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Clinical application of 3D ultrasound in neonatal intraventricular hemorrhage

Priyanka Roy
The University of Western Ontario

Supervisor
de Ribaupierre, Sandrine
The University of Western Ontario Co-Supervisor
Fenster, Aaron
The University of Western Ontario

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Abstract

Preterm neonates are at risk for intraventricular hemorrhage (IVH) and subsequent post-hemorrhagic hydrocephalus (PHH). A well-accepted interventional therapy for PHH is ventricular tap (VT). Permanent treatment, ventriculo peritoneal shunt surgery (VPS) is required in the case of some neonates under some conditions (weight, immunological status, CSF protein level) who receive multiple interventions. The objective of this study was to apply a 3D ultrasound system clinically to determine CSF volume within the ventricle, to guide the neurosurgeon regarding the amount of CSF should be removed during every intervention, which lateral ventricle is better to intervene and to predict the possibilities of the requirement of the shunt. After ethics approval and parental consent, this 3D US system was used in a clinical study where data of 70 neonates having IVH were analyzed retrospectively and 22 preterm neonates were recruited prospectively. 3D US system was used to measure the ventricle volume of the neonates. In addition, we have changed the posture of some neonates to find the volume variation in two lateral postures. We found that 3D US ventricle volume had a higher correlation (Pearson correlation 0.739) with the amount of CSF removed in each tap than other parameters (weight, age, head circumference). After changing the posture of the neonates, we did not find any significant volume change of two lateral ventricle volumes (P-value was 0.353 in case of the right ventricle in two different postures and 0.473 in case of the left ventricle in two different postures). We also found more volume change after VT in those patients who required VPS than who did not need a VPS (volume

change was18.70 ± 10.98 cm^3 in shunt treated patients and 7.52 ± 3.35 cm^3 in patients with no shunt where P- value was 0.0001). Therefore, our study suggests that a volumetric measurement of total lateral ventricles by the 3D US could be used concurrently with other physical parameters for better management of the neonates having PHH.

Keywords: Preterm, Intraventricular hemorrhage, Post-hemorrhagic hydrocephalus, 3D ultrasound, Ventricular tap, Cerebrospinal fluid, Intracranial pressure, Head circumference, Ventriculo peritoneal shunt

Summary for Lay Audience

Babies who are born earlier than the expected time of delivery usually suffer from many health hazards. One of the most common hazards is bleeding inside the brain. In the human brain, there are fluid-filled spaces called ventricles. This bleeding often occurs inside the ventricle and causes dilatation of ventricles by the excess amount of fluid that cannot circulate well because of the bleeding. This situation is very threatful for babies' development and may even cause death. This condition is diagnosed by a 2D head ultrasound (2D US) and monitoring head enlargement. Primary treatment is the removal of excess fluid from the ventricles by needle aspiration. 2D US cannot measure how much fluid is inside the brain, therefore cannot guide the physician how much fluid should be removed safely at one time. Thus, we have developed a new 3D head US system where the exact volume measurement of the ventricle is possible. We recruited 22 babies who were born earlier than expected, and also, we analyzed data of another 70 babies with bleeding in the ventricles for this study. We measured the fluid amount in the ventricle using the 3D US system. We also changed the position of some of the babies to see if the ventricle volume changes with the position of the head, but we did not find significant changes in ventricle volume after changing position. But we found a good correlation between how much fluid is inside the brain and how much fluid should be removed at any time. Moreover, we could identify those babies for whom only removing fluid is not enough, treatment by permanent surgery is needed by calculating the 3D US volume difference before and after removing the fluid. We

are hoping that this research will help the clinicians to manage the babies with ventricle bleeding more effectively.

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List of Abbreviations

2D	two dimensional
3D	three dimensional
AHW	anterior horn width
CPC	choroid plexus cauterization
CSF	cerebral spinal fluid
CT	computed tomography
CS	Caesarean section
cm	centimeter
cm^3	cubic centimeters
DRIFT	drainage, irrigation, and fibrinolytic therapy trial
ETV	endoscopic third ventriculostomy
EVD	external ventricle drain
GA	gestational age
GW	gestational week
GMH	germinal matrix hemorrhage
Hb	hemoglobin

HbO_2	oxygenated-hemoglobin
HC	head circumference
ICC	intra-class correlation
ICP	intracranial pressure
IV	intravenous
IVH	intraventricular hemorrhage
LP	lumbar puncture
LV	left ventricle volume
Lt	left
MRI	magnetic resonance imaging
ml	milliliter
NICU	neonatal intensive care unit
NIRS	near infrared spectroscopy
NVD	normal vaginal delivery
PDA	patent ductus arteriosus
PHH	post hemorrhagic hydrocephalus
PHVD	post hemorrhagic ventricle dilatation
Rt	right

RV	right ventricle volume
TOD	thalamo-occipital distance
TVV	total ventricle volume
US	ultrasound
USB	universal serial bus
VADs	ventricular access devices
VI	ventricle index
VLBW	very low birth weight
VP	ventriculo-peritoneal
VSGS	ventriculosubgaleal shunt
VT	ventricle tap
VV	ventricle volume
Wt	weight

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Chapter 1

1. Introduction

1.1 Overview:

Premature birth is an unexpected event that leads to the early birth of an infant, or sometimes is the result of a medical decision that is unavoidable in some conditions to save the life of the mother and the baby. It was reported that approximately 11.1% of all live births worldwide are born preterm.[1] The World Health Organization (WHO) defines premature births as any birth before 37 completed weeks of gestation. This can be subdivided based on gestational age; extremely preterm (<28 weeks), very preterm (28 - <32 weeks) and moderate or late preterm (32 - <37 weeks) of gestation. Hypertensive disorder during pregnancy is the commonest obstetrical risk factor of premature birth and this prematurity is the leading cause of neonatal mortality and the second leading cause of mortality in children under 5 years old.[2]

Intraventricular hemorrhage (IVH) is the bleeding inside the ventricles, which is the most common intracranial hemorrhage in the preterm neonates. According to recent reviews, the rate of IVH is 25% to 30% for very low birth weight infants (VLBW <1500 grams) although survival of small premature babies has improved due to advances in specialized obstetric and neonatal intensive care in the past several decades.[3,4] Inflammatory reaction from blood breakdown products and blood clots can block the flow of the cerebral spinal fluid (CSF), leading to post-

hemorrhagic ventricle dilatation (PHVD), which is the abnormal, progressive dilatation of the ventricular system due to increased amount of CSF.[5] This enlargement can compress the surrounding brain and can lead to severe neurological disability and even death. The severe form of PHVD is called post-hemorrhagic hydrocephalus (PHH), which usually affects 25% to 28% IVH patients.[5]

Approximately 40% of patients with PHVD resolve spontaneously and the other 60% suffer from rapidly progressing and persistently progressing PHVD and require interventions.[6] Currently used temporizing interventions are ventricular tap (VT), lumbar puncture (LP), ventricular reservoir, ventricular access device (VAD), ventriculo subgaleal shunt (VSGS). Once the early phase is over, and the infant is older and the proteins in the cerebrospinal fluid are lower an endoscopic third ventriculostomy and ventriculoperitoneal shunt (VP) can be done as a permanent treatment. The main goal of these treatments is to reduce intracranial pressure (ICP) and protect the brain from damage.[7] Though much research has been done to improve the diagnostic and treatment modalities of IVH patients, currently there is no absolute guideline regarding when and how to treat neonates with IVH to prevent morbidity and mortality for better neurological outcomes.

1.2 Anatomy

1.2.1 Anatomy of the neonatal brain:

The human brain is a complex organ, which grows at an amazing rate during development. The first sign of the developing nervous system is the formation of the neural plate that can be seen as early as 16 days of embryogenesis. By the age of 2 years, the brain is about 80% of the adult size. Brain and ventricle development during embryogenesis are shown in figure 1.1.

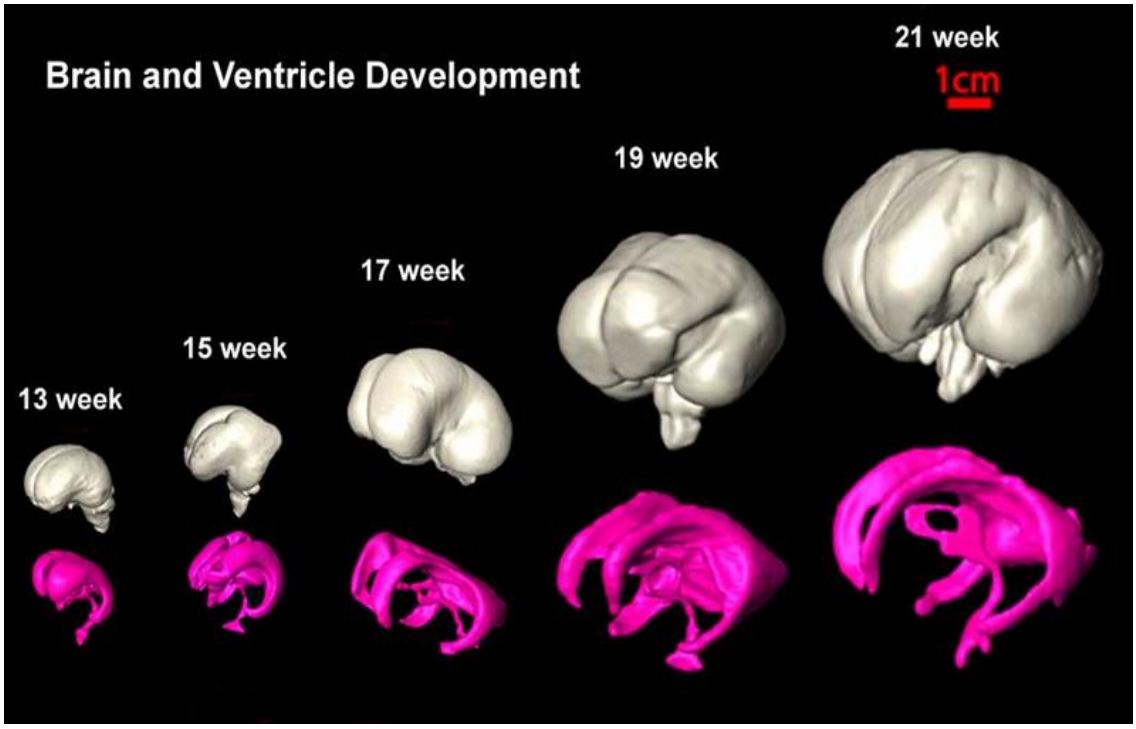

Figure 1.1: Development of whole-brain (gray) and ventricle (pink). Image adapted from J. Neurosci. 29; 4263-4273 (2009). (open access)

The premature neonatal brain is much different from the mature neonatal brain. During the last 10 weeks of pregnancy, the brain volume and surface area change dramatically and the cortex becomes more folded.[9] Though all the primary sulci are present by the age of 20 - 24 gestational weeks (GW), the

secondary sulci begin to appear between 30-35 GW, and the tertiary sulci develop during GW 36 and extend into the postnatal period.[8] Thus, the brains of babies who are born prematurely lack mature sulci, which makes the brain vulnerable to a range of insults. The brains of premature babies still develop in the extrauterine environment, which may result in some adverse outcomes. One of the most common insults to the premature brain is IVH. This is mainly caused by immature and fragile vasculature of the germinal matrix located between the lateral ventricles and caudate, which is highly vascularized and responsible for migrating neuronal cells to the cortex during development.[9]

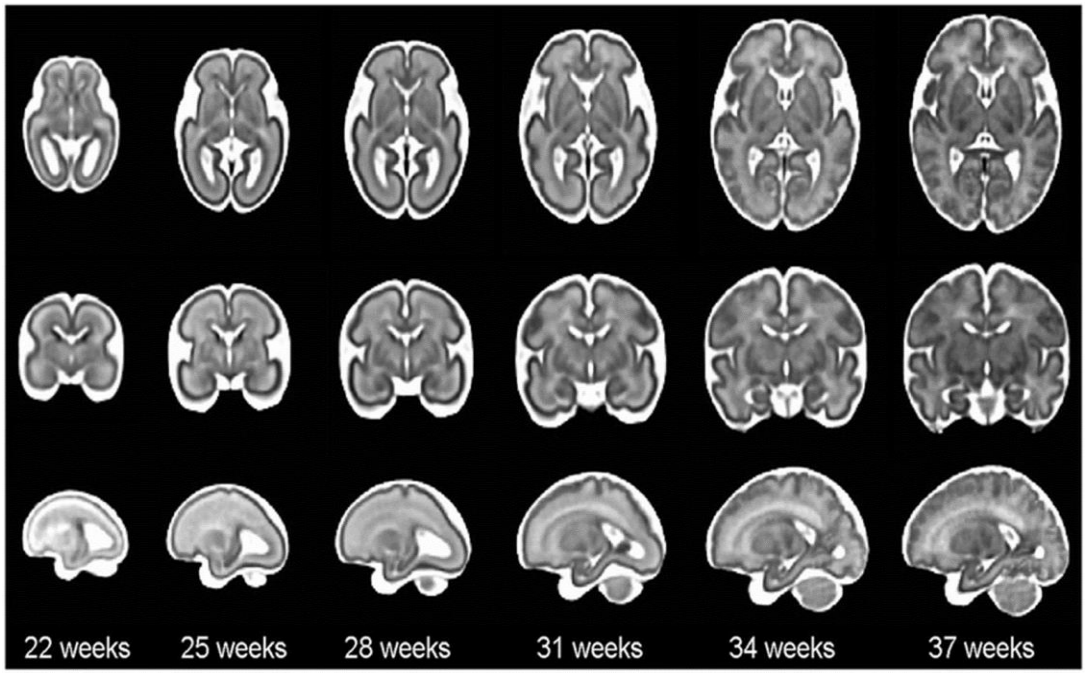

Figure 1.2: The spatiotemporal fetal brain MRI atlas (CRL fetal brain atlas) at six representative gestational ages (GA): 22, 25, 28, 31, 34, and 37 weeks. Images adapted from *Sci Rep.* 28; 7(1): 476 (2017). (open access)

1.2.2 Ventricular system:

The human ventricular system is a set of four interconnected cavities inside the brain that lies in the core of the forebrain and brain stem. The ventricular cavities are derived from an elaboration of the lumen of the cephalic portion of the neural tube. Each ventricle is lined with an internal layer of the ependyma and an outer layer of delicate connective tissue (pia mater) in which blood vessels invaginate to form the choroid plexus.[10] The four ventricles are composed of two lateral, one third and one-fourth ventricle. The presence of other ventricles is rare but occurs in some cases.

1.2.2a Lateral ventricles:

The lateral ventricles are C shaped cavities, which lie in each cerebral hemisphere. Each lateral ventricle is composed of a body centrally with the anterior (frontal), inferior (temporal), and posterior (occipital) horns. Each of these parts has medial and lateral walls, a roof, a floor, and an anterior wall.[11,12] They are the largest of the ventricles and extend through all four cerebral cortex lobes with the central area of each ventricle being located in the parietal lobe. Each lateral ventricle is connected to the third ventricle by channels called interventricular foramina or foramen of Monro.

1.2.2b Third ventricle:

The third ventricle is a narrow, funnel-shaped cavity situated between two thalami in the diencephalon. Like other ventricles, the third ventricle has a cavity, an

anterior wall, a posterior wall, a floor, a roof, and two lateral walls. It communicates with the lateral ventricles via the foramen of Monro superiorly and inferiorly with the fourth ventricle through the cerebral aqueduct of Sylvius.[11]

1.2.2c Fourth ventricle:

The fourth ventricle is a diamond-shaped midline cavity in the brainstem, posterior to the pons and medulla oblongata. It is composed of a floor, roof, and 2 lateral recesses.[12] The fourth ventricle is continuous with the cerebral aqueduct and the central canal of the spinal cord. CSF exits into the subarachnoid space from the fourth ventricle by the paired lateral foramina of Luschka and the single midline foramen of Magendie.[12]

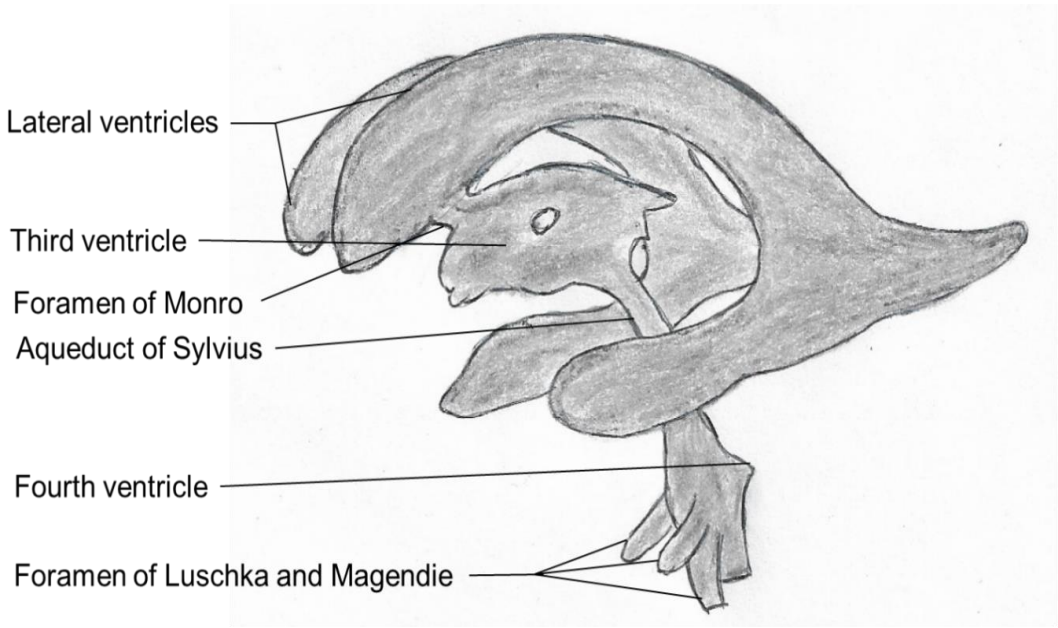

Figure 1.3: Drawing of the anatomy of the ventricular system

1.2.2d Other CSF filled spaces:

In some cases, some other CSF filled structures are present. These structures normally begin to close in utero but may continue into the first several months of postnatal life. These are:

Cavum septum pellucidum – Located in between the septal laminae.

Cavum vergae – Located posterior to the anterior columns of fornix and may extend to the splenium of the corpus callosum.

Fifth ventricle – Located in the close proximity to the conus medullaris just like an expansion of the caudal portion of the central canal of the spinal cord. Its persistence is rare.[12]

1.3 Cerebrospinal fluid:

Cerebrospinal fluid (CSF) is a clear colorless body fluid within the ventricles of the brain and the subarachnoid spaces of the cranium and spine.[13] CSF is produced predominantly by the choroid plexus in the lateral, third, and fourth ventricles. CSF flows from the lateral ventricle to the third ventricle through the interventricular foramen called the foramen of Monro. CSF is delivered from the third ventricle to the fourth ventricle by a cerebral aqueduct called the Aqueduct of Sylvius. CSF then flows into the subarachnoid space through the foramina of Luschka (there are two of these) and the foramen of Magendie. Absorption of the CSF into the bloodstream takes place in the superior sagittal sinus through structures called arachnoid villi. When the CSF pressure is greater than the venous pressure, CSF usually flows into the bloodstream. However, the arachnoid villi act as "one-way valves", if the CSF pressure is less than the

venous pressure, the arachnoid villi do not let blood pass into the ventricular system.

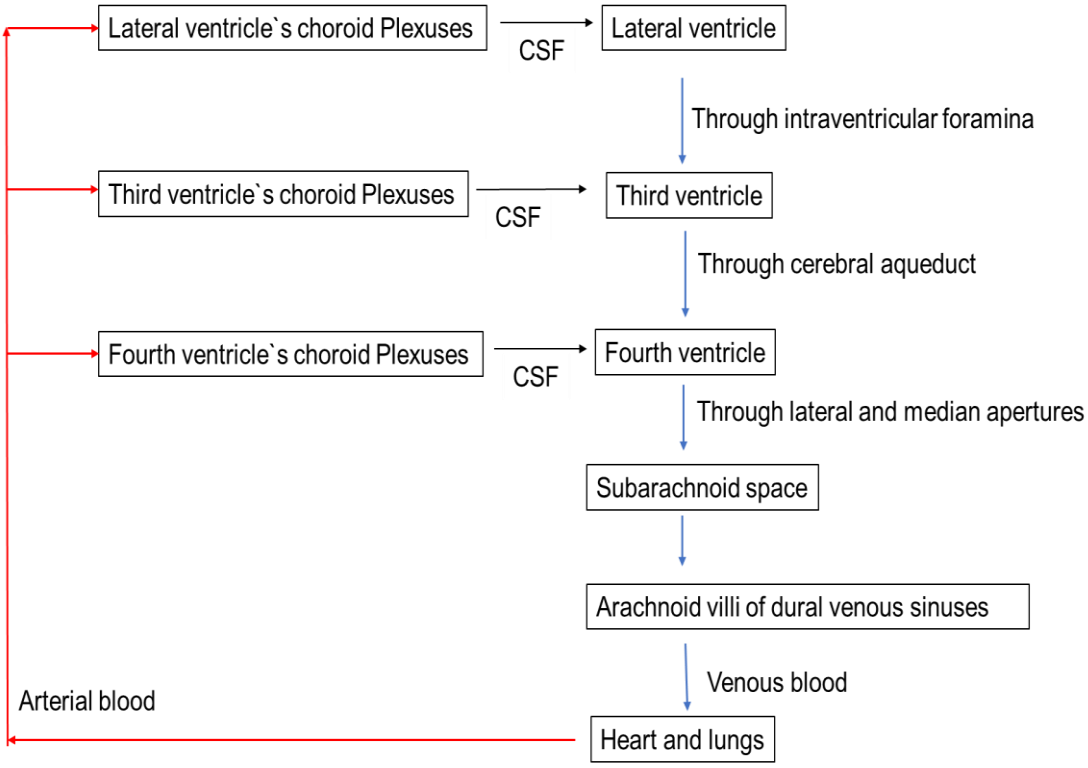

Figure 1.4: Flow diagram of the CSF flow pathway

The secretion of CSF varies in a normal adult individual between 400 to 600 ml per day. CSF turns over about 3 to 4 times per day. At any time an average adult has about 150 ml CSF with a distribution of 125 ml within subarachnoid spaces and 25 ml within the ventricles.[13,14] CSF provides hydromechanical protection of the brain by acting as a shock absorber and cushioning the brain against the skull. It also reduces the effective weight of the brain from its normal 1,500 grams to 50 grams. Other functions of CSF are to maintain hemostasis, provide nourishment and waste removal.[15,16]

CSF is derived from blood plasma and is largely similar to it, except that CSF is nearly protein-free compared with plasma and has some different electrolyte levels. A comparison of average serum and CSF is shown in table 1.

