LUMBAR PUNCTURE IN CHILDREN WITH ACUTE LYHMPHOBLASTIC LEUKAEMIA

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ABSTRACT

Title : Lumbar puncture in children with acute lymphoblastic leukaemia.

Introduction : Acute lymphoblastic leukaemia (ALL) is the most common malignancy diagnosed in children, representing more than a quarter of all paediatric cancers. Lumbar puncture (LP) is a diagnostic and therapeutic clinical procedure in paediatric oncology. Diagnostically, LP is routinely performed to detect the existence of cancer cells in the cerebrospinal fluid (CSF) whilst therapeutically, lumbar puncture is performed to deliver intrathecal chemotherapy. For the past 6 years, Ma-Spore ALL 2010 protocol have been used in University Malaya Medical Centre (UMMC), for the treatment of paediatric acute lymphoblastic leukaemia (ALL) based-on patient risk stratification, which involved diagnostic and multiple therapeutic LP. The aim of this study is to identify the prevalence of performing successful LP in single attempt, risk factors associated with it, to describe the complications related to lumbar puncture and sedation used. This study also aim to identify the prevalence of parental reluctance in giving consent for their children first LP and whether they needed re-consenting/re-explanation for subsequent LPs, as well as to identify the relationship between parental reluctance and need for re-consenting and their psychosocial background. Another aim of this study is to validate a previous formula used for an ideal depth of needle insertion for a successful LP (Chong, 2009).

Methods : This was a prospective, cross-sectional study with a mix method of observation and interview based study in UMMC involving all paediatric ALL patients aged 3 to 18 years old, that underwent LP (either first LP or subsequent LP) for diagnostic or therapeutic purposes in oncology ward or paediatric daycare UMMC. Subjects were recruited from July 2017 until September 2017. Patients with chronic headache and CNS involvements were excluded. Their lumbar puncture experience particularly successful

attempts, complication of LP and sedation used were analysed. Chi square test was used to compare dependent and independent variables, particularly to look for risk factors that was associated with successful single attempt LPs. All *p*-values quoted are two-sided, with a level of significance of 0.05. Spearman rank correlation test was used to correlate between 2 variables (actual measurement by operator and calculated value using mathematical formula) in order to validate a mathematical formula from previous study by Chong et.al for an ideal depth of needle insertion.

Results: 73 patients were recruited with only 2 of whom underwent their first LP. The median age was 6.4 years old (range 3 – 13 years old). The prevalence of successful single attempt LP in ALL children in UMMC was 74%. The complications from LP and sedation were identified; 26 (35.6%) patients complained of vomiting and 3 (4.1%) had developed excessive bleeding from LP site. For patients more than 5 years old (n = 41), 36.6% had headache, 19.5% had backache, 14.6% had limb numbness, 15.7% had nightmares and 36.8% had hallucination. The combination uses of IV ketamine and midazolam reduced the complications rate compared to the use of ketamine alone. Even though operator seniority in relation to a successful LP did not show statistical significance, specialists had higher success rate of 81.1% compared to the other operator group. In this study a trend was observed toward patients with normal BMI and a successful LPs, even though it was not statistically significant (p=0.072 RR 1.314 (95% CI 0.941-1.835)). Similarly, even though adequacy of sedation in relation to a successful single attempt LP was not statistically significant, a trend was observed in patients who received adequate sedation towards a successful LP (p= 0.067, RR 1.574 (95% CI 0.881-2.813)). The prevalence of parental reluctance in giving consent for their children first LP was 31.5% and out of these, 20(86.9%) parents were concern regarding complication of the procedure and 3(13.1%) parents were concern regarding the side effects of sedation used. Parental psychosocial background particularly father's education level and parental total

household income were associated with parental reluctance in giving first LP consent (p = 0.048 and 0.029 respectively). This study showed that 15 (20.5%) parents still needed re-explanation regarding LP, its complication and complications of sedation used for each LP and father education level was associated with it (p = 0.02). Spearman rank correlation test, r = 0.761 which showed very good correlation between two variables.

Conclusions: Even though this study revealed a high prevalence of a successful single attempt lumbar puncture in ALL patient in our institution, the success of LP is not only measured by the success rate but also parental psychosocial background. Parental low education level (non-tertiary education) and low total household income were associated with parental reluctance in giving consent for first LP. Similarly, parental low education level was associated with the need for re-explanation for each LP. Therefore, to improve parental perception, acceptance and knowledge towards the procedure, operator (s) must re-emphasize and provide re-education to parents for each LP procedure. The mathematical formula from previous study (Chong et al., 2009) can be use as a valid tool to estimate the ideal depth of needle insertion and can be used as a guide for a more successful LP especially for a less senior operator.

