction (scoring 1 to 3)

Number of attempts:

Rating for parental separation

Awake and crying	1
Awake and Calm	2
Drowsy	3
Sleepy	4

Houpt Behaviour Rating Scale (modified)

Level of consciousness	Score

Rating for sleep

Fully awake, alert	1
Drowsy	2
Asleep	3

Rating for movement

Violent movement interrupting treatment	1
Continuous movement making treatment difficult	2
Controllable movement that does not interfere with treatment	3
No movement	4

Rating for overall behaviour (by audiologists)

Poor – procedure aborted 1

Fair —procedure interrupted, but completed 2

Good- procedure performed without any interruption 3

At recovery,

Brietkopf and Buttner—Nature of recovery

Score	Description
1	Irritated: awake, restless, crying
2	Normal: awake, calm
3	Inactive: tired, hardly moving
4	Sleepy: drowsy, without reaction, but arousable

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VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr.Gagandeep Kang, MD, Ph.D, FRCPath
Secretary, Research Committee, IRB
Additional Vice Principal(Research)

January 12, 2012

Dr. Marie Christy Sharafine S
PG Registrar
Department of ENT
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
Comparison of efficacy and safety of intranasal Midozolam with syrup Triclofos for procedural sedation of children undergoing Auditory Brainstem evoked response Audiometry – a Randomized, Double-blinded, Placebo controlled trial.
Dr. Marie Christy Sharafine S, P.G. Registrar, ENT, Dr. John Mathew, Dr. Mary Kurien, Dr. Ajoy Mahtew Varghese, ENT, Dr. George Ani Mathew, Dr. Manickam Ponnaiah, Anaesthesia, Dr. Annadurai, P, Pharmacy,Dr. Grace Rebekah, Biostatistics.

Ref: IRB Min. No. 7697 dated 12.12.2011

Dear Dr. Sharafine,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Comparison of efficacy and safety of intranasal Midozolam with syrup Triclofos for procedural sedation of children undergoing Auditory Brainstem evoked response Audiometry – a Randomized, Double-blinded, Placebo controlled trial" on December 12, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi and Bengali)
3. Proforma
4. Cvs of Drs. Manickam Ponniah John Mathew Mary Kurien George Ani Mathew.
5. A CD containing documents 1 – 4

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Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee & Principal

Dr.Gagandeep Kang, MD, Ph.D, FRCPath
Secretary, Research Committee, IRB
Additional Vice Principal(Research)

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on December 12, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

Name	Qualification	Designation	Other Affiliations
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	Non-CMC
Mr. Harikrishnan	BL	Lawyer	Non-CMC
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC
Mrs. Ellen Ebenezer Benjamin (on behalf of Dr. Jayarani Premkumar)	M.Sc. (Nursing), Ph.D.	Nursing Superintendent, CMC.	
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

A sum of ₹ 68,000/- (Rupees Sixty eight thousand only) is sanctioned for 2 years.

Yours sincerely,

Dr. Alfred Job Daniel
Principal& Chairperson (Research Committee)
Institutional Review Board

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