Examination of the cerebrospinal fluid (CSF) may provide critically important diagnostic information in several infectious, non-infectious diseases and also some neurological and mental condition. CSF analysis includes observing the color of the fluid, measuring CSF pressure, and counting and identifying white and red blood cells within the fluid; measuring protein and glucose levels, and culturing the fluid.[17,18]

Table 1.1: Comparison of average serum and cerebrospinal fluid. Chart adapted from Wikipedia.

Substance	CSF	Serum
Water Content (%)	99	93
Protein (mg/dL)	35	7000
Glucose (mg/dL)	60	90
Osmolarity (mOsm/L)	295	295
Sodium (mEq/L)	138	138
Potassium (mEq/L)	2.8	4.5
Calcium (mEq/L)	2.1	4.8
Magnesium (mEq/L)	2.0–2.5	1.7
Chloride (mEq/L)	119	102
pH	7.33	7.41

1.4 Intraventricular hemorrhage, post-hemorrhagic ventricle dilatation, and hydrocephalus:

Intraventricular hemorrhage (IVH), bleeding into the ventricles inside the brain is a major complication of prematurity with multifactorial etiology.[19] Low gestational age and low birth weight are considered to be major risk factors for severe IVH.[20] Maternal substance abuse especially cocaine, smoking and any other morbidity like gestational hypertension, preeclampsia, kidney disease, heart disease, any infectious disease can cause premature delivery. Some additional risk factors for developing IVH are having been conceived via fertility treatment (especially in vitro fertilization), no use of antenatal steroid or magnesium sulphate when necessary, having neonatal early sepsis, acidosis, hypotension, pneumothorax (presence of air between the lungs and the chest wall), and treated by high fraction of ventilated oxygen in the first day of life.[21-23] Most of the very premature neonates are affected by IVH within 72 hours of their birth and post-hemorrhagic ventricle dilatation (PHVD) occurs soon after the hemorrhage. The origin of hemorrhage is considered to be from the germinal matrix where rapid angiogenesis happens during the early neonatal period. The angiogenic vessels lack pericytes with immature basal lamina where fibronectin is low and have astrocyte with deficient in glial fibrillary acidic protein. These are the contributing factors for the fragility of the germinal matrix vasculature.[24] Fluctuations of cerebral blood flow by other stressful stimuli and the inability of the preterm neonate to adapt and regulate the body’s cardiovascular system are other contributing factors to the developing germinal matrix hemorrhage, which

progresses to IVH upon the rupture of the underlying ependyma.[24] Following an IVH, red blood cells are hemolyzed and hemoglobin is released into the ventricular space. Many proinflammatory pathways are induced and potentially damaging substances like free iron, free radicals, inflammatory cytokines are released.[25] Over time, as the blood clots are broken down, the end product of hemoglobin breakdown named hemosiderin can become lodged in the subarachnoid space and reduce the amount of CSF absorption. As a result, CSF accumulates within the ventricular cavity. This is called post hemorrhagic ventricle dilatation (PHVD) and when this situation is severe it is called post-hemorrhagic hydrocephalus (PHH).

The grades of IVH range from I to IV as first reported by Papile et al,[26] and are the most commonly used classification of IVH. This grading includes:

Grade I – Mildest form of bleeding where the bleeding is confined to the subependymal germinal matrix. Most of these cases resolve spontaneously.

Grade II – Here the hemorrhage extends into the lateral ventricles without ventricle dilatation.

Grade III – Here the bleeding leads to distension of the ventricles.

Grade IV – This Grade is defined by bleeding outside the ventricles and is also called periventricular hemorrhagic infarction.

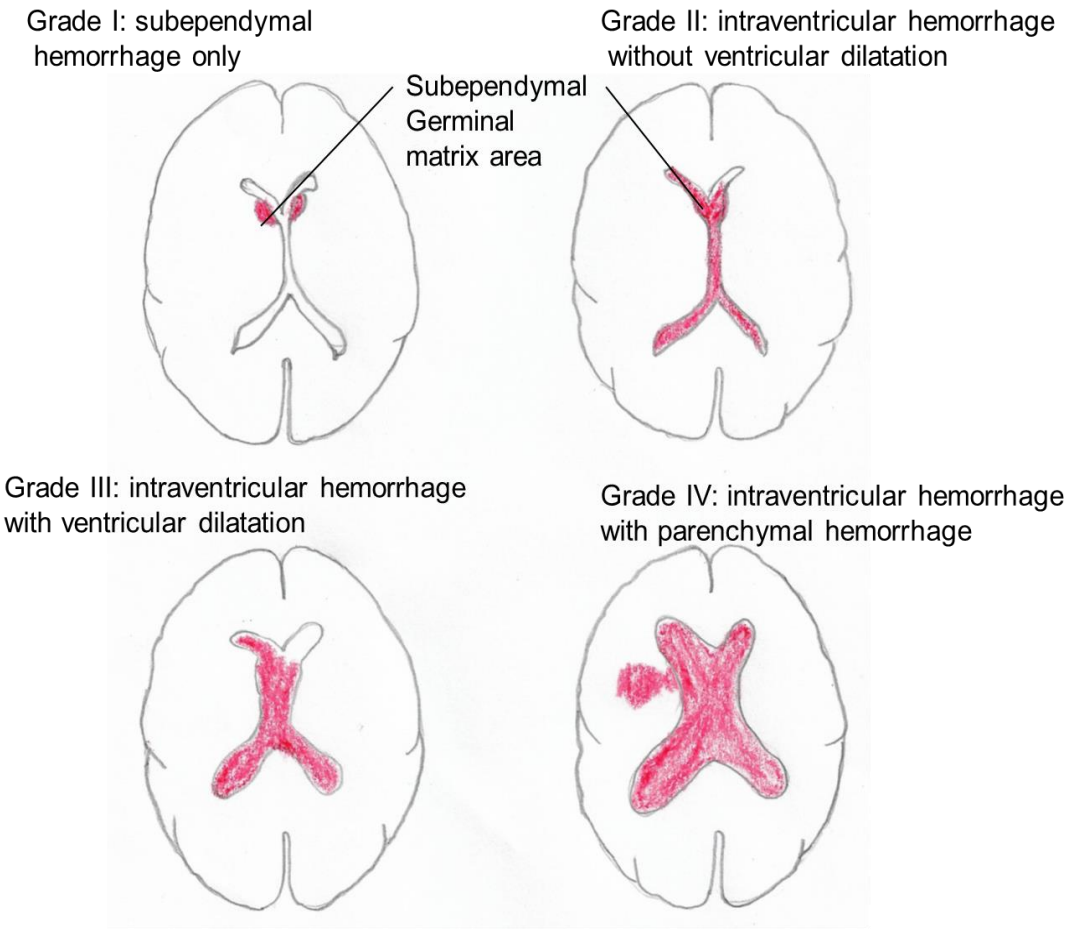

Figure 1.5: Drawings showing different grades of IVH

It is reported that 80% of infants with grade IV and 50% with grade III eventually develop PHVD or PHH and are considered the major causes of poor later neurodevelopmental outcomes including cerebral palsy.[27]

PHH is also be divided into three categories:

Obstructive hydrocephalus – Enlargement of the ventricles is caused by the blood clots, which can block the smaller aqueduct between third to fourth ventricles.

Non-obstructive or communicative hydrocephalus - If the CSF flow is not impaired between the ventricles and the subarachnoid space, the enlargement of the ventricles is mainly from lack of reabsorption, which may cause 'communicating' hydrocephalus. This lack of reabsorption is mainly due to obliteration of the arachnoid villi by microthrombi with subsequent inflammation and fibrosis.[28]

Complex hydrocephalus – When both communicating and non-communicating hydrocephalus persist simultaneously it is called complex hydrocephalus.

All types of hydrocephalic infants require permanent or temporary interventions to alleviate the symptoms of raised intracranial pressure and to prevent further damage to the brain matter.

1.5 Diagnosis of IVH, PHVD, and current monitoring:

Premature neonates are always at risk of developing IVH and subsequent PHVD. Most of the IVH is diagnosed by the third day of postnatal life.[29] Thus, it is now routine in most centers to perform a head ultrasound (US) of all premature neonates within 1 week of their life. At our center, neonates born at less than

1500g are screened during the first week of life as well as the fourth week of life if no pathology is present on the first image. If IVH or PHVD is detected on any scan, neurological exams are routinely performed to assess for worsening signs and symptoms of increased ICP, as well as subsequent head US is required. Though IVH may have no initial symptoms, raised intracranial pressure (ICP) due to severe IVH may be obvious just by looking at the baby. Because the ventricles in the brain are dilated, the pressure is increased. As the skull bones have not fused, swelling of the head or bulging of the fontanelles may be visible. This can be monitored by regular measurements of head circumference (HC) and palpation of the fontanelle. Also, because weakened blood vessels in the brain are susceptible to damage from sudden blood pressure changes, abnormal blood pressure readings may be found. Additionally, Symptoms of raised intracranial pressure like apnea, vomiting, papilledema, altered consciousness, Cushing's triad (increased systolic pressure, widened pulse pressure, bradycardia) are not uncommon in case of severe PHH. But these symptoms are not specific to IVH because some other conditions like a brain tumor, brain abscess, stroke, epilepsy, meningitis, encephalitis can cause these types of symptoms. To confirm the diagnosis, physicians rely on imaging of the neonatal brain.

1.6 Imaging modalities of neonatal brain:

Brain imaging is an important step in the diagnosis and management of various neurological conditions for both the adult and neonatal populations. In recent decades advancement in various imaging modalities has resulted in improved

brain imaging, which is providing a better understanding of brain functional activity. Thus, brain imaging has become one of the most preferred non-invasive diagnostic methods for both physicians and patients. However, imaging premature neonates is not as feasible as imaging the adult population. The main obstacles to overcome are: control the temperature outside the incubator, immobilization, ventilation for the immature lungs and IV access for antibiotics or nutrition. Among various imaging techniques, cranial ultrasound is still the preferred method for the neonatal population because of its low cost, minimal handling and ability to image the baby inside the incubator. The following are short descriptions of different imaging modalities of the neonatal brain.

1.6.1 Computed tomography (CT):

CT images are produced by combining a series of x-ray projections using a computer to form cross-sectional images. The first images of the preterm neonatal brain were performed using CT in the late 1970s.[26] But a recent retrospective study showed that CT was less likely to detect injuries to the deep gray nuclei, brainstem and cerebellum, as well as strokes ($P<0.001$ for each).[30] Furthermore, because of the lack of myelination in the newborn brain, gray/white matter contrast on CT is poor.[31] Moreover, CT uses ionizing radiation, which can cause DNA damage, so, it should be avoided as much as possible in infants because of their rapid cell division in many organs and induction of radiation dose-related cancer in later life.[32]

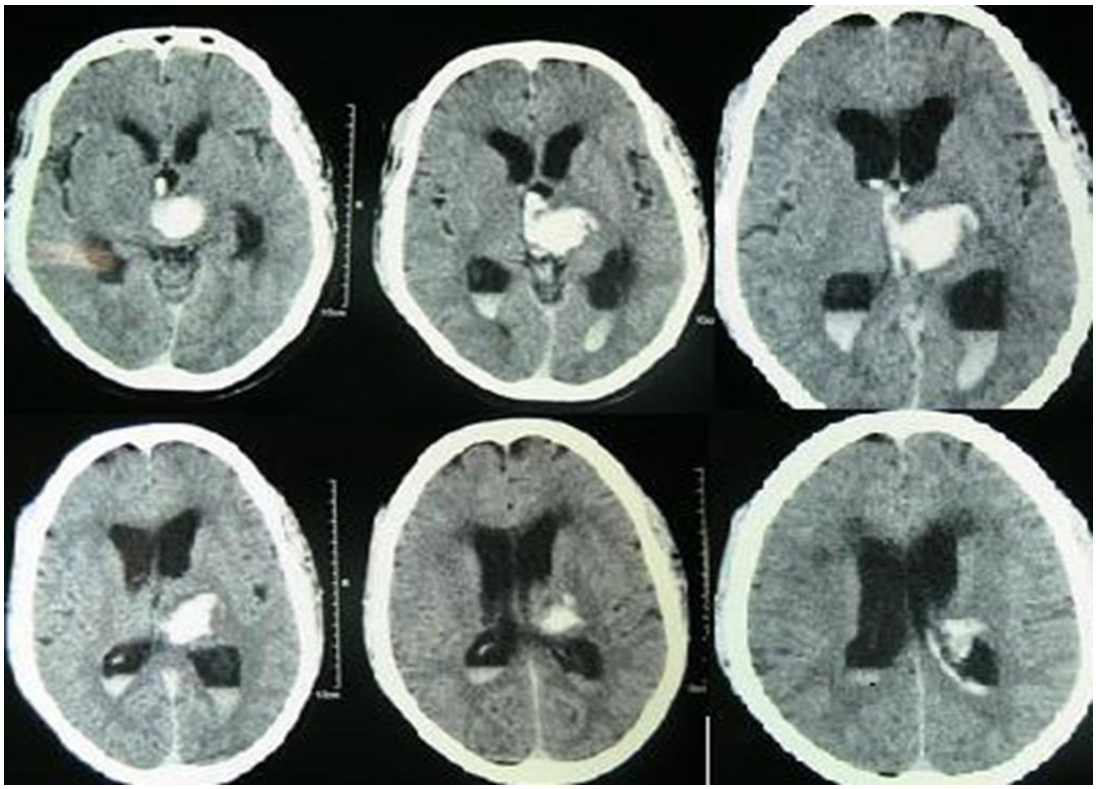

Figure 1.6: CT images of intracerebral hemorrhage. Image adapted from BMC Neurol 7; 1(2007). (open access)

1.6.2 Magnetic resonance imaging (MRI):

MRI is based on the body's natural magnetic properties and uses a hydrogen nucleus (a single proton) to produce detailed images from any part of the body.[33] MRI has high tissue contrast, which is better for differentiating white and grey matter along with hemorrhage and allows better structural visualization. The first human scan using MRI was performed in late 1970[34] and the first neonatal brain scan was performed shortly after in early 1980.[35] Most of MRI imaging of neonates require removal of the neonate from the neonatal intensive care unit (NICU), transporting the neonate to the radiology department and imaging in a

conventional adult-sized scanner.[36] The following are some other reasons, which make MRI imaging of a neonate challenging.

(1) It is difficult to maintain the temperature and other facilities outside the incubator.
(2) The small size of the premature neonatal brain requires higher resolution to clearly delineate brain structures.
(3) The neonate's movement may create unusable images as babies are unable to follow instructions to lie still.
(4) Optimization of the MRI pulse sequences is required as the immature brain has higher water content and more unmyelinated white matter compared with adults, resulting in different tissue contrast from that of the adult brain.[37]

Significant efforts have been taken to improve the MRI imaging process of neonates and to overcome the obstacles. For the most premature infants, the use of an MR compatible incubator can overcome some of the obstacles.[36] Immobilization of the neonate can be achieved using an immobilization blanket, but it is not suitable for all the neonates. The use of medical equipment such as IVs, ventilation devices, infusion pumps, and resuscitation devices, which are not safe to use in the MRI suite, is the largest problem for neonatal MRI scans. Overall, MRI for the neonate is expensive because making all medical devices to be MRI compatible is not always possible.

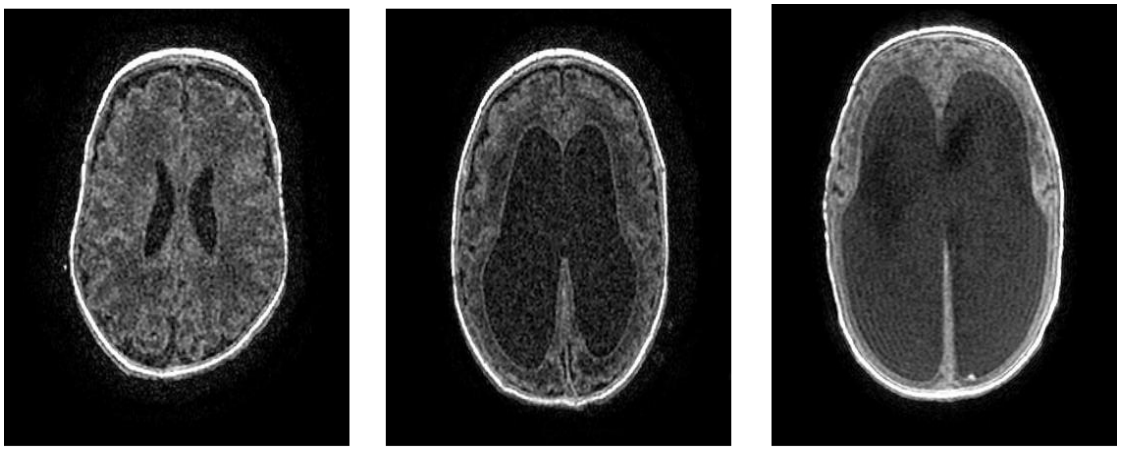

Figure 1-7: MRI of the brain of a) 26 weeks neonates with grade I IVH b) 27 weeks neonate with grade III IVH with hydrocephalus and c) 25 weeks neonate with grade III IVH with severe hydrocephalus.

1.6.3 2D cranial ultrasound (2D US):

Since its clinical introduction in the late 1970's cranial ultrasound (CUS) has been used worldwide for detecting various neonatal conditions including both congenital and acquired.[38] Cranial US involves exposing the head to high-frequency sound waves to produce images of the brain. Linear array, higher frequency transducers (7–12 MHz) are used for near-field imaging and sector transducers are used for a wider far field of view. Neonatal cranial sonography represents the first-line imaging modality in neonates due to its portability, lower cost, speed, lack of ionizing radiations, no need of sedation and rapid acquisition of images at the bedside.[39]

Initially, ultrasound was performed through the temporal bone, which allowed for measurement across the anterior horn.[40] Later, the anterior fontanelle was used as an acoustic window for imaging. Imaging is performed via the anterior fontanelle in the coronal and sagittal planes. Mastoid and posterior fontanelle approaches are useful in the demonstration of a subtle intraventricular bleed in the occipital horn in patients with suspected bleeding in the brain stem and adjacent cerebellum. Screening via supplemental fontanel may have some added value.[41] The acoustic windows of the neonatal brain for the US are shown in figure 1.8.

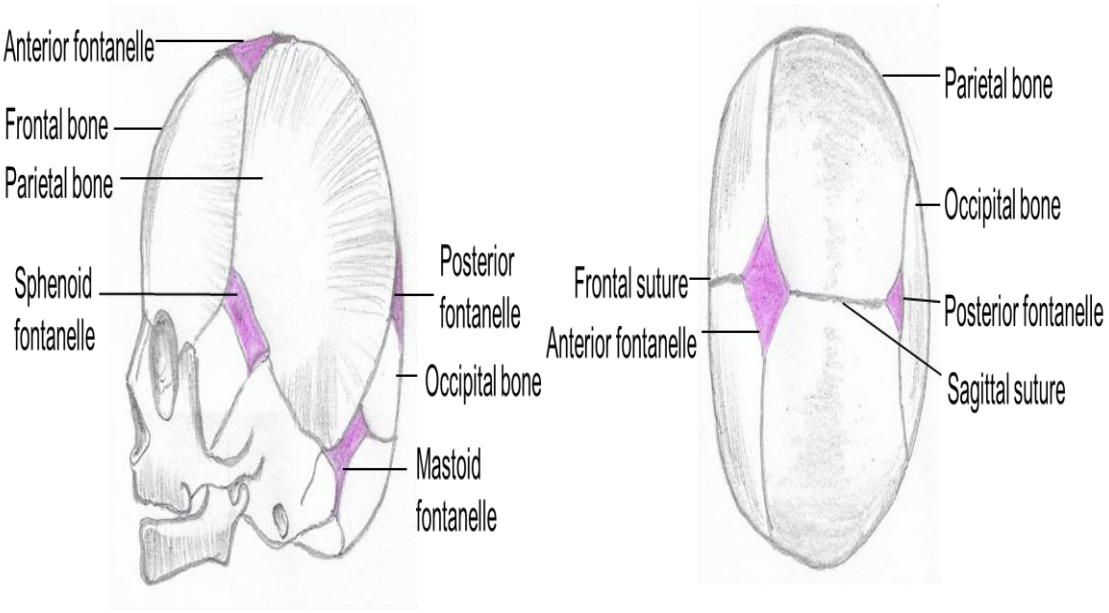

Figure 1.8: Drawings showing fontanel of the neonatal brain used as an acoustic window for the US

In US images, ventricles are anechoic (black) as they contain fluid CSF, whereas the choroid plexus, small hemorrhages, and areas of infarction appear hyperechoic (white). Moreover, gray matter tends to be hypoechoic and white matter tends to be hyperechoic. Also, the normal brain is always nearly symmetric.[41] Any asymmetry allows for the detection of early changes of infarction or focal ischemia. PHVD then appears as an increasing CSF, which appears as an increased black area inside the brain. The mixture of blood within the CSF makes it hypoechoic and large blood clots appear to be hyperechoic. 2D US images of patients with mild, moderate, and severe PHVD can be seen in Figure 1.9(a-c).