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This study is dedicated to all the paediatric oncology patients and their caregivers.

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ALL	Acute lymphoblastic leukaemia
BM	Bone marrow
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CNS	Central nervous system
CSF	Cerebrospinal fluid
HR	Heart rate
HR	High risk
LP	Lumbar puncture
IR	Intermediate risk
MTX	Methotrexate
PLPH	Post-lumbar puncture headache
PSIS	Posterior superior iliac spine
SR	Standard risk
UMMC	University Malaya Medical Centre
6-MP	6-Mercaptopurine

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 Acute lymphoblastic leukaemia (ALL)

Acute lymphoblastic leukaemia (ALL) is the most common malignancy diagnosed in children, representing more than a quarter of all paediatric cancers. The annual incidence of ALL within the United States is 3.7-4.9 cases per 100,000 children age 0-14 years, with a peak incidence in children aged 2-5 years. Children with acute lymphoblastic leukaemia (ALL) often present with signs and symptoms that reflect bone marrow infiltration and/or extramedullary disease. When leukemic blasts replace the bone marrow, patients will be presented with signs of bone marrow failure, including anaemia, thrombocytopenia, and neutropenia. Other presenting signs and symptoms of paediatric ALL include the following:

- Patients with B-precursor ALL: Bone pain, arthritis, limping; fevers (low or high); neutropenia; fatigue, pallor, petechiae, and bleeding; lymphadenopathy and hepatosplenomegaly
- Patients with mature-B ALL: Extramedullary masses in the abdomen or head/neck; CNS involvement (eg, headache, vomiting, lethargy, nuchal rigidity)
- Patients with T-lineage ALL: Respiratory distress/stridor due to a mediastinal mass

Symptoms of CNS involvement are rarely noted at initial diagnosis but are more common in T-lineage and mature B cell ALL. Testicular involvement at diagnosis is also rare; if present, it appears as unilateral painless testicular enlargement.

1.1.1 Diagnostic investigations

Other than routine laboratory investigations, a complete morphologic, immunologic, and genetic examination of the leukemic cells is necessary to establish the diagnosis of ALL.

A bone marrow examination and trephine biopsy are required to make a diagnosis of ALL. Lumbar puncture is performed to send a **cytospin morphologic analysis to assess for CNS involvement before administration of systemic chemotherapy.** Laboratory tests that help classify the type of ALL include the following:

- Immunophenotyping - To detect surface immunoglobulin on leukemic blasts (diagnosis of mature B-cell leukemia) or the expression of T-cell–associated surface antigens (diagnosis of T-lineage ALL)
- Cytogenetic studies - To identify specific genetic alterations in leukemic blasts
- Molecular studies (eg, FISH, RT-PCR, Southern blot analysis) - To identify translocations more rapidly and those not detected on routine karyotype analysis; to distinguish lesions that appear cytogenetically identical but are molecularly different
- Minimal residual disease studies - To detect chimeric transcripts generated by fusion genes, detect clonal *TCR* or immunoglobulin heavy-chain (*IgH*) gene rearrangements, or identify a phenotype specific to the leukemic blasts
- Genome-wide association studies - To detect the presence of genetic changes where routine techniques are unhelpful (eg, activated tyrosine kinase pathways in Ph-like ALL), not in clinical use yet

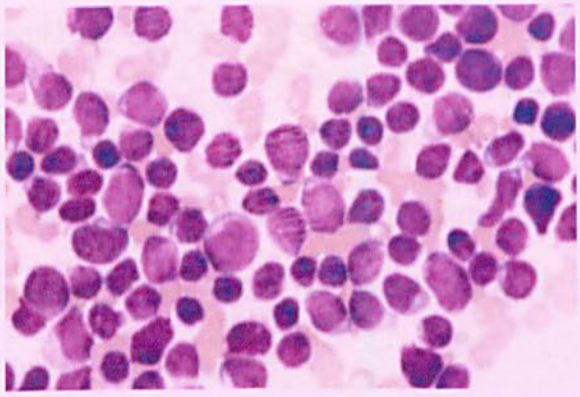


Figure 1.0 : Bone marrow aspirate from a child with B precursor ALL. Bone marrow is replaced with a small immature lymphoblast that show open chromatin, scant cytoplasm and a high nuclear-cytoplasmic ratio

1.1.2 Treatment of ALL

Leukaemia is a systemic disease, and treatment is primarily based on chemotherapy. However, the different forms of ALL require different approaches for optimal results. Treatment of subclinical CNS leukaemia is an essential component of ALL therapy. Treatment for ALL typically consists of the following phases:

- Remission-induction phase
- Intensification/consolidation phase
- CNS-directed therapy consists of systemic chemotherapy that enters the CSF, as well as intrathecal chemotherapy administered throughout the entire course of treatment, which is primarily Methotrexate (MTX) but sometimes includes hydrocortisone and cytarabine ("triple-intrathecal therapy").
- Continuation therapy targeted at eliminating residual disease (eg, Methotrexate (MTX), 6-mercoptopurine (6-MP), vincristine and glucocorticoid pulses)

1.2 ALL treatment protocol in UMMC

Lumbar puncture (LP) is a diagnostic and therapeutic clinical procedure in paediatric oncology. Diagnostically, lumbar puncture is routinely performed to detect the existence of cancer cells in the cerebrospinal fluid (CSF) and therapeutically, lumbar puncture is performed to deliver intrathecal chemotherapy.

Lumbar puncture is routinely done in UMMC paediatric ward or day care as part of their treatment regime as per chemotherapy protocol (intrathecal methotrexate). Ma-Spore ALL 2010 protocol have been used for the past 6 years in UMMC. It is a customized therapy based on risk stratification which aim at a central strategy that has led to substantially improved outcomes for children diagnosed with ALL. ALL patient will undergo lumbar puncture according to their risk stratification which is divided into standard risk, intermediate risk and high risk according to clinical remission at day 33, presence of t (9;22)/BCR-ABL, 11q23, MLL gene rearrangement, and hypodiploid ALL. It consists of different block of treatment protocol. The first lumbar puncture will be done during induction Protocol Ia at day 8 of induction, followed by day 15, 22 and 33 if there is no CNS involvement. The subsequent lumbar punctures will be done according to chemotherapy protocol based on their risk stratification for a total treatment duration of 2 years. Total lumbar puncture required for each patient is different based on their risk stratification. For standard risk group of patient, they will undergo total of 23 lumbar puncture, while 25 and 23 for intermediate risk group and high risk group respectively (Table 1.0). Additional 2 lumbar puncture will be required for patient with CNS involvement for all group during the induction period.

When diagnosis of ALL is made, parents will receive explanation regarding the course of treatment, side effect of chemotherapy, indication and complications related to common

procedures done in the course of treatment which include bone marrow aspiration and lumbar puncture.