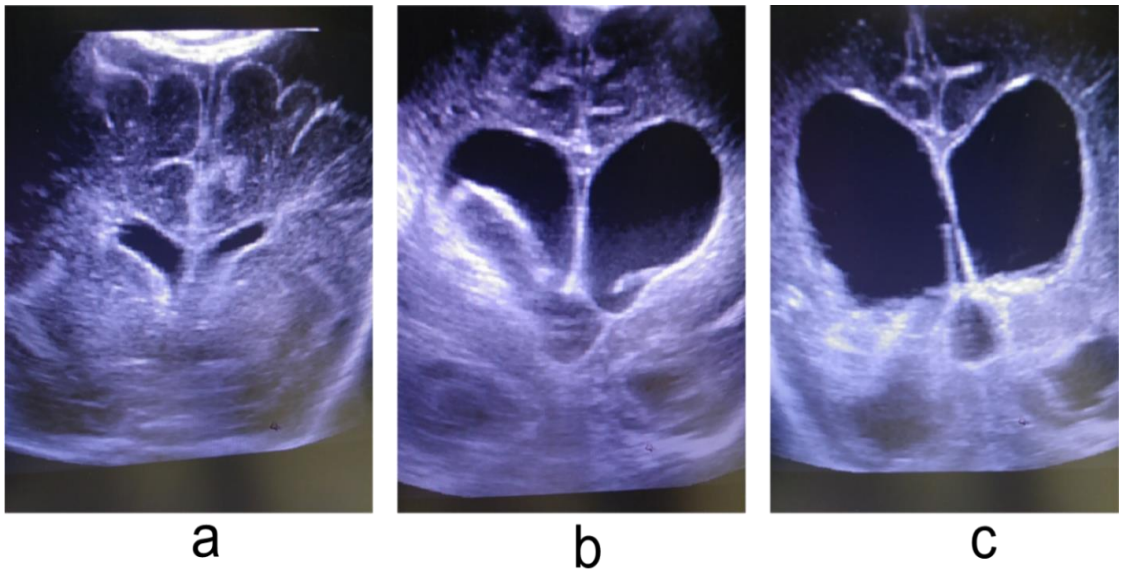

Figure 1.9: Coronal US images of the patients suffering from a) mild, b) moderate and c) severe PHVD

In 2D cranial US, mostly used ventricular parameters measured in the coronal and sagittal planes are VI = ventricular index, AHW = anterior horn width, TOD = thalamo-occipital distance. The ventricular index (VI) is defined as the distance between the falx cerebri (midline of brain) and the lateral wall of the anterior horn in the coronal plane, anterior horn width (AHW) is defined as the diagonal width of the anterior horn measured at its widest point in the coronal plane, and thalamo-occipital distance (TOD) is defined as the distance between the outermost point of the thalamus at its junction with the choroid plexus and the outermost part of the occipital horn in the parasagittal plane.[42] Some other parameters occasionally are used, such as the frontal horn ratio (FHR), hemispheric width (HW), ventricular height (VH), third ventricular width.

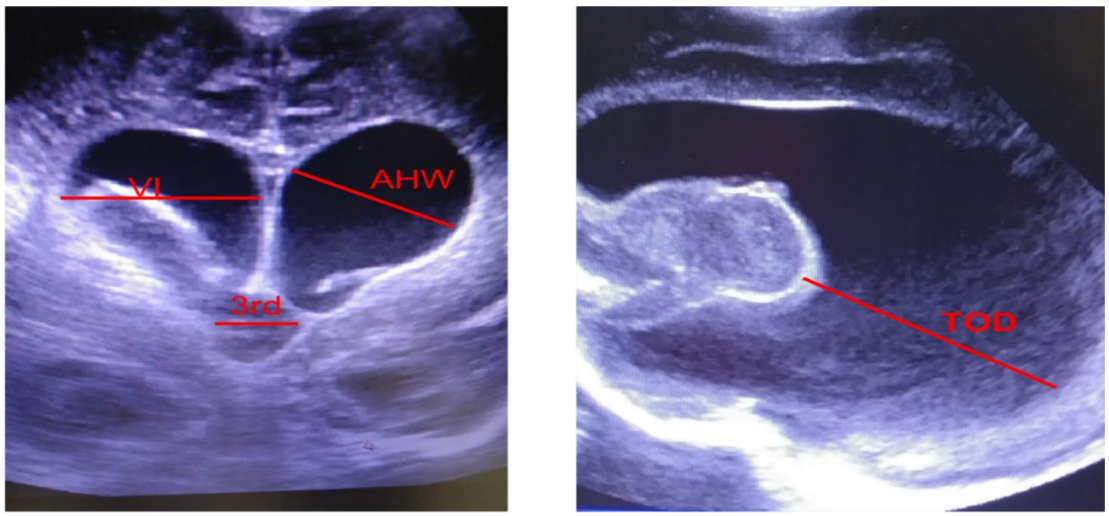

Figure 1.10: US images of different ventricular measurements a) VI, AHW, 3rd ventricle b) TOD

These parameters have been used for years to define the severity of IVH, but these measurements may have some limitations of plane selection that are technician dependent, also they have some Intra- and inter-observer variability. Between 1980 and 1990 some researchers tried to develop a method to minimize the limitations of 2D US images. Brann et al. developed a cylindrical coordinate-based method to estimate ventricular volume (VV) from 2D US images assuming that the 2D planes were recorded at equal angular spacing, and found good agreement in phantom experiments.[43] Brann et al. found good agreement of VV from 2D US images with the removed fluid during interventions.[44] In another study, Brann et al. were able to create guidelines using images of 48 patients with severe IVH and then used these guidelines prospectively to predict the necessity of intervention.[45] All of these methods were never used clinically because of the long-time needed for segmentation and difficulties in reproducing ultrasound planes.

1.6.4 Introduction of 3D cranial ultrasound (3D US):

3-dimensional ultrasound (3D US) is a technique where conventional 2D US images are converted into a volumetric image. In 1986 the first 3D images of a fetus were captured using 3D US technology in Japan. At first 3D US image was confined to obstetrical cases, and then expanded to gynecological and cardiac imaging. In the late 1990s, 3D US systems became more readily available in the clinical research setting. Imaging was accomplished initially using a mechanical device to rotate a conventional 2D US transducer to produce the third

dimension.[46] Other groups generated 3D US images by tracking a 2D US transducer during freehand scanning using electromagnetic tracking.[47] The use of 3D US for scanning the neonatal brain has been reported in several papers.[48-51] Salerno et al. in their single-center study on 30 patients proved that 3D US is a diagnostically accurate and efficient imaging tool for evaluation of the neonatal brain. They found shorter NICU acquisition time and smaller standard deviation in 3D US compared to the 2D US.[48] Mclean et al. found that 2D US measurements (VI and AHW) can be accurately reproduced from 3D US images.[51] In another separate single centered study with 59 patients Romero et al. could successfully differentiate normal as well as IVH, PHH, periventricular leukomalacia cases from both 2D and 3D US images.[52]

Most of the 3D images were acquired using a motorized device to translate, tilt, or rotate a transducer during image acquisition. These captured images were recorded by a computer. The computer that recorded the images and controlled the motor reconstructed the 3D US image. Although the commercially available 3D US system (Philip, APEC, Canon) are accurate, their high cost may limit the use in clinical practice. More recently, commercially available matrix transducers have been used to image the neonatal ventricles.[5]

1.7 Treatment of IVH, PHVD, and PHH:

There is no specific treatment for IVH, except to treat any other symptoms that may worsen the condition. Minimally invasive surgery and definitive surgery are

the standard management method for neonates with PHVD that do not resolve spontaneously. Research is still ongoing to improve treatment modalities.

1.7.1 Medical treatment and minimally invasive treatment:

Medical treatment means oral or intravenous administration of drugs that reduce the symptoms of a specific disease. Some of the drugs that were used to treat PHH are described below.

1.7.1a Diuretics:

Acetazolamide and furosemide are the diuretics that can reduce the production of CSF. These two drugs have been suggested as non-invasive therapies to reduce the production of CSF and as a result, reduce the risk of surgical treatment.[55] But no trial could prove a decreased risk for the need for a VP shunt or death with acetazolamide and furosemide therapy.[56,57] Moreover, diuretic therapy increases the risk of nephrocalcinosis, biochemical anomalies, motor impairment, and disability.[58] After comparing the risk and benefits this therapy is no longer in use or recommended.

1.7.1b Fibrinolytic agent:

The intraventricular administration of the thrombolytic agent streptokinase was considered effective in an early, non-randomized study. When intraventricular streptokinase was compared with standard treatment modalities of PHVD in a study, the numbers of deaths and babies with shunt dependence were almost

similar in both groups. Indeed, more of the fibrinolytic treated patients' required shunt surgery than those who were not treated by streptokinase.[59] Moreover, streptokinase carries a high risk of triggering new hemorrhages.[55] So, this therapy is also not recommended.

1.7.1c Drainage, irrigation, and fibrinolytic therapy (DRIFT):

Intraventricular administration of tissue plasminogen activator (tPA) and 72 hours drainage via two ventricular catheters (one frontal on the right, and one occipital on the left) has been proposed recently by Whitelaw et al.[58] But they found that DRIFT failed to reduce the need of VP shunt surgery or death in preterm infants with PHH when compared with tapping of CSF from hydrocephalic neonates.[60] However, due to the significant risk of meningitis from the indwelling catheters and increased risk of secondary hemorrhage, DRIFT therapy failed to prove its recommendation.[61]

1.7.2 Temporary surgical interventions:

The most commonly used temporary methods include ventricle tap (VP), lumbar puncture (LP), external ventricle drainage (EVD), ventricular access devices (VAD), and ventriculosubgaleal shunts. In our center, the ventricle tap is the most preferred method for temporary ICP relief.

1.7.2a Ventricular tap (VP):

VP in the most commonly used temporary method for relieving ICP created from hydrocephalus in most of the institutions especially for those patients with extremely low birth weights who might have sensitive skin and require minimal handling. VP is the removal of CSF from the lateral ventricle by insertion of the needle through the anterior fontanelle. This is an effective method for obstructive hydrocephalus. It should be noted that the neonate will experience periods of high ICP because of hydrocephalus followed by low ICP immediately following the intervention. Thus, the change in pressure must be monitored carefully and the risk of infections can be minimized by aseptic precautions.

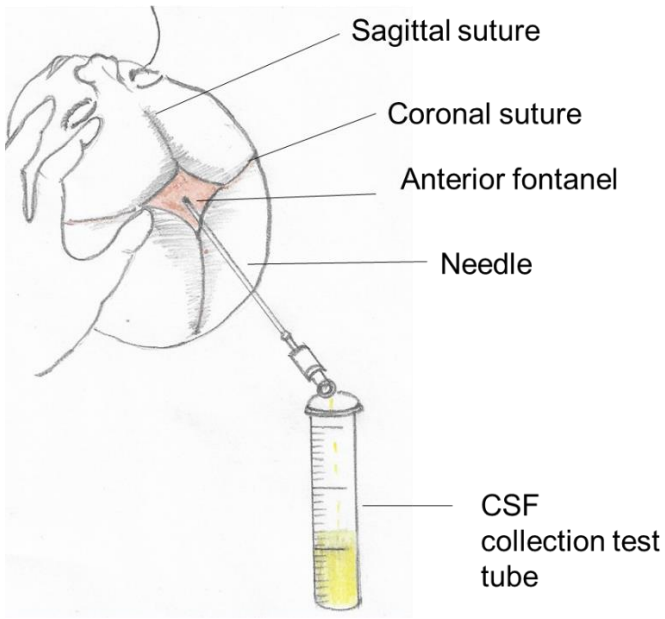

Figure 1.11: Drawing showing ventricular tap

1.7.2b Lumbar puncture (LP):

Lumbar puncture is another method of CSF removal from subarachnoid space through a needle inserted into the lumbar spine. Lumbar puncture had previously

been shown to improve hydrocephalus in patients who appeared to have communicating hydrocephalus (not a full blockage in the flow of CSF).[62] This is not the recommended method for obstructive hydrocephalus.

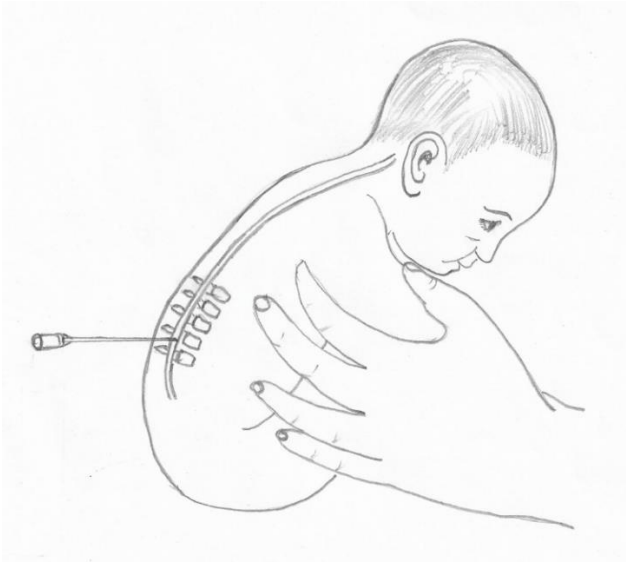

Figure 1.12: Drawing showing lumbar puncture

1.7.2c External Ventricle Drainage (EVD):

To avoid repeated VT or LP, sometimes EVD is inserted in some cases of neonates with progressive PHH, which allows constant removal of CSF and control ICP. A catheter is inserted through the fontanelle into one of the lateral ventricles and the other end of the catheter is placed within an external, closed drainage system where the amount of CSF drainage can be adjusted manually. It is reported in one study that 32% of survivors treated by EVD did not require permanent VP shunt.[63]

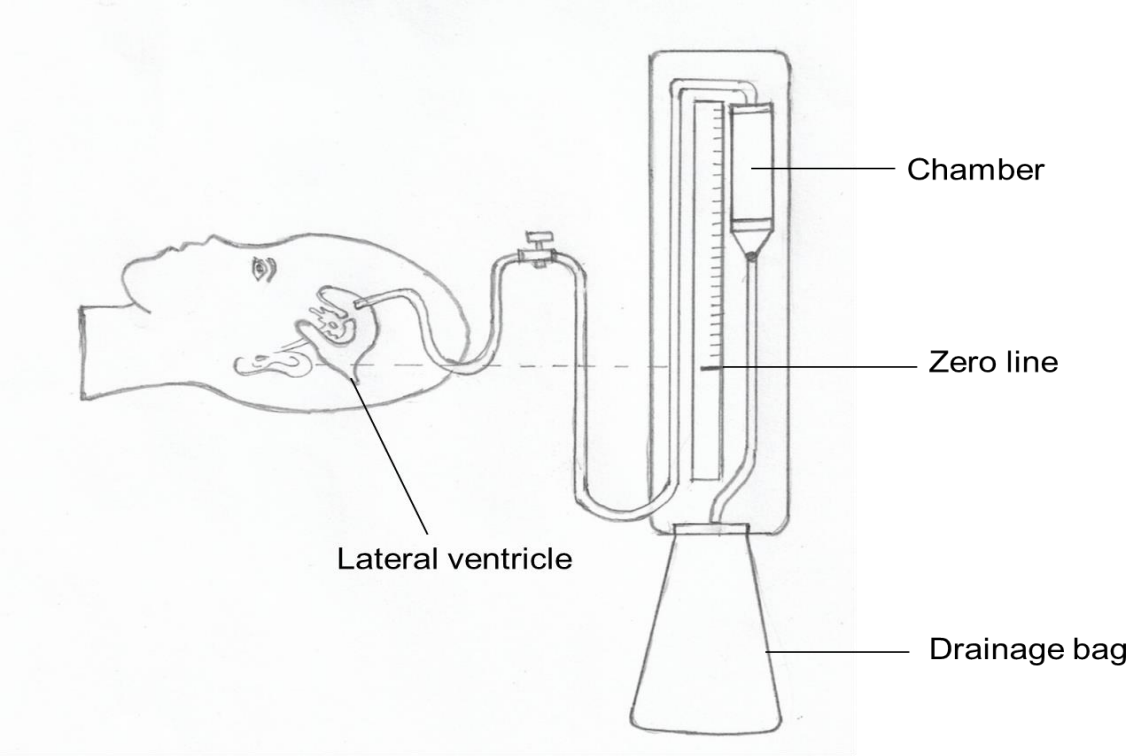

Figure 1.13: Drawing showing external ventricular drainage

1.7.2d Ventricle Access Devices (VAD) and Reservoirs:

Like EVD, ventricular access devices (VADs) have a catheter placed into the anterior horn of one of the lateral ventricles, but instead of an external container constantly collecting CSF at the end, a subcutaneous reservoir is present that collects CSF. This reservoir can be aspirated through a needle puncture to remove CSF intermittently. The difference between VT and VAD is that it allows more controlled removal of CSF. VAD has some drawbacks, such as peri-operative infection, skin defects, and CSF leaking.[64]

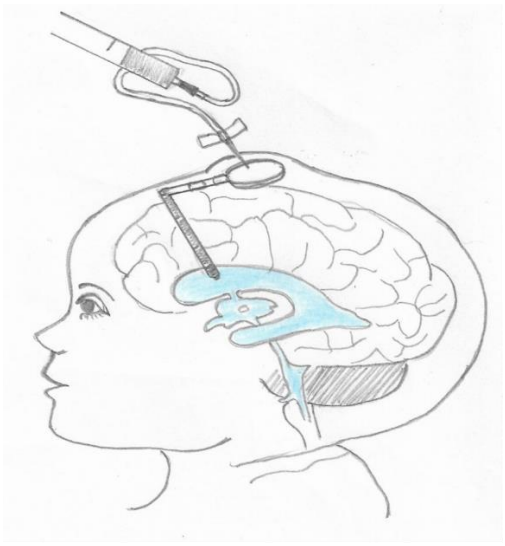

Figure 1.14: Drawing showing ventricular reservoir device

1.7.2e Ventriculosubgaleal shunt (VSGS):

VSG was first used for temporarily diverting CSF in a more physiological manner for those infants who are less than 1500 g in weight and are not capable of tolerating a ventriculoperitoneal (VP) shunt.[65] A catheter is inserted to connect the lateral ventricles into a large ‘pocket’ made in the subgaleal potential (space between epicranial aponeurosis and the periosteum of the skull), which allows temporary continuous drainage of CSF until the pocket becomes full of CSF. In some cases, VSG can be converted into a VP shunt when the infant gains the desired weight. VGS may have a lower risk of infection due to fewer aspirations. Despite favorable reports, the procedure has not gained universal acceptance probably because the protrusion of the CSF filled pocket from the patient’s head does not look good cosmetically.

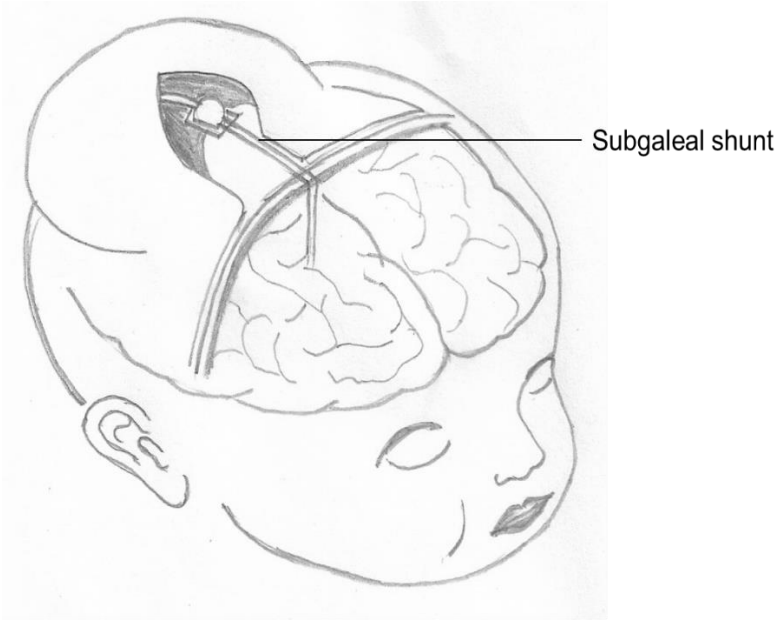

Figure 1.15: Drawing showing ventriculo-subgaleal shunt

1.7.3 Permanent endoscopic and surgical treatment method:

1.7.3a Endoscopic Third Ventriculostomy:

This is an endoscopic approach to make a hole on the floor of the third ventricle so that CSF can drain into the basal cistern (a dilatation of subarachnoid space rostral to the basilar pons and ventral and caudal to mammillary bodies) from where it can be reabsorbed by the arachnoid granulation.[66] Choroid plexus cauterization (CPC) is often combined with ETV, which allows a decrease production of CSF. The success rate of ETV in obstructive hydrocephalus is better than in communicating hydrocephalus.[67] It was reported that the initial failure rate is higher in ETV than shunt in children, but the relative risk becomes progressively lower for ETV after about 3 months.[68] This procedure is not

suitable for the neonates who are less than 6 months of age and who are suffering from communicative hydrocephalus.

1.7.3b Ventriculo-peritoneal Shunt (VPS):

The ventriculo-peritoneal (VP) shunt is the definitive surgery for patients with PHH. A shunt is a soft, flexible tube-like catheter. The top end of the catheter is placed in the ventricle fluid spaces inside the brain and the other end is introduced into the abdominal cavity. This tube is attached to a one-way valve that allows flow only from the ventricles to the peritoneum. Sometimes a special type of shunt can be used, named programmable shunt valve, where the pressure setting is adjustable so that the neurosurgeon can program the shunt to control how much CSF is draining. Nowadays antibiotic-impregnated shunt catheter has been introduced to minimize the risk of infection. Although Continuous development of the shunt device has provided significant improvement to the outcome of hydrocephalus patients, the main obstacles remain infection and obstruction, which require shunt revision surgery. Recently some groups of researchers have shown that intraoperative ultrasound guidance catheter placement is associated with a significantly lower shunt obstruction rate.[69] VP shunt complications can differ according to a patient's age and the etiology of the hydrocephalus. The incidence of complications following VP shunt placement is reported to be around 20 to 40%.[70] Though VP shunt can be a treatment option for a wide range of patient ages, from premature to very old patients, it is not suitable for the neonates who are less than 1500 g of weight.

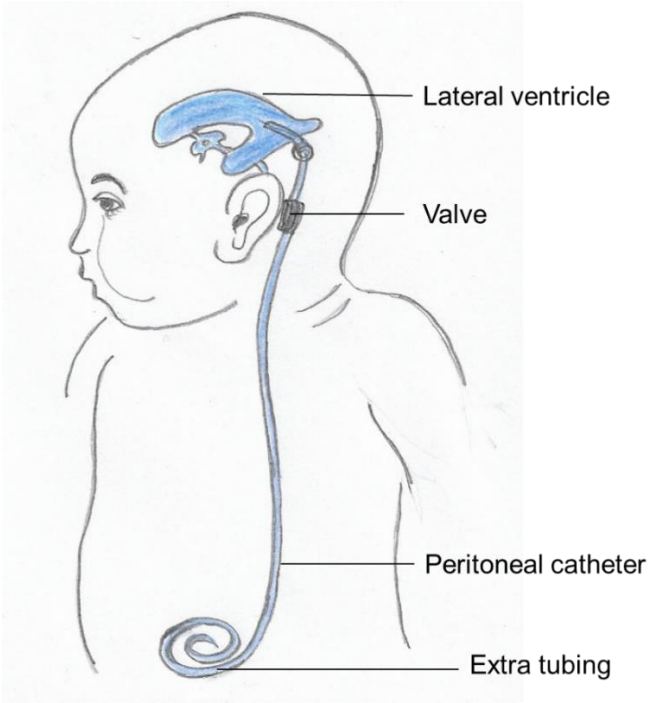

Figure 1.16: Drawing showing ventriculo-peritoneal shunt

Another type of VP shunt that lacks a valve, called valveless shunt, is also used in some institutions. In one study of the adult population, there was no difference in the rate of surgical shunt revision or differences in the time interval from insertion to first surgical revision between the two shunt modalities. The duration of neurosurgical hospitalization was shorter for patients receiving a valveless shunt.[71] The use in preterm neonates with PHVD requires either the removal or conversion to a valve regulated VP-shunt once the infant becomes ambulatory enough to sit upright.[72] This valveless shunt may allow patients to go home earlier but it has more risk of over drainage.

1.8 Robarts 3D US imaging system:

To minimize the cost of 3D imaging and to improve the overall system a new 3D US scanner system has been introduced in our lab that can be coupled to any clinical 2D US machine with an appropriate conventional transducer used for imaging neonatal brains. In addition, a volumetric phantom was developed using three-dimensional rapid prototyping technology to mimic a neonatal head with both mild and severe ventriculomegaly. This 3D US system was shown to be able to measure ventricle volumes accurately through a fontanelle in neonates, as well as able to measure simulated ventricles in test phantom accurately.[53] This system was also introduced in the NICU of Victoria Hospital, London, Ontario to image premature babies with IVH, and was used to further validate its use for measuring VV by comparing volume measurements from 3D US images obtained before and after ventricular tap (VT) with the reported volume of removed CSF from the tap.[54] This 3D US system is now being used clinically to monitor IVH neonates and to decide when to tap and how much CSF to draw.

1.8.1 The 3D US system:

The 3D US system acquires 2D US images and reconstructs them into a 3D image. Different researchers have tried to develop their 3D US imaging systems using different techniques.[48-51] A new 3D US system has been developed in our lab that can be coupled to any clinical 2D US machine with an appropriate conventional transducer used for imaging neonatal brains. This system consists of a handheld motorized device with a button and a transducer housing that can

house a 2D US probe. Although this system can be used with any US machine and an appropriate transducer, HDI 5000 (Philips, Bothel WA) US machine and C8-5 (Philips, Bothel WA) curved array 5 - 8 MHz broadband transducer was used until 2016.[11] A new machine (Philip iU 22) was used during the period 2018 – 2019 with the same transducer. After pressing the button of the motorized device, which is connected to a computer via USB, the US probe tilts about its front face. While the probe tilts, the 2D US images are acquired into a computer and reconstructed into a 3D image. The software was developed in our laboratory to control the motor's movements and to accept the 2D US images to reconstruct them into 3D images. A photograph of the motorized device with a transducer attached is shown in figure 1.17.

a b

Figure 1.17: Device for 3D US imaging a) with USB cable b) with neonatal transducer

1.8.2 Image acquisition and image segmentation:

For image acquisition, the person who performs the scanning locates the anterior soft part of the brain first, and then firmly holds onto the device's hand grip (see Fig. 1.17) while the device tilts the transducer on an axis at the probe tip, which is against the patient's head. Images are acquired at 25 frames/second over a scan angle of 30-72 degrees with the image acquisition time between 4-14 seconds. Typically, for neonatal studies, we used an angular spacing of 0.3 degrees and a total scan angle of 65 degrees, for a scan time of 8.7 s. The most commonly used depth was 8cm for most of the neonates and 9 cm for relatively older babies. Because of the movement of the patients, sometimes both lateral ventricles cannot be obtained in the first attempt. Usually, it requires 1-8 attempts to acquire both lateral ventricles. This makes the total bedside scan time about 2-15 minutes.

After 3D image acquisition, the lateral ventricles are manually segmented by trained observers in parallel sagittal slices with 1 mm spacing between adjacent slices and verified by a pediatric neurosurgeon. The boundaries of the ventricles must be carefully observed in both the sagittal and coronal plane and the lateral margins of the contours need to be manually adjusted to ensure the full segmentation of the ventricle. Each image required 20 - 45 min to segment a ventricle. The process of segmentation is shown in figure 1.18. Sometimes the right and left ventricles have to be segmented separately in separate images due to their large size. After full segmentation, the software automatically calculates the volume of the ventricle. The software has been validated for volume

measurements using known volume phantoms and by the interobserver correlation of the same images segmented by different observers.[11]

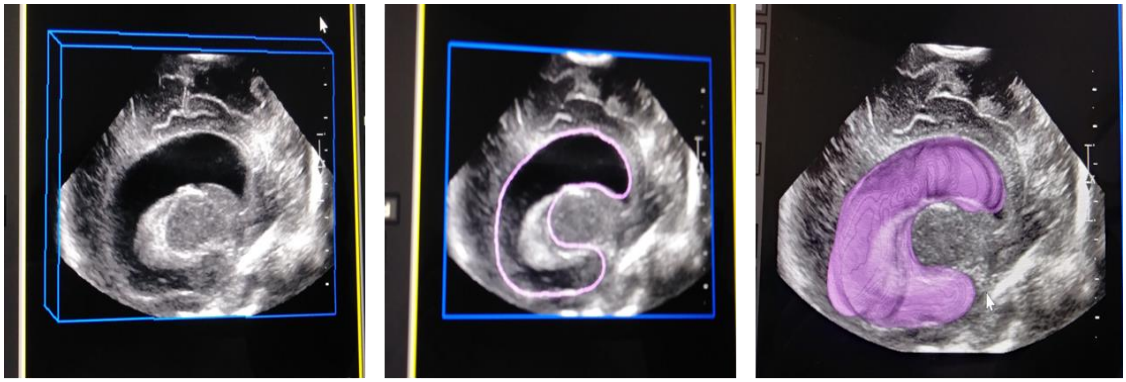

Figure 1.18: Process of segmentation a) 3D US cube of the ventricles before segmentation, b) the segmented ventricle boundary, c) segmented ventricle after full segmentation.

1.9 Research hypothesis and objectives:

The overall objective of this thesis is to introduce the 3D US system into the clinical practice of the neonates suffering from IVH. Previously this system was used only for research purposes. We have successfully used this system to monitor IVH babies and to make decisions about the management protocol. For example some neurosurgeons are using the 3D US ventricle volume to determine when to tap and how much to tap. All the studies described in this thesis were conducted using this 3D US system.

In chapter two, our objective was to determine the amount of CSF that should be removed during each VT. We expected to find a better correlation of tap amount

with 3D US total lateral ventricular volume than the traditional rule of removing CSF using the weight. We used a retrospective dataset to test this hypothesis. In this chapter, the findings met our expectations and supported the hypothesis that 3D US improves the volume determination of ventricular tap in neonates with intraventricular hemorrhage.

In chapter three, we proposed a hypothesis that the volume of two lateral ventricles may be affected by the posture of the neonates. We started a new experiment using this hypothesis. We changed the posture of the baby and scanned two times after 30 mins of changing each posture. This study was never done before. We found the change of volume is not significant enough to be strong statistically. In this chapter, the findings did not support our hypothesis.

In chapter four, an overview and summary of the important findings of Chapters 2-3 and the appendix have been presented. The limitations of the current findings and potential solutions for those limitations were also highlighted. Finally, some directions for future research are addressed in the end.

In the appendix, another study was included where we tested the fact that how short-term volume change of the total lateral ventricular volume after a VT can influence the further management protocol of IVH neonates. We used a combined retrospective and prospective data for this experiment. Our hypothesis for this chapter was that higher ventricular volume difference after the tap is a predictor of the future requirement of VP shunt. The results of this chapter supported the hypothesis.

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Chapter 2

2. Ventricular tap for post-hemorrhagic ventricle dilatation: How much CSF should be removed?

2.1. Introduction:

Intraventricular hemorrhage (IVH) is the bleeding inside the ventricles, which is the most common intracranial hemorrhage in preterm neonates. Recent reviews showed that the rates of IVH have remained 25% to 30% for very low birth weight infants (VLBW, <1500 grams) although survival of small premature infants has improved due to advances in specialized obstetric and neonatal intensive care in the past several decades.[1,2] Severe degrees of IVH, grades II-IV can lead to post-hemorrhagic ventricle dilatation (PHVD), which is the enlargement of ventricles by an increased amount of cerebrospinal fluid (CSF). PHVD is related to higher mortality and poor neurodevelopmental outcome later in life,[3] requiring accurate diagnosis and proper treatment when necessary.

Cranial ultrasound (US) has been shown to be superior to diagnose IVH, PHVD, and to evaluate the need for intervention.[4] Clinicians base their intervention mostly on a combination of clinical signs of elevated intracranial pressure (ICP), apnea, bradycardia, a rapid increase in head circumference (HC), and ventricular size assessed by 2D US; however, the timing of interventions is subjective.[5] Though the definitive treatment for PHVD is the placement of ventriculoperitoneal (VP) shunt to divert CSF from the brain to the peritoneal cavity, there is a general agreement that early VP shunt is not an option for small infants whose body

weight is less than 2000 gm, and also there is a risk of shunt failure, blockage, infections, and skin ulcerations.[6] Other temporary methods include ventricular tap (VT), lumbar puncture (LP), ventricular reservoir, ventricular access device (VAD), ventriculo subgaleal shunt (VSGS), endoscopic third ventriculostomy. The main goal of these treatments is to reduce ICP, protect the brain from damage and avoid the need for a permanent shunt.[7]

Previous works have been performed to compare various treatment methods,[6-9] which are still controversial. Since many cases of PHVD resolve after temporary CSF diversion procedures and do not require a shunt,[10] the primary treatment option in our institution is ventricle tap (VT), which involves the removal of CSF by insertion of a needle into the lateral ventricle through anterior fontanelle. Traditionally 10 ml/ kg CSF is removed in each VT. But it has been observed that this rule is not always followed.

We aimed to gather all the information of the infants who have undergone at least one VT in our institution from 2012 to 2016, with an objective to correlate the tap amount with infants' age, weight, and 3D US volume of the total lateral ventricles and to identify the strongest correlation.

2.2. Methods:

This study is a retrospective review of physical, neurological parameters and 3D US volume charts of premature infants affected by IVH and PHH who were intervened by at least one VT. The research protocol was approved by the Research Ethics Board at the University of Western Ontario (REB no.100315).

2.2.1. Patient selection:

Premature neonates in the neonatal intensive care unit (NICU) of Victoria Hospital, London, Ontario with a positive diagnosis of IVH on an initial clinical head ultrasound exam were recruited upon parental informed consent during the years between 2012 and 2016. Once enrolled recruited infants underwent serial 3D ultrasound exams one or two times per week according to the severity of IVH until discharge from NICU or transfer to another center. Neonates with congenital hydrocephalus and any other congenital anomaly with IVH were excluded. We included patients with IVH and comorbidity like meningitis who required intervention. Clinicians based their interventions according to some qualitative findings of 2D cranial US images and some combination of clinical and neurological findings (apnea, bradycardia, increase in HC, pupil condition and fontanelle palpation). The clinical care team was not aware of 3D US images and volume measurements. 70 premature neonates with IVH were recruited in our center between April 2012 to May 2016 by the previous graduate student of our lab. Among them, 54 resolved without any intervention and were excluded. Only 16 patients required ventricular tap, among them 5 patients had insufficient information and we could not include those 5 in this study. Finally we have identified 11 infants who have had at least one VT, allowing us to analyze the data of 42 individual taps from those 11 patients.

2.2.2. 3D US system: Described in chapter one, section 1.8.1 of this thesis.

2.2.3. 3D US image acquisition and segmentation: Described in chapter one, section 1.8.2 of this thesis

2.2.4. Data analysis and statistics:

We analyzed the data of each patient who had a VT after their birth. The variables recorded were gestational age, gestational weight, HC at birth, gender, age at IVH diagnosis, 3D US volumes of each ventricle in every scan, number and date of tap for each patient, amount of CSF removed in every tap, age, weight at the day of individual tap, HC just before and after tap, 3D US volume before and after tap, requirement of shunt placement and neurological outcome. Linear regression (R) was performed among selected variables (tap amount, weight, age, HC, TVV). A regression of $R^2 > 0.5$ was considered strong and $R^2 < 0.5$ was considered weak in this study. Bivariate correlation (measure of association of relationship between two variables), the coefficient for all linear regression and marginal model analyses (multiple assessments of the same subject at different time points) were also performed. The software used was SPSS v.25 (IBM Corp., Armonk, NY, USA).

2.3. Results:

2.3.1. Patients characteristics:

Ventricular taps were performed in the case of 11 infants among 70 hydrocephalic neonates during this study period who were treated by VT ranging from 1 to 9 times. The demographic and clinical details of the 11 infants are shown in table 2.1.

Table 2.1: Clinical characteristics of the study population

Characteristics	Details
Average gestational age (wk)	29.57 ± 4.7
Average birth weight (gm)	1491.63 ± 869.57
Average head circumference (cm)	27.43 ± 6.1
Sex ratio	Male 6/Female 5
No. of C/S deliveries	7
No. of vaginal deliveries	4
Average age of IVH diagnosis (days)	4.5 ± 2.1
Grade of IVH	
Grade I	0
Grade II	2
Grade III	4
Grade IV	5
Other comorbidities	
Respiratory distress syndrome	8
Hyperbillirubinemia	5
Retinopathy of prematurity	4
Patent ductus arteriosus	6
Sepsis	7
Meningitis	2

2.3.2. **Determining tap amount:**

Decisions of intervention by VT were decided by the clinical team based on the measurement of 2D cranial US and other clinical parameters. Moreover, tap

amount was also calculated by clinicians by following the traditional rule of 10 ml/kg and the other clinical status such as, heart rate, respiratory rate, blood pressure, oxygenation of the patient at that time to determine how much CSF can be removed safely. While analyzing various parameters related to the tap we found that this traditional rule was no longer in use and the tap amounts varied with a wide range. The differences of the expected tap amount according to the clinical rule of 10 mg/kg with the actual tap amount were from -19 ml to +23.15 ml. The actual tap amount, expected tap amount, deviations along with weight and TVV by the 3D US are listed in table 2.2. Information that was not recorded is marked as not determined (N.D.).

Table 2.2: Measured variables on the day of tapping

Patient ID	Number of taps	TVV by 3D US just before tap (cm^3)	Weight on the day of tap (gm)	Expected tap amount (ml) 10 ml/kg	Actutal tap amount (ml)	Deviations from the expected tap amount (ml)
P007	1	36.97	1460	14.6	21	6.4
P012	1	47.90	850	8.5	21	12.5
	2	42.00	1000	10	23	13
	3	39.60	1050	10.5	9	-1.5
	4	36.20	1100	11	16	5
	5	45.80	1240	12.4	20	7.6
	6	N.D	2758	27.58	25	-2.58
	7	305.00	3224	32.24	36	3.76
	8	408.07	N.D	N.D	48	N.D
P019	1	87.60	1220	12.2	27	14.8
	2	86.70	1300	13	9.5	-3.5
	3	117.60	1360	13.6	22	8.4
	4	N.D	1540	15.4	25	9.6
	5	146.90	1690	16.9	15	-1.9
	6	N.D	2300	23	25	2
P023	1	79.20	3900	39	20	-19
	2	92.00	N.D	N.D	20	N.D
P032	1	N.D	2530	25.3	36	10.7
	2	N.D	2685	26.85	50	23.15
P037	1	107.96	N.D	N.D	14	N.D
P041	1	45.67	1000	10	11	1
	2	59.41	1090	10.9	11.5	0.6
	3	74.68	1180	11.8	18	6.2
	4	96.23	1300	13	16	3
	5	103.7	1400	14	21	7
P043	1	56.4	1350	13.5	15	1.5
	2	63.1	1550	15.5	28	12.5
	3	48.65	1600	16	10	-6
	4	71.61	1840	18.4	N.D	N.D
P052	1	37.6	1480	14.8	9	-5.8
P055	1	44.7	1270	12.7	10	-2.7
	2	48.5	1270	12.7	22	9.3
	3	46.3	1270	12.7	23.5	10.8
	4	N.D	1320	13.2	31	17.8
	5	N.D	1410	14.1	22	7.9
	6	119	1820	18.2	15	-3.2
	7	N.D	2320	23.2	37	13.8
	8	N.D	2650	26.5	48	21.5
	9	N.D	2780	27.8	45	17.2
P057	1	79.75	1100	11	22	11
	2	76.19	1210	12.1	19	6.9
	3	98.52	1880	18.8	24	5.2

2.3.3. Correlations of tap amount with age, weight, head circumference, and 3D ventricular volumes:

We used linear regression in Microsoft Excel to find any correlations between the actual tap amount with the age, weight, head circumference, and 3D ventricular volumes. R^2 of tap amount with TVV, HC, weight and age were 0.55, 0.39, 0.33 and 0.29 respectively shown in figure 3.1 (a-d). The lowest correlation of tap amount was with age, HC just before the tap was better correlated with the actual tap amount, and the total lateral ventricle volume had the highest correlation with tap amount. To compare and confirm the findings of linear regression we analyzed the data in the marginal model (Multiple assessments of the same subject at different time points). The software used was SPSS v.25 (IBM Corp., Armonk, NY, USA). The Pearson correlation of tap amount with TVV, HC, weight, and age were 0.739, 0.622, 0.595 and 0.468 respectively, which supports our findings of linear regression. In both analyses, our result suggests that ventricle volume had the highest correlation with tap amount among the 4 predictors of interest. Bivariate correlations among 4 predictors and tap amounts are shown in table 2.3.

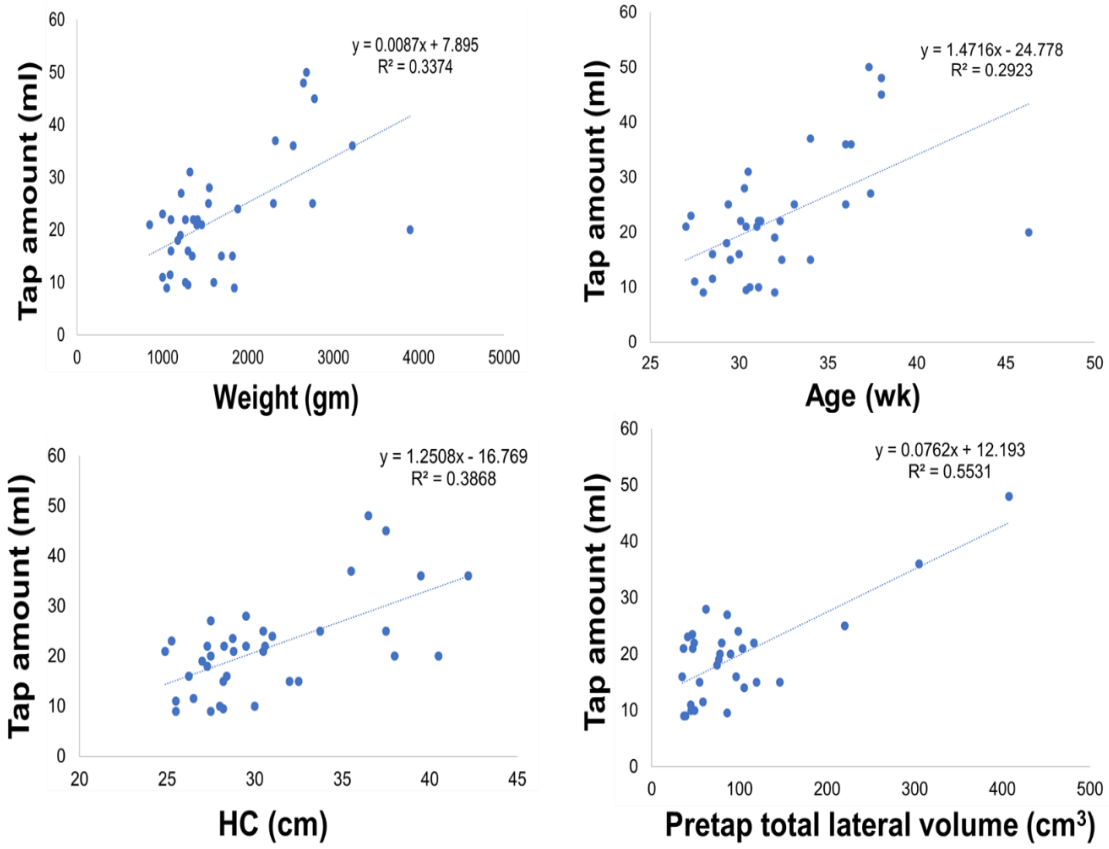

Figure 2.1: Linear regression of tap amount with weight, age, HC, and the total lateral ventricle volume before tap.