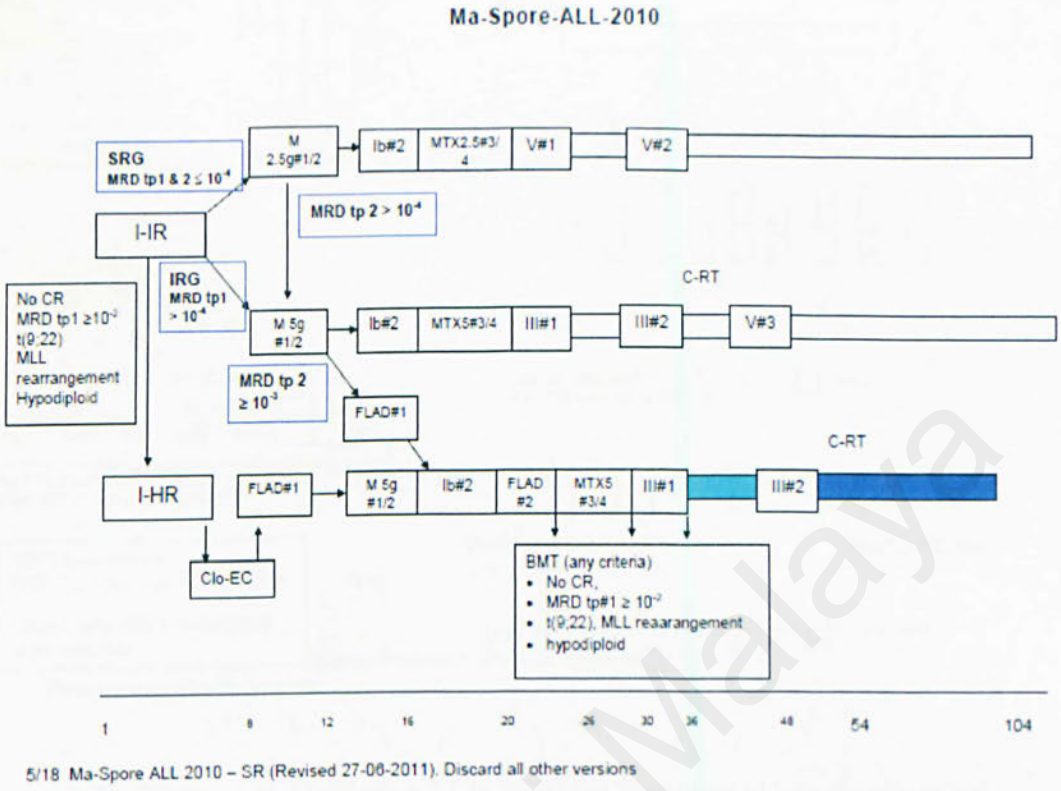


Figure 1.1 : Ma-Spore ALL 2010 protocol

Table 1.0 : Total lumbar puncture requirement according to risk stratification

	Standard risk (SR)	Intermediate risk (IR)	High risk (HR)
Induction arm	5 *additional 2 if CNS involvement	5 *additional 2 if CNS involvement	5 *additional 2 if CNS involvement
Post-induction arm	12	15	17
Maintenance **cycle**	6	5	4
Total LP (without CNS involvement)	23	25	23