Table 2.3: Results of Bivariate correlation between tap amount and 4 predictors (age, weight, HC and total ventricle volume)

		Tap amount (ml)	Weight (gm)	Age (wk)	HC (cm)	total ventricle volume (cm^3)
Tap amount (ml)	Pearson Correlation	1	0.595**	0.468*	0.622**	0.739**
	Sig. (2-tailed)		0	0.014	0	0
	N	42	38	27	37	32
Weight (gm)	Pearson Correlation	0.595**	1	0.953**	0.911**	0.646**
	Sig. (2-tailed)	0		0	0	0
	N	38	40	27	38	29
Age (wk)	Pearson Correlation	0.468*	0.953**	1	0.846**	0.531**
	Sig. (2-tailed)	0.014	0		0	0.006
	N	27	27	27	26	25
HC (cm)	Pearson Correlation	0.622**	0.911**	0.846**	1	0.692**
	Sig. (2-tailed)	0	0	0		0
	N	37	38	26	39	30
TVV (cm3)	Pearson Correlation	0.739**	0.646**	0.531**	0.692**	1
	Sig. (2-tailed)	0	0	0.006	0	
	N	32	29	25	30	32

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed)

In addition, table 2.4 shows some coefficient summaries, which show that ventricle volume is best at predicting tap amount even when accounting for age, weight, and head circumference separately. Age, weight, and HC were not significant when included in the model with ventricle volume, which further supports the suggestion that ventricle volume is a better predictor of tap amount than age, weight, or HC.

Table 2.4: Coefficient summaries of 3 linear regression results evaluating ventricle volume with each of the other 3 predictors (Wt, age, HC)

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	13.18	2.64		4.98	0	7.75	18.61
	Weight (gm)	0.001	0.002	0.06	0.27	0.78	-0.004	0.005
	TVV (cm^3)	0.055	0.024	0.502	2.32	0.028	0.006	0.103

a. Dependent Variable: Tap amount (ml)

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	11.39	9.72		1.17	0.25	-8.78	31.57
	Age (wk)	0.05	0.33	0.03	0.14	0.88	-0.64	0.74
	TVV (cm^3)	0.058	0.021	0.56	2.75	0.012	0.014	0.102

a. Dependent Variable: Tap amount (ml)

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	10.78	9.015		1.19	0.24	-7.71	29.28
	HC (cm)	0.11	0.34	0.075	0.33	0.74	-0.59	0.82
	TVV (cm^3)	0.053	0.024	0.49	2.19	0.037	0.003	0.103

a. Dependent Variable: Tap amount (ml)

Overall, there was a significant relation between tap amount and each predictor (ventricle volume, age, weight, HC) on their own. But TVV had the highest relation among all predictors.

Table 2.5: Results in the Marginal model with all 4 predictors (tap amount, weight, age, HC, total ventricle volume)

Estimates of Fixed Effects[a]							
Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	28.17	35.16	20	0.801	0.43	-45.16	101.50
Weight (gm)	0.005	0.008	20	0.63	0.53	-0.012	0.02
Age (wk)	-0.69	0.97	20	-0.71	0.48	-2.72	1.32
HC (cm)	-0.006	1.36	20	-0.001	0.99	-2.85	2.84
TVV(cm^3)	0.046	0.037	20	1.26	0.22	-0.03	0.12

a. Dependent Variable: Tap amount (ml)

2.3.4. Outcomes of VT and requirement of VP shunt and revision shunt:

Serial tapping was performed on these neonates before the placement of the V-P shunt. The average number of taps performed per patient was 4. Among those 11 patients, 2 patients did not need any shunt placement, the other 9 infants received V-P shunt for management of PHVD. Among the 9, 2 infants received a revision shunt. No infant died during this study period. The infants were observed for developmental and neurological assessments after the placement of shunts.

2.4. Discussion:

In our retrospective study, we investigated the potential for 3D US-based measurements of ventricular volume (VV) from neonatal brain images to characterize the volume of CSF that should be removed in each tap. Currently, it is not known how much CSF is safe to drain, and practices vary among neurosurgeons and among institutions. However, one study reported that 10 ml

of CSF should be removed for each kg weight,[12] but minimum and maximum limits have not been studied. One recent study has claimed that cerebral oxygenation would improve after the removal of less CSF than the standard of 10 mL/kg.[13] Removing a larger amount of CSF can cause transient apnea, bradycardia after the intervention,[14] but the removal of a too-small amount may not improve the clinical status and may lead to excessively repeated interventions if the infant does not improve clinically.

Previously the 3D US measurement of the ventricular volume was validated against a test phantom with a known volume and showed that the 3D US geometric reconstruction was found to be accurate with an error of < 0.2%.[11] This system was also used to compare the ventricle volumes of IVH patients measured with 3D US and MRI and found high agreement ($R^2 = 0.99$).[3,15] but with a systemic bias toward lower VV measured by the 3D US due to issues in the visualization of some midline structures that are near the posterior fossa.[3] But the volume difference of pre tap and post tap VV measured by the 3D US was highly correlated with the tap amount. Kishimoto et al. found the Pearson correlation coefficient of $R^2 = 0.92$,[3] while Brann et al obtained $R^2 = 0.84$.[19] 2D cranial US is still the clinically preferred method to diagnose IVH and to evaluate the necessity of intervention, but this method may have few errors, variability and cannot be fully relied on to provide accurate volume measurements. Although the 3D system was proven to be better to predict interventional necessity, it has not yet been adopted clinically as a standard care tool.[3]

In this study we compared the amount of CSF removed in each tap with the age on that day from conception, weight in grams on the same day, HC measured just before tap and the total volume of the lateral ventricles measured by the 3D US just before VT. Based on guidelines, the tapped volume should be well correlated with neonate weight as this is the well-accepted biomarker to determine how much fluid should be removed in each tap. However, in our study, the tap amount was better correlated with pre-tap total volumes of the lateral ventricles measured by the 3D US. As the clinical team was not aware of the volume of the 3D measurements, removal of CSF was done according to the weight and another clinical status. However, there is no known parameter in 2D US-based measurements depending on which clinician can determine the tap amount in each VT; they mainly rely on weight and other neurological and clinical parameters. In our study, the weak correlation between tap amount and weight suggests that this biomarker might not be sufficient to determine the CSF amount that should be removed. 3D US-based volume measurements can be used concurrently to avoid frequent taping and to improve the clinical status of the infant.

Some researchers have found improved cerebral hemodynamics and oxygenation during CSF removal after 50 % of planned CSF removal that was 10 mL/kg.[13] But it was not reported that cerebral hemodynamics fell after 100% or more than 100% of planned CSF removal. However, it was shown that too little aspiration (< 10 ml/kg body weight) has no effect on ventricle size or ICP.[12] Moreover, in our retrospective study of 42 VTs, the given amount of CSF removal

was tolerated by all the infants and no deterioration of clinical status was observed during this period.

One limitation of the measurement of VV is the time required to segment each ventricle (20- 45 mins) and requirements for training to perform this task. If this limitation can be overcome with methods such as deep learning, the 3D US-based measurement of VV might be adopted clinically considering that it might be a better tool for the management of PHVD.

There are wide variations of interventional treatments such as lumbar puncture, VT, ventricular reservoirs tapping but we only considered VT in this study, which is a limitation of this study. The determination of tap amount by 3D US-based measurement of VV should be also validated among the other interventional treatments. An additional limitation in our study is the small number of patients (n = 11) who required interventions (total VT = 42) and that some information on some of the days were not recorded. Also, some manual segmentations were not possible when the dilatation of the ventricles was very large and resulted in bad 3D US images on some interventional days. These cases were excluded from our study. In some cases, the fontanelle size was a limiting factor and the probable cause of producing bad 3D US images.[16,17] The median age of fontanel closure is about 13.8 months in the term group and fontanelle size in preterm infants do not differ significantly from that of term infants after reaching term age.[18] But the anterior fontanelle usually shrinks as the neonates get older and the posterior acoustic shadow of the edge the frontal bone reduces the image quality and increases invisibility of US image.

Because of the diversity among various centers and also among neurosurgeons regarding the amount of CSF that should be tapped, it has become a high priority to investigate a standard guideline for the neurosurgeons. As such, we have tried to present a potential clinical use of 3D US-based measurement of total lateral ventricular volumes in this regard. However, future larger, multicenter studies are required before generating guidelines for tap amount during intervention.

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Chapter 3

3. Does the head position affect ventricular volume?

3.1 Introduction:

Ultrasonographic examination of the neonatal brain has remained the superior method of identifying intracranial structural abnormalities. Recently, reports have shown that 3D ultrasound imaging can be used to measure the volume of the ventricles accurately especially in neonates who have intraventricular hemorrhage (IVH) and post-hemorrhagic ventricle dilatation (PHVD).[1] Asymmetries in the volumes of lateral ventricles have been found in a significant number of premature neonates, but whether this is normal physiology or is due to any other underlying pathology is not clear.[2]

Preterm infants have an increased risk of intraventricular hemorrhage, which can lead to cerebral palsy, motor problems, cognitive delays. Nursing or care plays an important role in neonates who are born prematurely. One of the earliest neurodevelopmental interventions in the neonatal intensive care unit (NICU) is the positioning of the neonates. It is reported that the prone position has been recommended for several decades to result in positive effects on preterm and low birth weight neonates.[3] One study showed that prone positions in neonates significantly reduce stress levels.[4] Another study investigated that a physiological flexed position is ideal for the neonates who have missed some or the whole part of their third trimester in the uterus.[5] However, according to the American

Pediatric Association, the supine position is best for neonates.[6] Karen A. et al suggested that positioning of neonatal head in a neutral position ensures optimal cerebral venous drainage through internal jugular veins and this position is especially important during first 3 days of birth because of the high risk of bleeding from germinal matrix during this time.[7] But some of the premature neonates are frequently nursed in different positions due to their irregular breathing and apnea to achieve postural drainage.[7,8] Each position has its own benefits and drawbacks. Thus, it is important to assess each neonate individually to be appropriately positioned according to their status.

Previously width of the lateral ventricles has been measured to diagnose ventricular dilatation and ventricular asymmetry. Due to gravity and soft brain, the width of the lateral ventricle may change due to the different head positions.[9] In this prospective study, we investigated this hypothesis more accurately by measuring the volume of each lateral ventricle separately from 3D US images acquired from the same patient in two different postures on the same day at two different time intervals. We used 30 minutes time interval for this study assuming that within this time total CSF volume will not increase or decrease in the neonates who have post hemorrhagic ventricle dilatation (PHVD). Moreover, sufficient time will allow the CSF to flow within the ventricles and around the subarachnoid spaces. Therefore, we studied prospectively the volumes of the lateral ventricles using 3D US and calculated the differences of each lateral ventricles in relation to the posture of the neonates. As ventricular tap (VT) can

be done from any side of the ventricle, it is important to know which ventricle is larger in a lateral posture to decide the site of VT.

3.2 Methods:

3.2.1 Selection of participants:

The research protocol was approved by the Research Ethics Board at the University of Western Ontario. As a part of a larger study to investigate the patients with IVH, this prospective study started in June 2018, in which we recruited premature neonates born before 30 weeks of gestation from NICU of Victoria hospital following informed consent from their parents. Once enrolled, neonates underwent serial 3D US scans until discharge or transfer to another center from our NICU. The babies who developed IVH were imaged two to three times per week, and those who did not develop IVH were imaged once per week. Neonates with any congenital anomaly and any brain abnormalities were excluded. Most of the neonates had some other comorbidities like sepsis, acidosis and respiratory distress. A total of 24 premature neonates were recruited during the period of June 2018 to November 2019. Among them, 22 had different grades of IVH and only 2 did not have any IVH.

3.2.2 Positioning and scanning:

Because of the comorbidities and clinical instability, we could not change the position of the babies in most of the imaging sessions to acquire images in the two different postures. In those cases, we noted the posture of the babies during the scan. We obtained 15 3D US images from different babies who were turned

to their right and 16 US images from different babies who were turned to their left. We compared the right and the left ventricles in the two different postures. But in these 15 right-sided scans and 16 left-sided scans, we didn't know how long the baby had been turning to that specific lateral position.

For 6 babies who were relatively stable to handle and were not suffering from conditions that could worsen from changing posture, we completed 20 posture change 3D US imaging sessions. For these imaging sessions, we first ensured from the nurse that the baby was clinically stable. If the baby was stable, we moved the baby to the right side and ensured immobilization for at least 30 minutes and then imaged the baby in that posture. After the 1st scan, we again changed the posture of the baby to the left side, waited for 30 minutes, and then we imaged the baby for the 2nd time in the left posture.

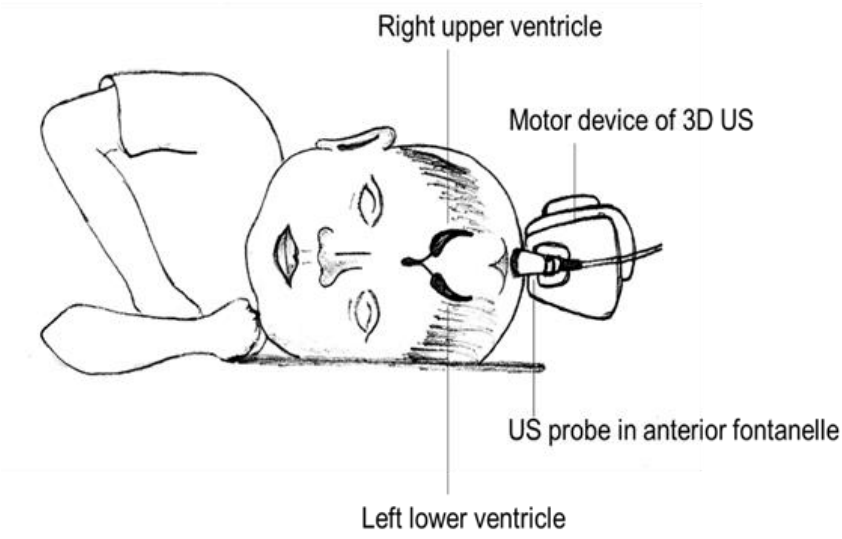

Figure 3.1: Head positioning during the imaging session. Here the right ventricle is in the upper position and the left ventricle is in the lower position.

3.2.3 3D US system:

We used the same 3D US system that is described in chapter one, section 1.8.1 of this thesis.

3.2.4 Image segmentation and measurement of volumes:

Described in chapter one, section 1.8.2 of this thesis.

3.2.4 Data analysis and statistics:

For this study, we measured each ventricular volume in each posture separately. For the patients who were not included in the posture change experiment, we performed a paired two samples for means t-test. For the 20 posture change experiments we measured every ventricle in each posture three times and averaged them. Two observers measured the volumes of the ventricles being blind to the values obtained by the other observer. The intraclass correlation coefficient (ICC) was calculated to investigate the inter- and intra-observer variability. We also performed a paired t-test to compare the left and right lateral ventricle volumes.

3.3 Results:

3.3.1 Patients characteristics:

In this study, we had two sets of patients. 1. Premature neonates with any grade of IVH who were imaged without changing their posture. 2. Relatively stable premature neonates with or without IVH who were moved to both their right and

left sides for 30 minutes. Clinical characteristics of the 1st set of patients are shown in table 1 and the 2nd set of patients are shown in Table 2.

Table 3.1: Clinical characteristics of 1st set of patients (N=18) who did not have their posture changed

Characteristics	Details
Average gestational age (wk)	27.89 ± 4.97
Average birth weight (gm)	1261.53 ± 810.08
Average head circumference (cm)	26.21 ± 5.33
Average length at birth (cm)	36.31 ± 5.96
No. of caesarian deliveries	6
No. of forceps deliveries	1
No. of vaginal deliveries	11
Average age of IVH diagnosis (days)	7.69 ± 8.98
Grade of IVH	
Grade I	2
Grade II	4
Grade III	7
Grade IV	5
Other comorbidities	
Chronic lung disease	1
Hyperbilirubinemia	5
Sepsis	3
Meningitis	2
Thrombocytopenia	1
Inguinal hernia	2
Hypotension	2
Bacteremia	2
Acidosis	3
GIT atresia	1

Table 3.2: Clinical characteristics of 2nd set of patients (N=6) who had their posture changed for the imaging sessions

Characteristics	Details
Average gestational age (wk)	27.4 ± 1.91
Average birth weight (gm)	1120 ± 211.19
Average head circumference (cm)	26.83 ± 2.88
Average length at birth (cm)	37.67 ± 3.82
No. of caesarian deliveries	1
No. of vaginal deliveries	5
No IVH	2
Presence of IVH	4
Grade I	0
Grade II	1
Grade III	3
Grade IV	0
Other comorbidities	
Respiratory distress syndrome	1
Meningitis	1
Pneumothorax	1
GIT hemorrhage	1
ASD	1

3.3.2 Observer agreement:

There was a high ICC between the two observers (ICC 0.98-0.99) and also between volume measurements made by a single observer (ICC 0.88-0.98) for the lateral ventricles in the two postures.

Table 3.3: Inter and intra-observer agreement. The intraclass correlation coefficient of the right ventricle and the left ventricle in both right side down and left side down

	Left side down		Right side down	
ICC	Left ventricle	Right ventricle	Left ventricle	Right ventricle
Intravariance	0.88	0.97	0.98	0.94
Intervariance	0.98	0.98	0.99	0.99

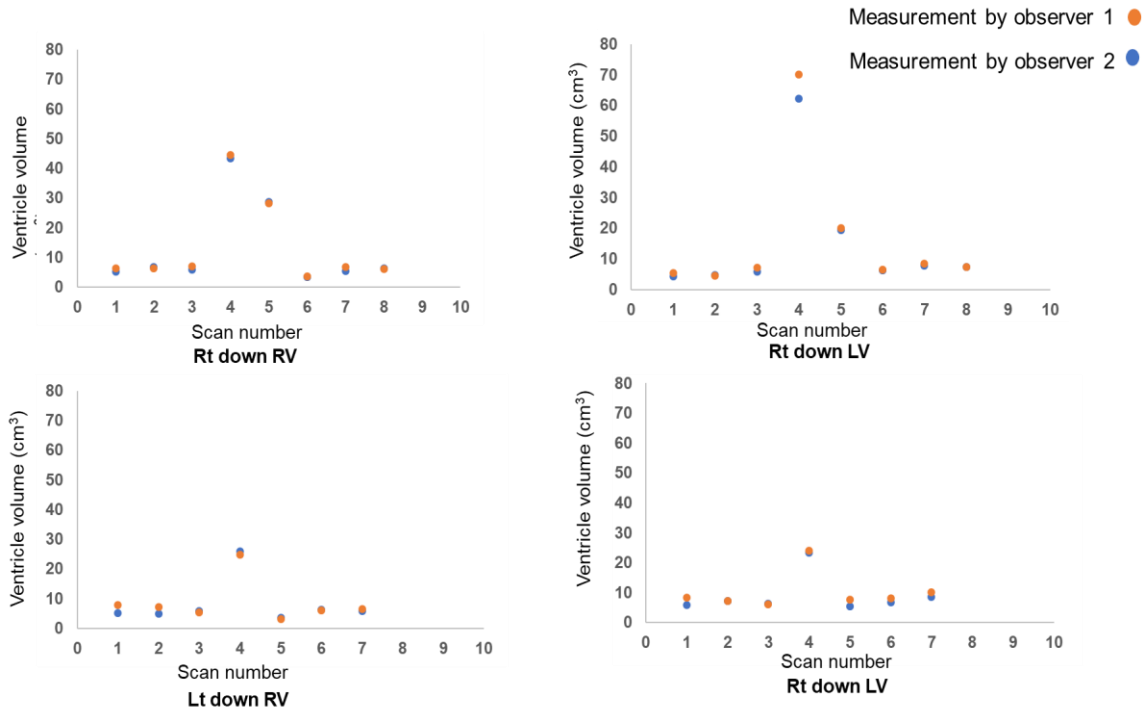

Figure 3.2: Graph showing measurements of ventricular volumes by two observers where the x-axis is the scan numbers and the y-axis is the ventricle volumes in cm^3

3.3.3 Comparing the volume of the two lateral ventricles who did not have their posture changed:

We imaged the babies 1-3 times per week according to the severity of IVH without changing their posture. We obtained a total of 15 3D US images from the neonates with different grades of IVH while the babies were turned to their right and another 16 3D US images of the babies who were turned to their left. The average volume difference between two lateral ventricles in the right lateral posture was 9.1 cm^3 and in the left lateral posture was 5.3 cm^3. Among 15 right lateral images, the right ventricles were larger in 7 scans, left ventricles were larger in 4 scans, and almost equal (volume difference ± 2 cm^3) ventricles volumes in 4 scans. Similarly, among 16 left lateral 3D US images, the left ventricles were larger in 8 scans, the right ventricles were larger in 2 scans, and in 6 scans both of the ventricles were almost equal (volume difference ± 2 cm^3).

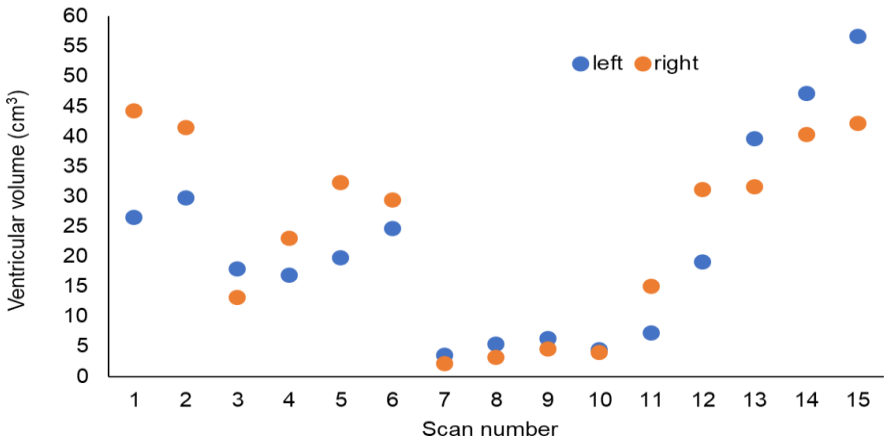

Figure 3.3: Plot of the measured two lateral ventricle volumes when the neonate was in the right lateral position where the right ventricle was the lower and the left ventricle was the upper ventricle.

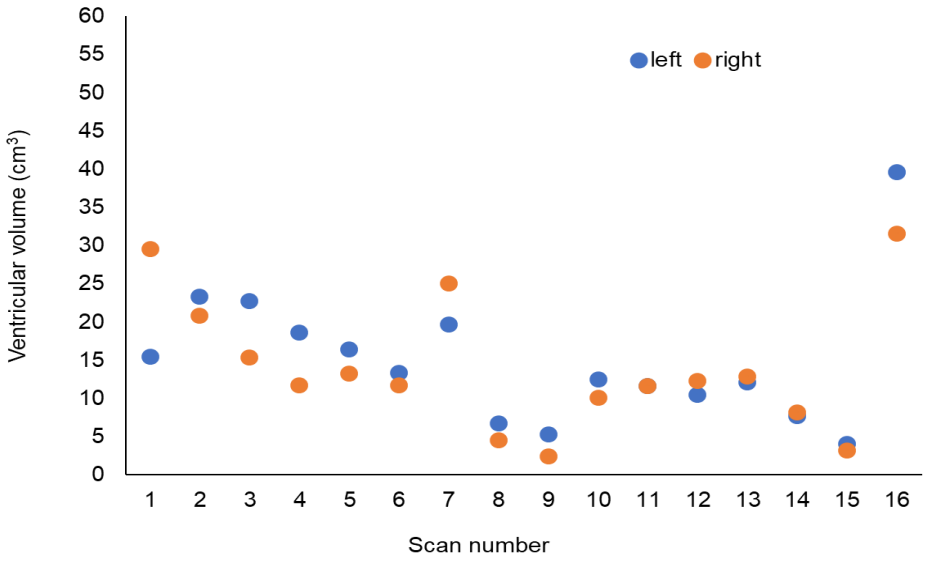

Figure 3.4: Plot of the measured two lateral ventricle volumes when the neonate was in the left lateral position where the left ventricle was the lower and the right ventricle was the upper ventricle.

The mean of right and left ventricle volumes were 23.81cm^3 and 21.61cm^3 respectively when the right ventricle was in the lower position. When the left ventricle was in the lower position the mean right ventricle volume was 13.96 cm^3 and the mean left ventricle volume was 14.92 cm^3.

Table 3.4: t-Test: Paired two sample for means in the right lateral position of the babies who did not have their posture changed testing the hypothesis that the lower ventricle is larger than the upper one in any lateral posture

	LV	RV
Mean (cm^3)	21.61	23.8
Standard deviation (cm^3)	16.19	15.58
Observations	15.	15
Pearson Correlation	0.83	
Hypothesized Mean Difference	0	
P(T<=t) one-tail	0.18	

Table 3.5: t-Test: Paired two sample for means in the left lateral position of the babies who did not have their posture changed testing the hypothesis that the lower ventricle is larger than the upper one in any lateral posture

	LV	RV
Mean (cm^3)	14.92	13.96
Standard deviation (cm^3)	8.77	8.69
Observations	16	16
Pearson Correlation	0.81	
Hypothesized Mean Difference	0	
P(T<=t) one-tail	0.23	

A difference of 2.2 cm^3 in right lateral posture and 1 cm^3in left lateral posture was found in the two lateral ventricular volumes measured by our 3D US system in the two different postures. These differences were not statistically significantly different (N=15 in right lateral posture where p = 0.183 and N = 16 in the left lateral posture where p = 0.239).

3.3.4 Comparing the volume of the two lateral ventricles in neonates with changed posture:

Six relatively stable neonates were imaged a total of 40 times with 20 imaging sessions on the right lateral position and 20 imaging sessions on left lateral positions. Each baby was imaged between 2 to 4 times. The difference between the two scans for one baby was at least one week. Volumes of the two ventricles in each posture for the 6 patients are shown in figure 3.5.

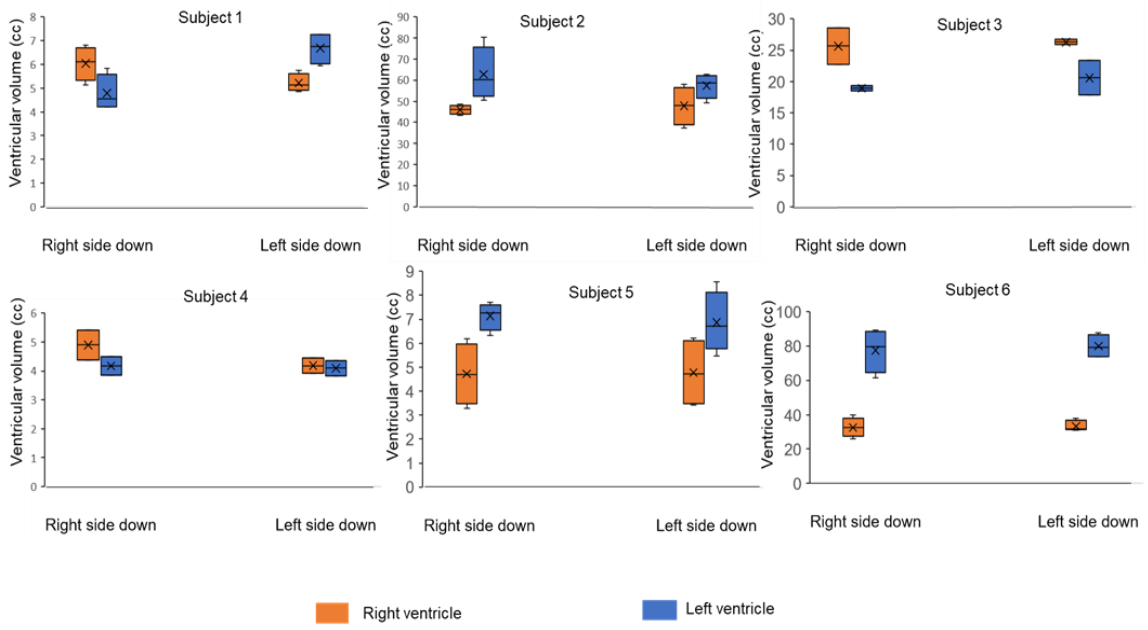

Figure 3.5: Box and whisker plot of the right and left ventricle volume of each patient in two different postures who had their posture changed.

Among 20 posture changes of the 6 different subjects, we found that, while the right ventricle was lower, the right ventricle was larger in 7 cases, the left ventricle was larger in 12 cases, and both were equal in 1 case. While the left ventricle was lower, the right ventricle was larger in 3 cases, the left ventricle was

larger in 14 cases and both ventricles were equal in 3 cases. Equal volumes were considered here when the volume difference of two lateral ventricles was less than 0.5 cm^3. Figure 3/6 shows coronal images obtained from a grade III IVH patient at two different lateral postures. It is apparent in these images that the shape of the ventricles changed, but the volume change was not significant enough to show the effect of postures on ventricular volume.

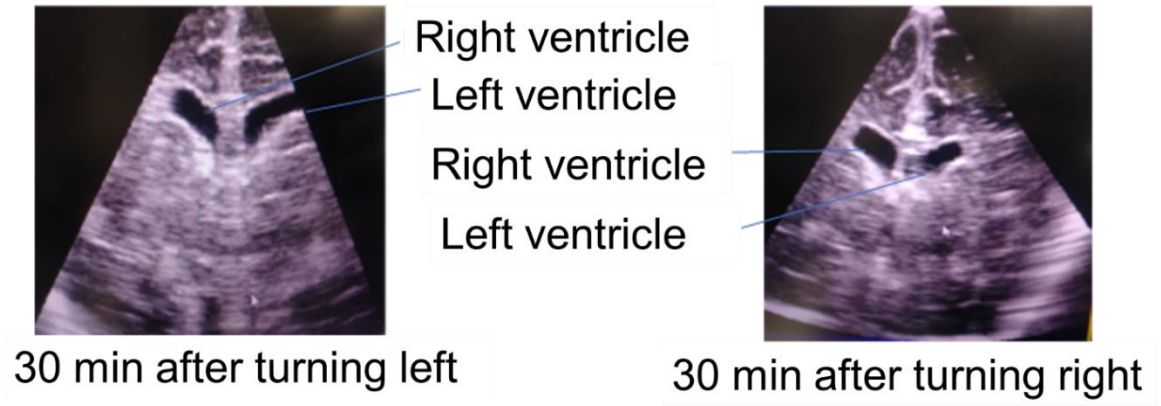

Fig 3.6: Coronal image of the same patient on the same day obtained when the neonate was imaged 30 min after the right and the left lateral posture.

After positioned for 30 minutes on the right side, the mean right and left ventricular volumes were 20.9 cm^3 and 32.8 cm^3 respectively. However, after positioning for 30 minutes on the left side the mean right and left ventricular volumes were 21.3 cm^3 and 32.7 cm^3 respectively.

Table 3.6: t-Test: paired two samples for means: Ventricles volumes of the neonates after positioned 30 minutes on the right side testing the hypothesis that the lower ventricle is larger than the upper one

	Rt down RV	Rt down LV
Mean (cm^3)	20.92	32.74
Standard deviation (cm^3)	17.302	32.73
Observations	20	20
Pearson Correlation	0.84	
Hypothesized Mean Difference	0	
P(T<=t) one-tail	0.009	

Table 3.7: t-Test: paired two samples for means: Ventricles volumes of the neonates after positioned 30 minutes on the left side testing the hypothesis that the lower ventricle is larger than the upper one

	Lt down RV	Lt down LV
Mean (cm^3)	21.25	32.65
Standard deviation (cm^3)	18.405	31.58
Observations	20	20
Pearson Correlation	0.81	
Hypothesized Mean Difference	0	
P(T<=t) one-tail	0.009	

A comparison of the mean ventricles in two postures showed that the mean right ventricle volume was 20.92 cm^3 when positioned in the right lateral posture and 21.25 cm^3 when positioned in the left lateral posture. The mean left ventricle volume was 32.74 cm^3 when positioned in the right lateral posture and 32.65 cm^3 when positioned in the left lateral posture.

Table 3.8: t-Test: paired two samples for means: Right ventricle volume after positioned 30 minutes of two lateral postures comparing the right ventricle volume in two postures

	Rt down RV	Lt down RV
Mean (cm^3)	20.92	21.25
Standard deviation (cm^3)	17.30	18.405
Observations	20	20
Pearson Correlation	0.98	
Hypothesized Mean Difference	0	
P(T<=t) one-tail	0.35	

Table 3.9: t-Test: paired two samples for means: Left ventricle volume after positioned 30 minutes of two lateral postures comparing the left ventricle volume in two postures

	Rt down LV	Lt down LV
Mean (cm^3)	32.74	32.65
Standard deviation (cm^3)	32.73	31.58
Observations	20	20
Pearson Correlation	0.98	
Hypothesized Mean Difference	0	
P(T<=t) one-tail	0.47	

3.3.5 Patient outcomes:

Among the 24 patients, 22 had different grades of IVH and 2 did not develop IVH. Among IVH patients, 8 required ventricular taps (VT) and another 16 IVH babies resolved spontaneously without any intervention. Among the babies who required VT, 2 babies required additional external ventricular drainage (EVD) for the continuous drainage of CSF. Six babies were finally treated by ventriculoperitoneal (VP) shunt but 2 babies presented shunt infection and required to be reshunted.

3.4 Discussion:

Our study investigated ventricle volume differences of extremely premature infants where IVH is the major cause of adverse short- or long-term outcomes characterized as the subsequent need for surgical interventions for PHVD. In this study, only 2 recruited premature infants did not develop IVH. 25% of the IVH population were the subjects of posture change experiments.

Although the left ventricle has been described as larger than the right by some investigators,[10-12] the cause behind this has not been established. It is believed that the cause behind this may be the site of germinal matrix or ventricular hemorrhage, the amount of hemorrhage, presence of blockage of the pathways by the blood clot or the position of the head at the time of imaging.[12] Koeda *et* al. suggested that the frontal horn width of the lateral ventricle changes with the position of the premature neonates, which may be due to gravity, but these changes decrease with the maturation when the brain structure becomes firm.[9] Asymmetry in occipital horn was also observed by Reeder *et* al.[11] But measuring only a particular horn cannot represent the whole ventricular system. Total volumetric measurement is required to quantify the actual amount of CSF inside the ventricle. Postural changes result in a redistribution of CSF within the craniospinal space and intracranial pressure is also affected by different head and body positions.[13] Prolonged lateral head positioning as a common practice in neonatal nursing may influence the lateral ventricle volume of low birth weight infants with immature brain structures. Nagdyman *et* al. found that the mean volume of the down-side ventricles of the premature neonates without any IVH

was slightly smaller than the mean volume of the up-side ventricles in the case of two-third of the study population.[14] Koeda *et* al. found almost no change of ventricular size with positioning in 10 healthy term infants.[9] In a small report of two cases with PHVD by Fawer C-L & Levene MI found that frontal horns of down-side ventricle were dilated and the frontal horns of the upper side were narrowed. The different findings in the different studies have not yet resolved this issue. It is important to know the actual amount of CSF in the lateral ventricles and the variation of the volumes of the ventricles in the different head postures in case of IVH premature neonates to determine which side of the ventricle should be tapped.

In the 1st part of the study, we imaged premature neonates with different grades of IVH by 3D US in a presented head position at that time of imaging. Among the 18 IVH neonates, 12 neonates resolved without any surgical intervention, 6 neonates received at least one intervention, 2 neonates were temporarily drained by external ventricular drainage (EVD), and 5 neonates were shunted. As a part of neonatal nursing care at the NICU, nurses keep changing the position of the babies to the right lateral, left lateral, or neutral according to an individual's clinical status. We excluded those scans when babies were positioned in the neutral position. Since we did not change the postures of the neonates for these babies, we included only those 3D US images when the babies were positioned in the right lateral or left lateral positions. We imaged 15 neonates when they had been turned to their right and another 16 neonates when they had been turned to their left. In the right lateral posture, we found a 2.2 cm^3 difference and in the left

lateral posture, we found only 1 cm^3 difference between two lateral ventricles. The difference of two lateral ventricles in any lateral posture was not statistically significant to show that the position of the head can affect the volume of lateral ventricles.

In the 2nd part of this study, we examined the difference of the lateral ventricular volumes of the same neonate after the 30 minutes positioned on the right lateral head position and again after 30 minutes on the left lateral head position. We compared each lateral ventricular volume obtained in the two different postures and also the two lateral ventricular volumes in each posture. We included both premature infants with or without IVH in this study and obtained a total of 40 3D US images (20 images after 30 min in the right lateral posture and 20 images after 30 min in the left lateral posture). Each baby was imaged two times in a day in two different postures. The time interval between the two imaging sessions each day was 30 minutes, and the time interval between the end of the two imaging sessions and the beginning of another imaging session was a minimum of one week. As observed by other investigators,[10-12] we observed that the left ventricle is larger than the right in most of the cases even after changing the posture of the babies irrespective of the presence of IVH. The mean right and left ventricle volumes were almost the same in both right lateral and left lateral posture after 30 minutes at that posture.

Since the right and left lateral hemisphere of the brain are separated by falx cerebri formed by the invagination of meningeal dura matter,[15] there is no evidence regarding the movement of brain matter to the dependent hemisphere

due to the gravitational force. But because of the presence of the valve-less foramina in the ventricular system, CSF can move in any direction within the ventricles and the subarachnoid spaces.[16] In this study, we tried to investigate the direction of CSF flow within the ventricles in the right and left lateral postures. As the specific gravity difference between healthy brain (ranges from 1.0318 - 1.0368 in different lobes)[17] and CSF (1.004 - 1.008), [18] is very small, thus it is important to investigate whether the CSF within the ventricles will float or sink inside the brain in a lateral head position. However, it should be noted that the specific gravity of the brain and CSF changes slightly with the alteration of components within them due to some pathological conditions. Thus, the relative density of different brain components of premature neonates varies according to the clinical status of the individual. In this research of 30 minutes of posture change, we found that CSF did not move significantly in any direction to cause a difference in ventricular volumes. But we observed a small difference in the mean volume of the lateral ventricles when the babies were positioned to either the lateral side for an undefined period of time though it is not significant statistically.

There are several limitations to our study. Premature neonates are often characterized by high inter-individual variable clinical status. That is why we did not change the postures of all of our recruited patients though none of the studies reported information regarding the occurrence of side effects of changing postures of the neonates. No effect on cerebral hemodynamics was observed after head rotation/ changing postures.[19,20] However, it was sometimes difficult to immobilize the neonate to a particular position for 30 minutes. Because of the

small size of the study, we could not provide statistically significant results, limiting our ability to provide a definitive conclusion as to the effect of head posture on ventricular volume.

In conclusion, this study demonstrates that 30 minutes of immobilization of the head to any lateral side does not have any effect on the volume difference of two lateral ventricles. It is possible that 30 min is insufficient to cause a volume difference in the two lateral ventricles, although our 3D US system allows quantification of small volume differences of the ventricles. Further research is recommended in a larger number of preterm infants, focusing on the effect of head posture on a lateral side for a longer time. This is clinically significant because if the head position influences the volume of the ventricles, then the position of the patient while removing CSF might be important and the neurosurgeons need to be aware of that effect to decide which side to tap.

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Chapter 4

4. Conclusions and future directions

4.1 Overview and objective of research:

Since the X-ray and MR imaging are not feasible for the neonatal population because of several drawbacks and the US is very good at detecting both fluid and blood, clinical 2D US has remained as an undebatable diagnostic tool for IVH and PHVD. Keeping that in mind, our aim was to improve the utility of clinical US imaging by extending 2D US to 3D US, which has the potential to allow better quantification of the fluid volume in each ventricle, be able to differentiate neonates with PHVD who will receive interventions only, and who will receive a shunt and who will undergo spontaneous resolution without any interventions. The overall objective of this thesis was to use our 3D US system clinically to follow the neonates with IVH and to investigate better management with greater confidence than currently used with the 2D US. Three objectives were focused on: 1) comparing the tap amount with infants' age, weight, HC and 3D US-based measured total volume of the lateral ventricles to determine the amount of CSF to remove in each tap (Chapter two); 2) quantify the amount of volume variations of the two lateral ventricles according to the posture of the neonates with IVH (Chapter three); and 3) predict the future requirement of neonatal V-P shunt by immediate ventricular volume change after VT measured by 3D US (Appendix 1).

4.2 Summary and conclusions:

In chapter two, we described the most common interventional treatment for IVH, ventricular tap (VT) and the current guideline to implement this. We retrospectively analyzed various physical parameters on the day of the ventricular tap and found that there are some conflicts with the current guideline of the ventricular tap. The tap amount was supposed to be better correlated with the weight of the neonate on the day of the tap according to the guideline for removal of 10 ml/kg CSF.[1] But, we found that the total ventricular volume measured by the 3D US was better correlated with the actual tap amount than the weight of the neonate. That supports our hypothesis 3D US improves the volume determination of ventricular tap in neonates with IVH.

In chapter three, we described our prospective posture change experiments where our hypothesis was that cerebral ventricle volume can change with the posture of the head and a larger amount of CSF is accumulated in the lowermost ventricle while the head position is right-lateral or left lateral for a long time. To conduct this study, we selected some relatively stable neonates. At first, we set the posture of the baby in such a manner where either the right or left sides of the brain remained lower than the other side. Then, we waited 30 minutes and we scanned the baby in that posture. After our 1st scan, we changed the posture of the same baby to the opposite side where the opposite part of the brain remained lower and again waited 30 minutes. After 30 minutes in that posture, we scanned the baby a 2nd time. We compared the difference of each ventricle in each posture of the same baby on the same day. But at the end of the 30

minutes in the right lateral or left lateral posture we did not find any statistically significant difference between two lateral ventricles.

In the appendix, we included another study where we attempted to predict the requirement of V-P shunt by the short-term ventricular volume difference of the neonates after VT. We hypothesized that higher ventricular volume difference after VT may be the risk factor for requiring a future V-P shunt.

In summary, we tried to improve the current diagnostic and treatment options of IVH by using the new 3D US technology.