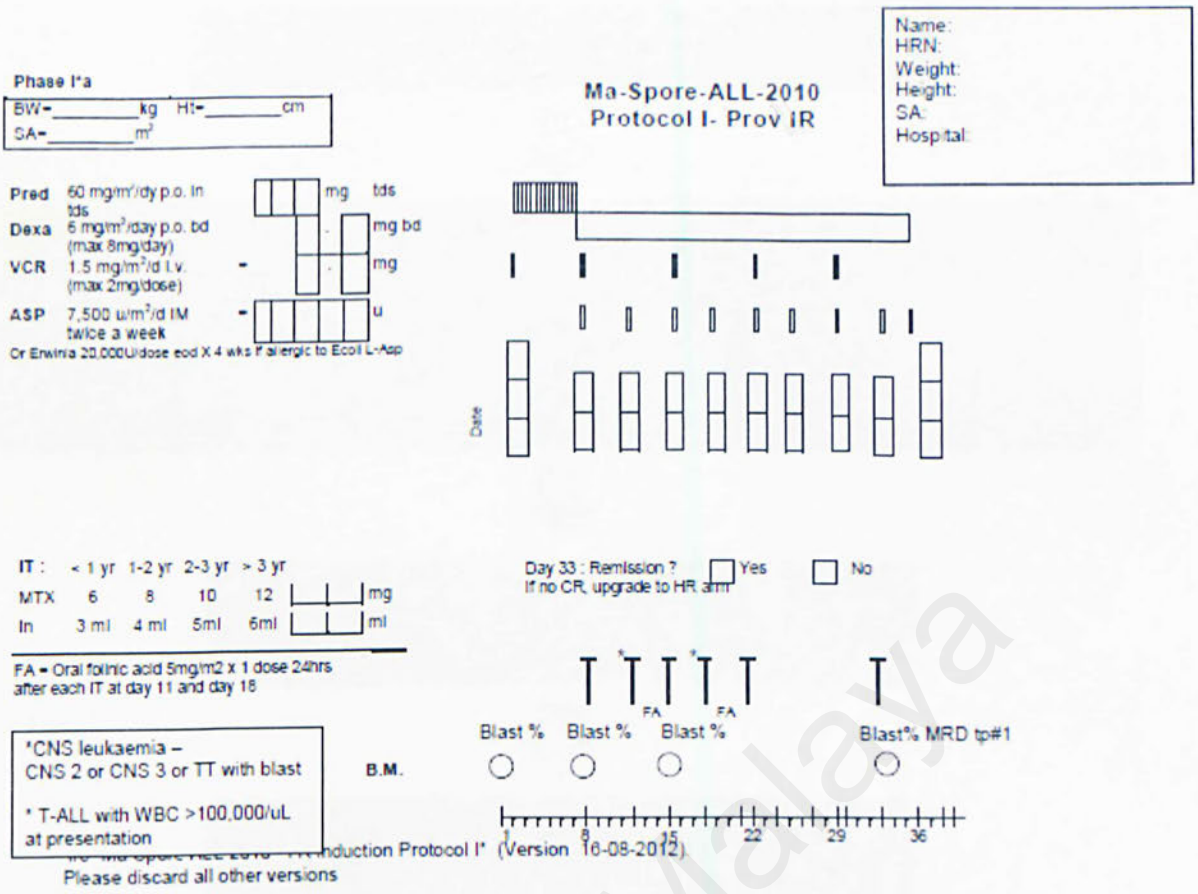


Figure 1.2 : Protocol Ia Ma-Spore ALL 2010 for Provisional Intermediate risk

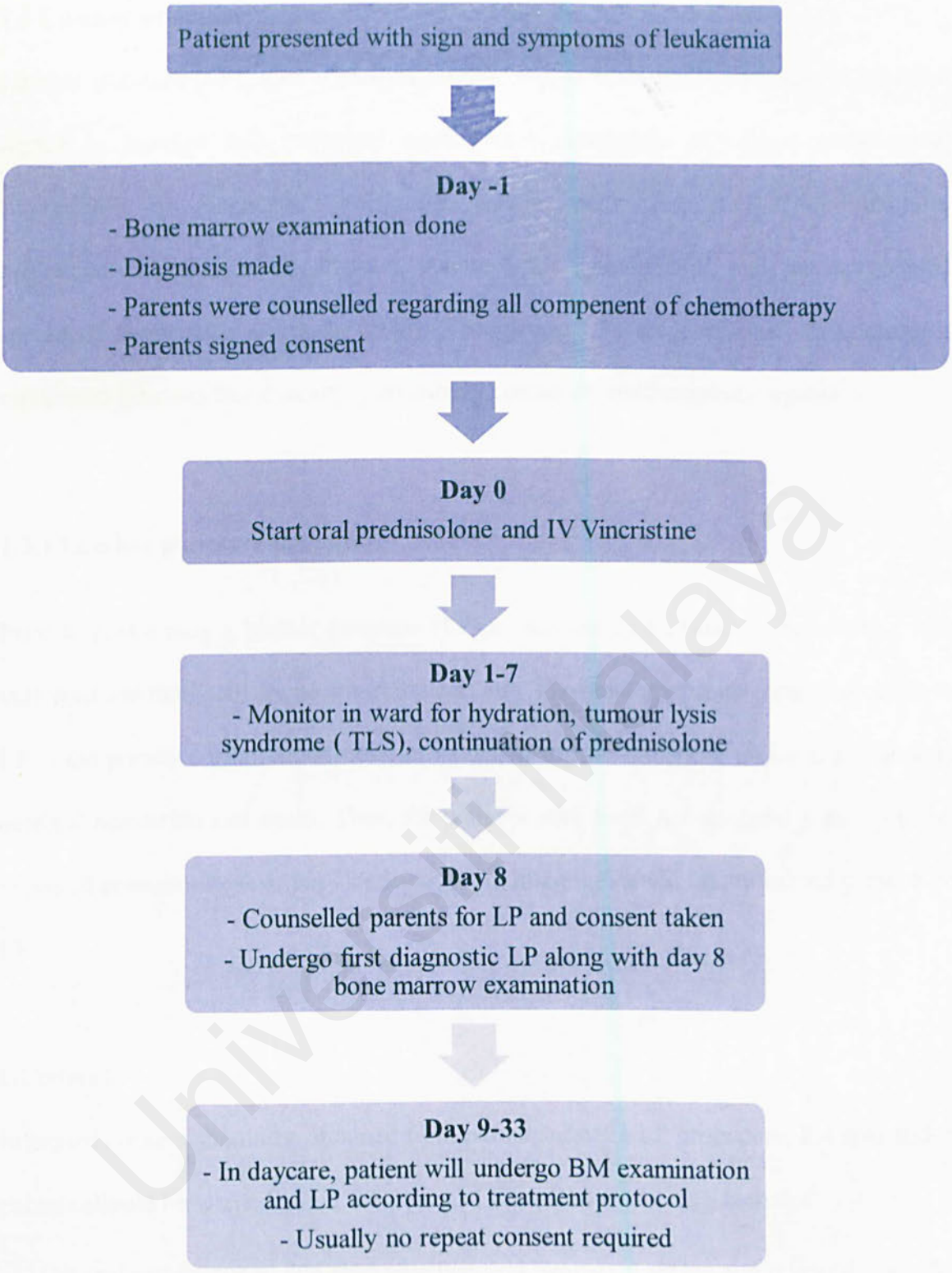


Figure 1.3 : Algorithm for newly diagnosed ALL patient

1.3 Lumbar puncture

Lumbar puncture (LP), also known as a spinal tap, is a medical procedure in which a needle is inserted into the spinal canal, most commonly to collect cerebrospinal fluid (CSF) for diagnostic testing for patients with suspected CNS infection, inflammation, autoimmune disorder, subarachnoid hemorrhage, and leptomeningeal spread of neoplasm (Gorelick, 1986). Therapeutic LPs are performed to administer certain medications intrathecally, particularly certain chemotherapeutic agents.

1.3.1 Lumbar puncture procedure

Prior to performing a lumbar puncture (LP),a care should be taken to ensure that it is indicated and that there are no contraindications. The most important contraindication to LP is the presence of an intracranial mass lesion. In this situation, an LP may result in cerebral herniation and death. Thus, for patients with focal neurological signs, seizure, impaired consciousness or papilloedema, brain imaging should be performed prior to an LP.