4.3 Limitations:

Although the chapter-specific limitations are presented in the discussion section of the respective Chapters, we discuss more general limitations common to Chapters 2-3 in this section and also some study-specific limitations.

4.3.1 General limitations:

One of the limitations for our 3D US is the requirement of some additional tools including a motorized device and a computer or laptop that is needed to be close to the US machine at the bedside of the neonates.

As our maximum scan angle is 70 degrees used for patients with severe PHVD, our device cannot capture both of the lateral ventricles in a single 3D image. Thus, in some cases, we had to scan each ventricle separately as shown in figure 4.1. Moreover, in a small number of extremely severe cases of PHVD, a 70-degree scan was insufficient to scan even a single lateral ventricle.

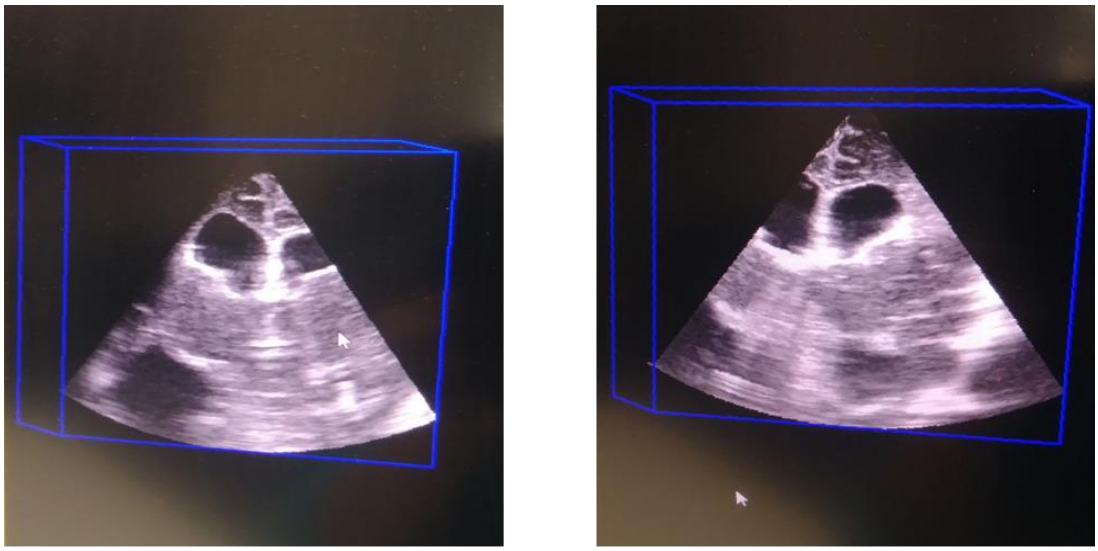

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Figure 4.1: 3D US images of a neonate with PHVD. Here a single scan could not cover both lateral ventricles. But each lateral ventricle could be imaged separately. a) left lateral ventricle, b) right lateral ventricle

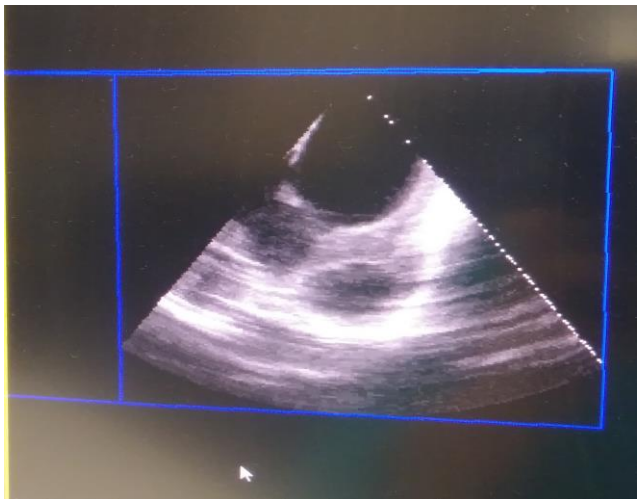

Figure 4.2: 3D US image of a neonate with severe PHVD. Here a single lateral ventricle could not fit in one image.

Another limitation of our system is the length of time of segmentation and the training required to be capable of segmenting correctly. Much training is required to raise the level of expertise in segmenting the ventricles with the software associated with the 3D US system. Although the level of expertise differs from person to person, the training time varies from a few days to a few months. The segmentation requires about 15 to 40 minutes to segment only one ventricle. Compared to the use of 2D US, this length of time is too long.

Inter-observer and intra-observer variability are present in segmentations of the same ventricles at different times. However, the variability is very small ranging from less than 1 to 7 cm^3.

Movement of the babies during scanning and the fontanel size especially for older neonates were another limiting factor resulting in bad 3D US images. The ventricles were not segmentable in those cases. Our system was designed in such a manner that it requires more space than the conventional 2D probe to rotate and produce a complete image. We had to discard some images because of the movement of neonates and the shadows of the bones that were produced in patients who had a small fontanel size

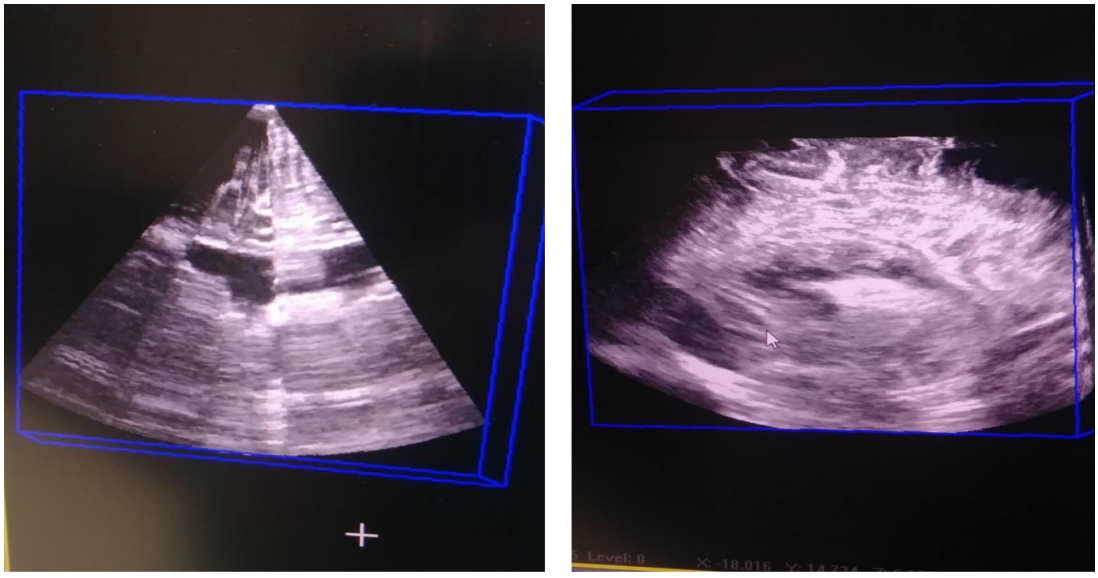

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Figure 4.3: 3D US images of the neonates with PHVD. Here, ventricles are not segmentable due to the movement of the neonate. a) coronal scan with movement b) sagittal scan with movement.

4.3.2 Study-specific limitations:

We did not find some patient information for the retrospective data included in chapter two and in the appendix, which is a general limitation in all retrospective studies. In chapter three, we changed the posture of the neonates after 30 minutes. But some babies moved by themselves within the 30 minutes causing us not to image those babies at that time. We had to wait another 30 minutes to ensure that the baby was still.

4.4 Future directions:

4.4.1 Multi-center study of IVH using 3D US:

A large multi-center study should be needed to gather a large sample size and to obtain a variety of clinical practices in managing PHVD. We are hoping that the 3D US will be accessible and commercially available to all other tertiary hospitals to carry out a multicenter study.

4.4.2 Image stitching:

I described that in some cases the whole ventricular system could not be imaged in one 3D image. In very few cases a single lateral ventricle was large enough to be included in one image. Multiple 3D US images can be used to fully capture the ventricles and surrounding brain regions of interest. In such cases, image stitching of multiple 3D US images will allow better visualization of both lateral ventricles in one 3D US image. We imaged the ventricles only from the anterior fontanelle because our system does not allow better visualization of the complete ventricle from the posterior fontanelle. However, the stitching of images from the anterior fontanelle view and posterior fontanelle view could allow better visualization and easier diagnosis. We are hoping to develop an automated stitching program based on image-based registration in the future.

4.4.3 Prediction of CSF amount using head circumference (HC) measurement:

Physicians from many centers rely on mainly 2D US-based measurement and HC or other clinical symptoms to predict how much CSF is inside the brain. Even

in some developing countries and in remote areas, 2D US is not available for imaging of neonates. Moreover, diagnostic and treatment costs are not covered by the health care systems of some countries. In those cases, some people cannot afford all the diagnostic procedures even if they are available. Thus, we are considering the use of HC measurements as a predictor of how much CSF is inside the brain. We are planning to record HC, 3D US ventricular volume, age and weight of the neonate on the same day and by analyzing these parameters we will be able to determine the relationship of HC and the CSF amount on the particular age and weight group of the patients.

4.4.4 Early detection of V-P shunt failure by 3D cranial US:

For severe post hemorrhagic hydrocephalic (PHH) patients, when they acquire desirable weight, permanent insertion of V-P shunt that constantly drains CSF from the ventricle to the abdomen is used to prevent further brain damage and to alleviate symptoms of increased intracranial pressure (apnea, bradycardia, vomiting, increased pressure). Although V-P shunts are widely used, 31% of the shunts fail within the first year and the patients require revision surgery.[2] Currently, there is no specific method to prevent shunt failure other than preventing infection by improved sterilization. Furthermore, there is no way to diagnose shunt failure other than clinical symptoms. 2D cranial US is used to follow the babies after shunt insertion but this method cannot provide the information that is provided by 3D US imaging. Moreover, it cannot predict future shunt failure. Shunt failure only becomes obvious when the clinical symptoms appear. Most babies with shunt failure present with signs of raised intracranial

pressure, such as irritability, nausea, vomiting and lethargy.[3] Headache is the early symptoms of shunt failure but that cannot be described by the neonatal population. These symptoms are not specific to V-P shunt failure. Thus, research should be pursued to find more specific diagnostic tools for V-P shunt failure.

We are performing 3D US imaging in the neurosurgical and developmental clinics of the neonates who have been shunted previously when they usually come for developmental follow up to see whether the shunt is working properly. As the fontanelle does not close until 18 months of age, our 3D US system can provide images of the ventricles when the baby is older. As the fontanel size varies from patients to patients, the average time for getting a good image is about 8 months of age. This is still enough time to follow the baby to determine whether the shunt is working or not. Good working shunts should result in a decreased CSF accumulation in the ventricles, so, the ventricle volume will be lower than before inserting a shunt. The continual increase in ventricle volume during follow up can predict future shunt failure or a sudden severe increase in ventricle volume can diagnose acute shunt failure. Additionally, subdural hemorrhage/hematoma and slit ventricular syndrome can be diagnosed by the 3D US system, which is caused by over-drainage of CSF. Shunt insertion after the appearance of clinical symptoms may be one of the risk factors of shunt failure. We are planning to compare two groups of shunted infants by 3D US who have been shunted earlier and who have been shunted later than the appearance of clinical symptoms during their follow up visit. This information will allow us to predict shunt failure.

4.4.5 Find cerebral oxygenation during tap using near-infrared spectroscopy:

NIRS measurement can detect cerebral oxygenation using the difference in NIRS signal from oxy and deoxy-hemoglobin. One study showed blood breakdown products in CSF following IVH can affect the accuracy of the NIRS signal.[4] Another study showed that ventricle tapping improved cerebral blood flow (CBF) by 15.6 ± 22%.[5] We are planning to measure the cerebral oxygenation 20 minutes before ventricular tap and up to 20 minutes after ventricular tap by NIRS to determine when and after how much CSF removal cerebral oxygenation improves during the period of the ventricular tap.

5.5 Significance and clinical impact of this research:

Though the death of small premature babies has been reduced due to advancement in specialized obstetric and neonatal intensive care in the past several decades,[6] IVH is still a complex problem to solve globally. Clinical status and 2D US measurements are being used to follow these patients, which are not considered sufficient enough to let the physician know how much CSF is inside the ventricle and give a complete guideline to treat IVH patients.

This thesis illustrates the importance of 3D US measurements of ventricle volumes of the neonates suffering from PHVD and how this volume measurement can be used clinically to confirm the best treatment to the individual patient. In spite of having some drawbacks, we believe that our 3D US measurements of ventricle volume can add confidence to the clinicians regarding

follow up of the neonates, deciding when to intervene, the amount of CSF that should be aspirated during an intervention, which side is better to intervene and possible requirement of a shunt. We are hoping that we will be able to overcome all the technical limitations through improvements in our technology in the future.

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Appendices

A. Does short term volume change predict the future requirement of V-P shunt?

A.1 Introduction:

Low birth weight preterm babies are at risk of bleeding from the germinal matrix of the developing brain, which can lead to intraventricular hemorrhage (IVH) and subsequent post-hemorrhagic hydrocephalus (PHH). PHH has been associated with significantly impaired long-term neurodevelopmental, cognitive and psychomotor delay and risk for cerebral palsy.[1] Premature infants whose weight <1500 gm at birth have 15%–20% chances to develop IVH.[2] Several temporary CSF diversion methods including a lumbar puncture (LP), ventricular tap (VT), external ventricular drains (EVD) or ventricular reservoir are used in the initial treatment of PHH in children born prematurely. Temporary removal of CSF might reduce the inflammatory reaction, decrease deposition of extracellular matrix proteins, and sometimes can re-establish normal CSF drainage, which helps to provide a better neurological function, decrease in periventricular edema and reduction in the need for a permanent shunt.[3-5] PHH which cannot be recovered through temporary interventions may require treatment with a ventriculoperitoneal shunt surgery (VPS). A shunt is sometimes limited to the patients whose weights are less than 2 kg and immunologically immature and it can be infected and often needs to be replaced or repaired through an operation.[6,7] VPS may also cause

sepsis, respiratory impairment and abdominal complications such as necrotizing enterocolitis.[8] It has been reported in a study of 36 infants who were shunt-operated for PHH, shunt blockage with infection occurred in those who were operated on before 35 days of age.[9,10] VPS treatment for PHH of premature neonates especially those whose gestational age is less than 28 weeks are correlated with unfavorable shunt-related surgical outcomes.[11] A few reports described the characteristics of neonatal IVH progression from acute to chronic and the factors related to the requirement of VPS treatment. It was reported that the severity of hemorrhage alone does not necessarily predict shunt requirement in premature IVH patients.[12] Another study with adult intracerebral hemorrhage (ICH) identified that hemorrhage in the thalamus and elevated intracranial pressure (ICP) more than 25 mm are associated with VPS.[13]

The objective of this study was to analyze ventricular taps as a temporary interventional method and comparing various parameters related to VT by 3D US between two groups of infants with PHVD who did not progress to VPS and those who required VPS. By identifying total ventricular volume differences after each tap by the 3D US, we aimed to predict the need for the requirement of a shunt and to improve the care practices that might either reduce or contribute to the early prediction of shunt requirement among neonatal IVH patients.

A.2 Method:

A.2.1 Selection of participants:

As a part of a larger study to investigate the patients with IVH, which started in 2012, we continued the study after obtaining approval by the Research Ethics Board at the University of Western Ontario. Patients were recruited during two time periods. The first group of patients was recruited after reanalyzing data from a previously reported prospective, randomized and blinded clinical trial during the period April 2012 to May 2016 where shunt analysis was not one of the end results of the study. We added a second group of patients recruited from June 2018 to November 2019 into a prospective study of IVH from the same center (NICU, Victoria Hospital, London, Ontario) where the inclusion criteria were the same in the two groups. Inclusion criteria for both groups of patients were any neonates diagnosed as any grade of IVH by routine clinical 2D cranial US. Neonates with a congenital anomaly and any other brain abnormalities were excluded. The neonatal population was enrolled with informed parental consent. Once enrolled, neonates underwent serial 3D US imaging about 2-3 times per week according to the severity of IVH until discharge or transfer to another center from our NICU.

From 2012 to 1016, 70 premature neonates with IVH were recruited, among them, 54 resolved without any intervention and 16 required at least one VT. We started another recruitment of IVH neonates from 2018 to November 2019 and recruited an additional 22 neonates with any grade of IVH. Among this group, 14 patients resolved without any interventions and 8 patients required at least one VT. In this study, we excluded all the data regarding the patients who resolved

spontaneously without any intervention. We studied only patients who required ventricular taps and compared all relevant parameters in the two groups of patients who required a VP shunt and who did not require a VP shunt. We analyzed 61 individual VTs obtained from 19 patients to predict whether a shunt would be required in the future. Flow diagram of all the recruited patients during two periods and the patients who required VT and VP shunt are shown in figure A1.

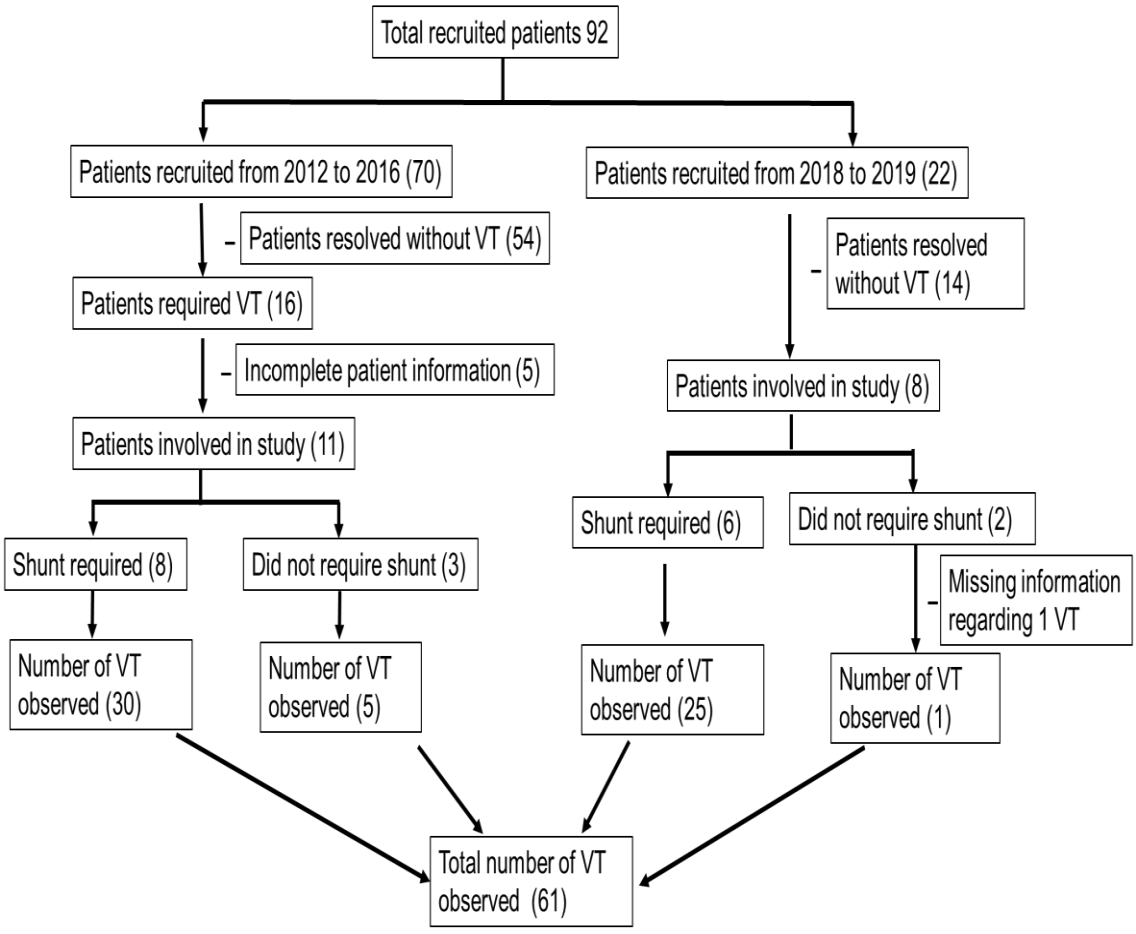

Figure A1: Flow diagram of recruited patients

Our institutional pathway for the management of IVH related PHVD is the initial intervention by VT. VT can be performed at the bedside of the patients and does not require any other facilities such as the operating room. Thus, it has remained the preferred temporary method for PHVD patients in our center. But to avoid repeated VT in some of the patients, an external ventricular drain (EVD) is needed to be inserted. In case of increasing ventricular volume, accelerating head circumference, other clinical signs of raised intracranial pressure, or failing gradual reduction of CSF aspiration, insertion of the ventriculoperitoneal shunt was considered under some of the conditions of the patients (e.g. weight, clinical status, the protein level in CSF).

A.2.2 3D Us system:

Described in chapter one, section 1.8.1 of this thesis.

A.2.3 Segmentation and measurement of ventricular volume:

Described in chapter one, section 1.8.2 of this thesis.

A.2.4 Statistical analysis:

We analyzed 61 individual taps from 19 patients. Among them, 55 taps were from those patients who ultimately required VPS surgery and only 6 taps were from those patients who did not require a VP shunt and resolved after their initial intervention by VT. We compared VT and the ventricular volumes before and after tap for both groups. A limitation of our study was low statistical power due to a small number of patients and a low number of taps who did not require VP shunt. T-test for unequal samples was performed for this study.

A.3 Results:

A.3.1 Patients characteristics:

Ninety-two IVH patients were recruited and treated in a single institution between April 2012 to November 2019. All patients survived until now. 74% of patients (n=68) resolved spontaneously without any intervention and 24% (n=24) of the patients required one or more VT. Among those patients who required taps, 58.3% (n=14) were permanently treated with a VP shunt. The demographic characteristics of the patients who were involved in this study are listed in Table A1.

Table A.1: Clinical characteristics of study patients

	Shunt group	No shunt group
Mean gestational age (wk)	27.9 ± 3.2	32.0 ± 5.96
Sex (Male/Female)	9/5	3/2
Delivery method (Vaginal/ Forceps/ CS)	7/0/7	2/2/1
Mean gestational weight (gm)	1290.64 ± 631.2	1795 ± 1137.74
Worst IVH grade		
Grade I	1	1
Grade II	1	0
Grade III	8	2
Grade IV	4	2
Age of diagnosis of IVH (days)	7.3 ± 6.5	4.5 ± 5.4
Other comorbidities		
Respiratory distress syndrome	6	2
Patent ductus arteriosus	5	1
Retinopathy	5	0
Hyperbilluribinemia	5	3
Sepsis	4	3
Meningitis	2	2

A.3.2 Comparison of shunt treated patients and non-shunt treated patients:

We compared various parameters between the two groups of patients: those who were treated with shunts and those who were treated by taps only. We analyzed pre-tap total ventricular volume measured by the 3D US, pre-and-post ventricular volume difference, the ratio of volume reduction (difference of ventricular volume after tap divided by actual tap amount), head circumference (HC) on the day of tap, HC difference after tap, days interval between the two taps, mean tap amount and compared each parameter for both groups.

A.3.3 Prediction of shunt dependent hydrocephalus (SDHC) with the volume reduction after each tap, and the ratio of volume reduction:

We imaged the neonates using 3D head US just before the removal of CSF. After 15-20 min after the end of VT, we again imaged the baby a 2^{nd} time. We measured the pre-tap and post-tap ventricular volume and calculated the difference as shown in Fig. A.2. The average ventricle volume difference (cm^3 ± S.D) after the tap for the shunt treated patients and for the patients who did not require a shunt was 18.70 ± 10.98 cm^3 and 7.52 ± 3.35 cm^3 respectively. A t-Test assuming unequal variances showed that there was a statistical significance difference ($p=0.0001$) between these mean values. Thus, the difference between pre- and post-tap volume can be considered as an important predictor for the requirement of the shunt.

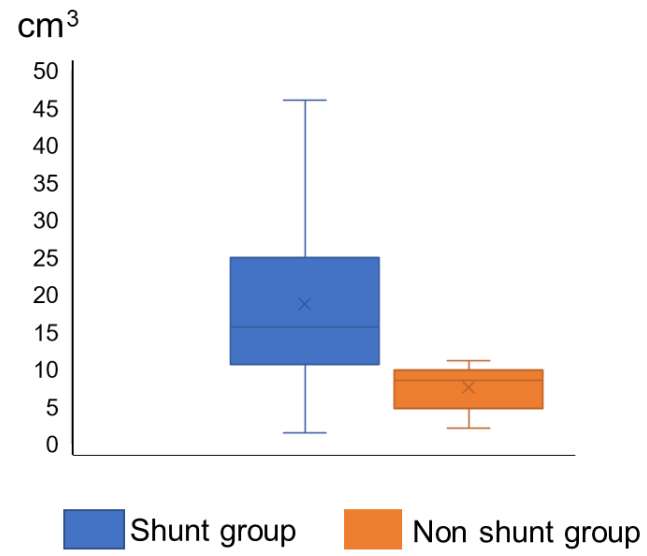

Figure A.2: Box and whisker plot of the total ventricle volume difference after the tap in the two groups of patients

The ratio of volume reduction in patients who required shunts and those patients who did not was 0.82 ± 0.36 and 0.45 ± 0.35 respectively as shown in Fig. A.3. A t-Test assuming unequal variances showed that there was a statistical significance difference (p=0.013) between these mean values.

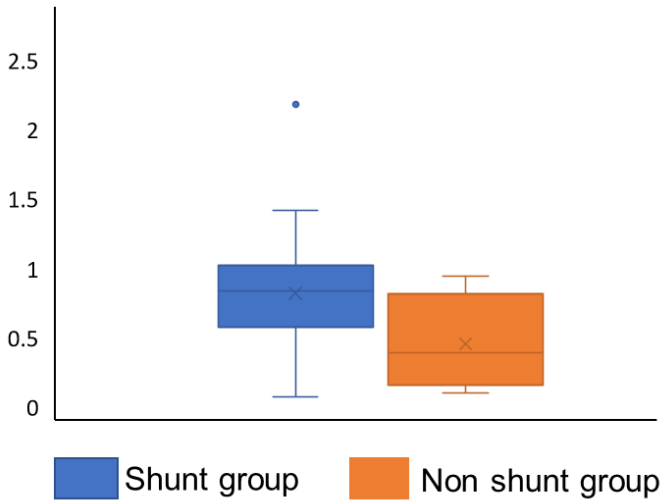

Figure A.3: Box and whisker plot of the ratio of volume reduction in the two groups of patients

A.3.4 Prediction of SDHC with the tap amount and days interval between two taps:

Each patient needed an unequal number of taps in the shunt and no shunt patient group. Patients who needed a shunt were tapped more times before the shunt insertion than the patients who did not need a shunt. The higher frequency of tapping did not help to prevent shunt insertion. Moreover, the average tap amount was greater in the shunt treated group than the non-shunt treated group. The mean tap amount in each tap for the shunt treated population was 23.2 ± 9.52 ml and the mean tap amount in each tap for non-shunted treated patients was 17.5 ± 5.68 ml (p=0.065).

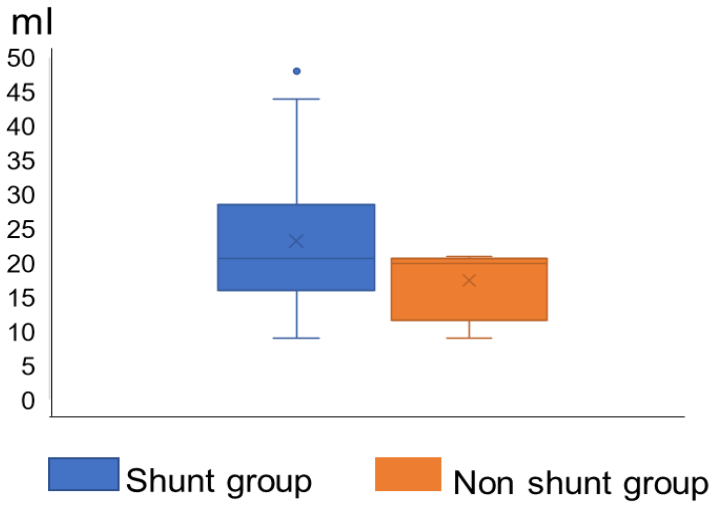

Figure A.4: Box and whisker plot of the average tap amount in two groups of patients

The number of days between taps was greater in those patients who resolved without getting a shunt. The average number of days interval was 5.89 ± 4.0 and 9.33 ± 6.25 for the shunt treated and non-shunt treated patients respectively (p=0.11).

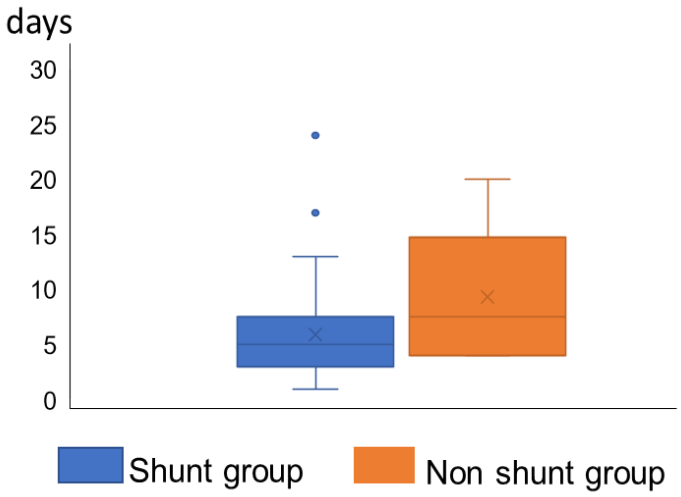

Figure A. 5: Box and whisker plot of the average number of days between two taps in the two groups of patients

A.3.5 Prediction of SDHC with total ventricular volume measured by the 3D US:

The average total lateral pre-tap ventricular volume measured by the 3D US just before taps in the case of shunt treated patients and non-shunted patients were 109.88 ± 56.18 cm^3 and 68.33 ± 28.96 cm^3 respectively as showed in Fig. A.6

(p=0.013). Thus, the total ventricle volume over 100 cm^3 is an important predictor of shunt requirement in the future.

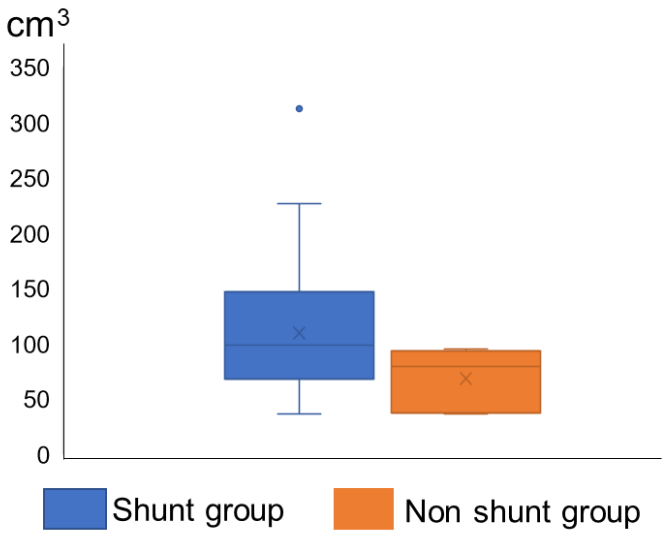

Figure A.6: Box and whisker plot of the average pre-tap total ventricle volume in the two groups of patients.

A.3.6 Prediction of SDHC with HC and the HC difference after tap:

The average HC of the shunt and non-shunt group of patients were 32 ± 5.35 cm and 32 ± 5.4 cm respectively as showed in figure A.7. The HC was measured on the day of the tap before starting the procedure of tap.

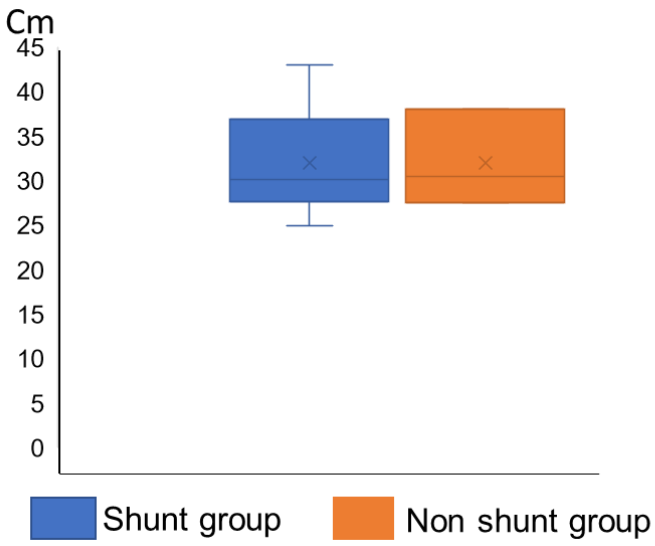

Figure A.7: Box and whisker plot of pre-tap HC in two groups of patients

The average HC differences (cm ± S.D) after the ventricular tap of the shunt and non-shunt groups of patients were 0.78 ± 0.77 cm and 0.60 ± 0.36 cm respectively as shown in Fig. A.7. A t-Test of two-samples assuming unequal variances showed that there was no statistically significant difference for both HC and the HC difference in two groups. P value for HC in both groups was 0.49 and for HC difference after tap was 0.25. This result shows that it is not possible to predict shunt dependency by measuring HC.

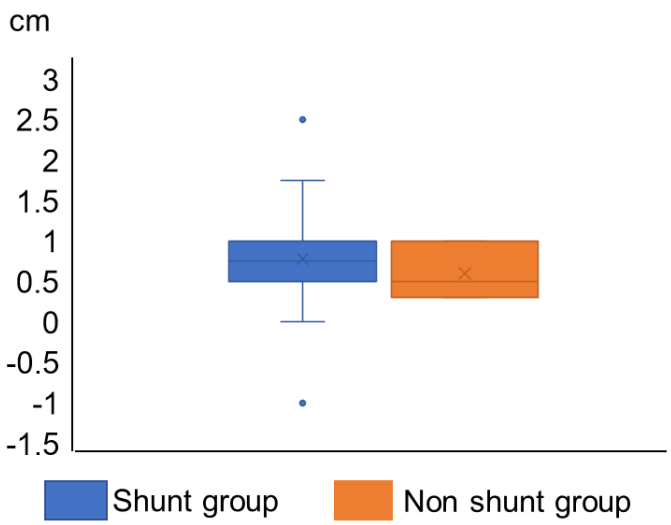

Figure A.8: Box and whisker plot of the differences of HC after a tap in two groups of patients.

A.3.7 The outcome of the patients:

During the study period, we could recruit a total of 92 IVH neonates. Among them only 26% (n= 24) patients received intervention. In this study, data for 19 patients who received interventions were analyzed. Among the observed patients, 73.6% (n=14) patients needed VP shunt, and the other patients (n=5) resolved after receiving one or more VT. Among the 14 shunt treated patients, 5 required additional shunt surgery due to infection or blockage of the shunt tube. No patients died during the study period.

A.4 Discussions:

About 80% of the CSF in the brain is produced by the choroid plexus located within the ventricular cavities of the brain and approximately 20% CSF is produced by transependymal movement of fluid from the brain parenchyma to

the ventricular system.[25] There may be several reasons to cause an increase in the volume of CSF in the ventricles. For example, disruption of the flow of CSF from the ventricles to the subarachnoid space, which is called non-communicating or obstructive hydrocephalus, whereas communicating hydrocephalous involves the impaired absorption of CSF from the subarachnoid space to the venous circulation.[14] In our study, we found that the immediate ventricular volume changes after VT were more consistent in the case of non-shunt treated groups as compared to the shunt treated patients, as shown in Fig A.2. After removing an amount of CSF directly from the ventricle, the reduction of ventricular volume should be the same as the amount of CSF removed. But we found that the mean difference of ventricular volume reduction after each tap was more than double (18.70 cm^3) in the shunt treated population than the patients who did not require shunt (7.52 cm^3). After the removal of CSF, the raised intracranial pressure in the hydrocephalic brain is suddenly lowered. Because of the sudden creation of low pressure inside the lateral ventricles, the surrounding areas of the brain may try to compensate. If there is no disruption or limited disruption of the flow of CSF from the lateral ventricles to the subarachnoid spaces, it may be possible that CSF can backflow from subarachnoid or 3rd or 4th ventricles to the lateral ventricles to compensate the sudden pressure decrease inside the lateral ventricles. This is a possible explanation for the reduced volume reduction after VT in the group of patients who did not require a shunt. That means that their CSF flow was not completely obstructed. For the patients who had VP shunt after having several taps, their volume reduction was

greater after VT because they didn't have any extra CSF coming from any other spaces due to obstruction of flow. Similarly, the ratio of volume reduction was lower in the non-shunted population than the patients who required a shunt. These findings support the presence of communication in flow allowing CSF to flow from the ventricles to the subarachnoid space and vice versa. Flow communication was better in non-shunted patients compared to the shunted group of patients. Therefore, the abnormal accumulation of CSF in the brain can gradually recover in those patients who have better circulation and their non-requirement of the shunt can be predicted by small volume change after VT.

The development of IVH associated PHH is the cumulative effects of the hemorrhage and metabolic products, which readily distribute to the ventricular system and/or the subarachnoid space.[15-17] Serial tapping of CSF by lumbar puncture or ventricular tap (at least 10 mg/kg) is a treatment option used with some efficacy.[18] However, one review reported that this treatment intervention could not effectively reduce the requirement for VPS and also caused an increased risk of infection.[19] Therefore, the determination of an early predictor of VPS through 3D US may help to reduce such types of complications in neonates. Taps were needed more frequently in those patients who were shunt dependent than non-shunt dependent patients.

We compared HC on the day of tap and HC differences after VT in the two groups of patients, but we did not find any significant differences between the two groups of patients. As HC is not only related to the fluid amount inside the brain but also related to the age, weight of the neonates, HC and HC difference after

tap are not good parameters to predict shunt dependency. In a randomized controlled trial, some researchers compared lumbar puncture performed in response to ventricular enlargement using the US with lumbar puncture performed in response to symptoms and increasing head circumference and found no reduction in the need for subsequent shunt insertion.[20]

2D US has been used effectively to diagnose IVH and PHVD for years. Although the US-based diagnosis of Germinal matrix hemorrhage (GMH) is not completely accurate, with a sensitivity of 61% and specificity 78%, the diagnosis of IVH shows high sensitivity (91%) and specificity (81%).[21] The efficacy of 2D US in diagnosing PHVD has not been studied. But 3D US can be used safely to diagnose and measure the ventricular volume of premature neonates with PHVD that is not possible with 2D US.[24] In a study, it was reported that serial lumbar punctures were unsuccessful for the prevention of hydrocephalus of preterm infants with intraventricular hemorrhage.[22] Formation of hydrocephalus after IVH and requirement of a shunt after having hydrocephalus cannot be prevented. But early detection of ventricle dilatation of the neonates having IVH and the volume difference after VT can be measured by the 3D US. Therefore, 3D US can be an effective approach to determine the ventricle volume difference in the case of serial ventricular taps and help to predict the requirement of VPS early. Future studies with a larger population may help to conclude the proposed approach in clinical practice.

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Appendix B

Western Research

Date: 3 January 2019

To: Sandrine de Ribaupierre

Project ID: 100315

Study Title: New technologies in the management of post-hemorrhagic hydrocephalus in preterm infants (REB #17827)

Reference Number/ID: N/A

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: January 15, 2018

Date Approval Issued: 03/Jan/2019

REB Approval Expiry Date: 05/Apr/2019

Dear Sandrine de Ribaupierre ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Healthy_LOI&Consent_IVH_Dec1	Consent Form	01/Dec/2018	
IVH_infants_HSREB_Dec4-2018-1.1	Protocol	04/Dec/2018	1.1

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix C

Curriculum vitae

Name:

Priyanka Roy

Education:

2018/1 (2019/12):

Master's Thesis, MSc in Medical Biophysics, University of Western Ontario

Degree Status: In Progress

Supervisors: Dr.Sandrine De Ribaupierre; Professor Aaron Fenster

2013/7 - 2013/12:

Certificate, Certificate Course on Diabetology, Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders,

Degree Status: Completed

2013/1 - 2013/12:

Diploma, Diploma in Medical Ultrasound, Daffodil International University, Dhaka, Bangladesh

Degree Status: Completed

2005/5 - 2010/7:

Bachelor's in Medicine and Surgery (MBBS), University of Dhaka, Bangladesh

Degree Status: Completed

Employment:

2018/4 - present

Research Assistant

University of Western Ontario

2017/7 - 2017/12

Sonologist

Reproductive Health Services Training and Education Program, Khulna Medical College

Hospital, Khulna, Bangladesh

2015/5 - 2016/12

Assistant Registrar

Department of Medicine, Gazi Medical College Hospital, Khulna, Bangladesh

Courses Taught

2015/05/01 - 2016/12/31

Instructor, Medicine, Gazi Medical College Hospital, Khulna, Bangladesh

Course Title: Clinical Examinations of Medicine Related Illness

Course Level: Undergraduate

Number of Students: 90

Community and Volunteer Activities

2017/1 - 2017/6 Honorary Medical Officer, Department of Radiology, Khulna Medical College Hospital, Khulna, Bangladesh

1. Performed ultrasonography of indoor and outdoor patients and provided the report with proper diagnosis
2. Recorded and stored suitable images for future references
3. Communicated effectively with other sonologists and team members

Other Memberships

2014/1 Member, Bangladesh Diabetes Association

2012/6 Registered Physician, Bangladesh Medical and Dental Council

Publications

Journal Articles :

1. Roy, Priyanka. (2015). Clinical Significance of HbA1c in the Management of Complicated Type 2 Diabetic Patients in Bangladesh. Malaysian Journal of Medical and Biological Research. 2(2): 133-138.

Oral Presentations:

1. Roy, P., Lo, M., Fenster, A., Bhattacharya, S., Eagleson,R., Ribaupierre, S. Lateral ventricle volume based on posture of the neonates having intraventricular hemorrhage. March 29, 2019. Imaging Network of Ontario, London, Ontario.
2. Roy, P., Lo, M., Fenster, A., Bhattacharya, S., Eagleson,R., Ribaupierre, S. Volume change of lateral ventricles in 3D ultrasound is a function of posture of neonates having intraventricular hemorrhage. June 12, 2019. London Imaging Discovery Day, London, Ontario.
3. Roy, P., Lo, M., Fenster, A., Bhattacharya, S., Eagleson,R., Ribaupierre, S. Determination volume of ventricular tap based on the total lateral

ventricle volume of neonates with intraventricular hemorrhage. June 12, 2019. London Imaging Discovery Day, London, Ontario.

Poster Presentations:

1. Roy, P., Lo, M., Fenster, A., Bhattacharya, S., Eagleson,R., Ribaupierre, S. Volume change of lateral ventricles in 3D ultrasound is a function of posture of neonates having intraventricular hemorrhage. April 30, 2019. London Health Research Day, London, Ontario.
2. Roy, P., Lo, M., Fenster, A., Bhattacharya, S., Eagleson,R., Ribaupierre, S. Volume change of lateral ventricles in 3D ultrasound is a function of posture of neonates having intraventricular hemorrhage. June 07, 2019. Robart Research Retreat, Western University, London, Ontario.