I)Consent

Informed consent should be obtained from parents prior to LP procedure. Patients and parents should be warned about the potential complications which includes:

- Generalized headache and markedly postural, worse on sitting and relieved lying flat
- Risk of infection because the needle breaks the skin's surface, providing a possible portal of entry for bacteria.
- A temporary pain or numbness to the legs or lower back pain
- Risk of bleeding in the spinal canal

II) Preparation

Preparation prior to performing a lumbar puncture is essential. A well-lit room with a firm, height-adjustable couch and an assistant should be arranged. The equipment required should be prepared on a sterile field which will include an appropriate lumbar puncture needle. Correct patient positioning is the key to successful lumbar puncture. The patient should be asked to lie in the left lateral position (for the right-handed operator) with their back along the edge of the couch. They should be asked to adopt the foetal position with their neck, hips and knees flexed. A care should be taken to ensure that their hips lie vertically above each other and likewise the shoulders. The operator should then examine the patient's back to identify the anatomical landmarks (Figure 1.4). First, locate the iliac crest and then palpate the spinous processes. The level vertically below the iliac crest should be between L3 and L4. This should be identified by carefully by palpation as visible surface landmarks can be misleading.

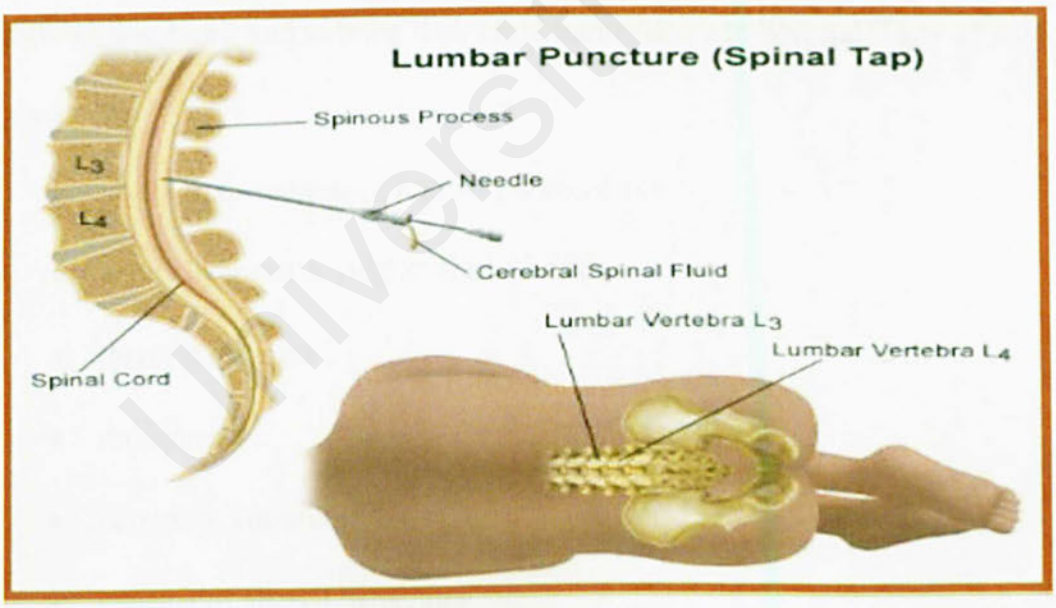


Figure 1.4 : Anatomical landmark for LP needle insertion

III) Technique

A sufficiently large area of surrounding skin should then be sterilized to maintain a sterile field. Lidocaine (2%) can then be infiltrated into the skin overlying the intervertebral space as far as the intervertebral ligament. The needle is then inserted in the midline pointing towards the umbilicus. Once beyond the subcutaneous fat, a steady level of resistance should be felt as the needle passes through the supraspinous and interspinous ligaments. An additional brief increase in resistance may then be felt as the needle passes through the dura before a feeling of give as the needle passes into the subarachnoid space. At this point the stylet should be removed and there should be backflow of CSF.

IV) Post-lumbar puncture care

Following lumbar puncture, patient will require to lying on the back for at least 30 minutes to 1 hour. Once discharge from hospital, parents were advice to monitor for the following at home and to bring their child immediately to hospital if any of the following presence :

- swelling or redness of lumbar puncture site
- fever (temperature higher than 37.5°C)
- tingling of limbs
- drowsiness
- persistent vomiting
- unusual or altered behaviour
- any leaking fluid from the lumbar puncture site

1.3.2 Factors associated with a successful lumbar puncture

There are several operator and patient factor that are associated with a successful lumbar puncture which include :

- Operator factor : operator experience
- Patient factor : Patient size, age, gender and adequacy of sedation received
- Parental factor : Parental knowledge and parental socioeconomic background can affect the success rate of lumbar puncture. Parental knowledge will affect their acceptance towards LP and their positive attitude towards LP will further reflect their children perception and acceptance towards LP.

CHAPTER 2: LITERATURE REVIEW

2.1 Risk factors for unsuccessful/ traumatic lumbar puncture

Lumbar puncture is a procedure that is commonly performed in children. A traumatic lumbar puncture occurs when the needle used to perform the procedure unintentionally causes bleeding into the subarachnoid space (Shah, 2002 & Mazor, 2003). For non oncology patient, traumatic lumbar puncture can result in diagnostic ambiguity that may lead to unnecessary antibiotic use and hospitalization (Mazor, 2003, Baskin 1992 & Jaskiewicz). Similarly for paediatric oncology patient, traumatic or unsuccessful LPs can cause diagnostic confusion and worsened patient's prognosis as bacterial or leukemic cells circulating in blood maybe introduced into CSF as a result of traumatic LP (Gajjar, 2000 & Gaur, 2001). Additionally, if the lumbar puncture is traumatic or unsuccessful, the patient may be subjected to the discomfort of multiple LP attempts. Few investigators have studied risk factors for traumatic or unsuccessful LPs. Risk factor that affect a success of LP can be divided into operator, procedure-related and patient factor:

2.1.1 Patient's factors :

a) Patient age

- Howard et al. performed a large retrospective study that identified subject younger than 1 year old as a risk factor for a traumatic LP in paediatric oncology patients (Howard et al, 2002). It is maybe due to the smaller intervertebral space and shallow depth of needle insertion required to reach the thecal sac.

- In a large prospective cohort of 1,474 lumbar punctures in a single emergency department Nigrovic at el. found that children less than 3 months had increased likelihood of having unsuccessful LP (Nigrovic at el.,2007).

b) Patient size

- Kirk et al. conducted a study to assess the ultrasound's ability to identify pertinent landmarks for lumbar puncture in patients of various body mass indices and found the difficulty to palpate LP landmark in obese subject (Kirk et. al, 2007)

- Edward C et at showed that patient BMI inversely correlates with the probability of a successful LP in the outpatient setting. Furthermore, this higher failure rate is mostly found in patients with BMI of 35 (Edward, C. et al, 2015).

2.1.2 Operator factor

- Baxter et al. found that there were no significant different in the proportion of unsuccessful LPs with increased experience of physician or holder

2.1.3 Procedure-related factor

- A prospective study of infants undergoing LPs found that the use of local anaesthesia in all infants in those infants younger than 12 weeks of age increased LP success rate.

- In a recent published cross-sectional observational study, Procter et al. showed that the prevalence of unsuccessful LP was 32.3% and they found that the used of sedation was associated with a reduction in the likelihood of unsuccessful LP except in those < 3 months of age, where sedation did not significantly reduce the likelihood.

- Ljungman et al. found that there was similar outcome in patient received local sedation compared to patient that underwent LP under general anaesthesia

2.1.4 Other factors :

- Baxter et al, found that patient position and drape use were not significant predictors for a successful LP (Baxter,2006).

- Procter et al found that presence of a family member, or LPs done during the day as opposed to the night gave no significant difference in unsuccessful LP (Procter, 2016)

- Nigrovic et al. found the presence of a family member(s) was not associated with an increased risk of traumatic or unobtainable lumbar puncture, nor was it associated with more attempts (Nigrovic et al, 2007)

- Srivastava et al. in 2012 showed that viewing educational video helps with provider comfort in performing the procedure, but it does not help in actually being successful

2.2 Complications of lumbar puncture

Despite their clinical values, LPs carry a risk of complications that include headache, backache, neck pain and stiffness, nausea, vomiting, vertigo, cranial nerve palsies, and a variety of visual and auditory disturbances (Chordas, 2001; Homer, 2002; Janssens et al, 2003; Turnbull &Shepherd, 2003).

2.2.1 Post-lumbar puncture headache (PLPH)

Post-lumbar puncture headache (PLPH) is the most common complication of LP. It is more common in oncology patient compared to general population. PLPHs occur less frequently in general paediatric populations, with an incidence ranging from 2% to 15% (Janssens et al, 2003; Lin & Geiderman, 2002). Several studies with paediatric oncology patients undergoing diagnostic or therapeutic LPs reported PLPH rates of 6% to 9% (Keiden et al, 2005; Ramamoorthy et al, 1998; Wee et al, 1998). Compared with recent study, the prevalence of PLPH noted to have increasing in trend. This maybe due to more

studies done in adult and paediatric group to look into the complications of lumbar puncture compared to 10 years ago, there was limited study identifying PLPH in children. In recent studies in adolescent and children, 27% of patients have been identified to had headache and 9% had positional headache (Ebinger et al.,2004).

a)Pathophysiology of post-lumbar puncture headache

Headache pain after a lumbar puncture was first noted in 1898 by August Bier (Evans, 1998). He described adverse effects from the procedure by having an LP performed on himself and on his assistant. Both experienced headache that increased during the day and resolved with recumbency. Bier hypothesized that the cause of the spinal headache was leakage of cerebral spinal fluid (CSF)through the dura puncture site (Evans, 1998). Today there is evidence that PLPH is caused by the persistent loss of CSF through the dura hole created by the LP needle causing cerebral hypotension. (Grant, Condon, Hart, & Teasdale, 1991).

b) Characteristic of PLPH

In PLPH, headache features are variable. The pain is usually severe, but may be mild or moderate. (Turnbull &Shepherd, 2003). The quality may be burning, dull and/or throbbing (Turnbull &Shepherd, 2003, Kuczkowski, 2006). The headache location is not diagnostic. Pain may be frontal or occipital with radiation to the neck and shoulders. (Turnbull &Shepherd, 2003). Headache can be aggravated by physical activity and movements of head may worsen the pain. (Ahmed, Jayawarna& Jude, 2006).

Valsalva manoeuvre, coughing, sneezing, straining, or ocular compression may worsen the headache. (Ahmed, Jayawarna& Jude, 2006). PLPH may have associated features including low back pain, vertigo, tinnitus, hearing changes, cranial nerve palsies, diplopia, and even cortical blindness. In addition, the associated features of migraine such

as nausea, photophobia, and phonophobia may occur. (Kuczkowski, 2006, Ahmed, Jayawarna& Jude, 2006, Clark, 1996). The onset of headache after lumbar puncture is usually within 24–48 hour after dural puncture, (Olsen, 2004, Evans, 1998) but it could be delayed by up to 12 days (Fearon, 1993).

c) Factors contributing to the development of headache after LP

There are several factors had been identified contributing to the development of headache after LP which includes needle size, direction of bevel, needle design, replacement of stylet and number of LP attempts. The size of the dural tear is directly proportionate to the amount of CSF leakage. As a smaller needle diameter produces a smaller tear in the dura, there is less potential for leakage and incidence of headache after lumbar puncture. The incidence of headache is 70% if the needle size is between 16 and 19G, 40% if the needle size is between 20 and 22G and 12% if the needle size is between 24 and 27G.(Dieterich & Perkin, 1996). As the collagen fibres in the dura matter run in a longitudinal direction, parallel to the long or vertical axis of the spine, the incidence of headache after lumbar puncture is less if the needle is inserted with the bevel parallel to the dural fibres, rather than perpendicular. (Lybecker, 1990). Three randomised, double-blind controlled studies concluded that atraumatic needles considerably reduced the incidence of headache after diagnostic lumbar puncture, although they were associated with a higher failure rate than the standard needles. As the tip has to be passed at least 0.5 mm into the subarachnoid space before the orifice enters into it and some patients may develop paraesthesia owing to the possible impingement on the stretched cauda equina by the tip of the needle. (Thomas, 2000, Strupp, 2001, Kleyweg, 1998). As the number of dural punctures directly relates to the size of the dural damage, making fewer attempts at dural puncture could be associated with lesser incidence of headache after lumbar puncture. However, no studies have been conducted.

d) Factors not influencing the incidence of headache after LP

The volume of the spinal fluid removed is not a risk factor for headache after lumbar puncture. (Evans, 2000). Mostly, lumbar punctures are performed with patients lying on their side, (Serpell, 1998) although it is considered to be quicker and technically easier with the patient sitting upright. So far, there is no convincing evidence to suggest any particular position to reduce the incidence of headache after lumbar puncture, and it depends mainly on the choice of the doctor unless it is to measure the CSF pressure, where the patient should be in the supine position. The incidence of headache after lumbar puncture does not depend on the CSF opening pressure, CSF analysis or the volume of CSF removed. (Kuntz, 1992).

2.2.2 Other complication of lumbar puncture

Another common complication after lumbar puncture is backache. The incidence has not well been described in children. In a prospective study of general paediatric and neuropediatric patients, they reported that 40% of patient developed backache and the incidence increasing with puberty (Ebinger, 2004).

Iatrogenic meningitis is an uncommon complication of diagnostic LP. Incidence is unclear because cases may not be reported. Physicians may not be aware of the potential association between meningitis and a preceding LP (Baer, 2006). Potential routes of infection include from operators' hands, the patient's skin or through aerolization of organisms from the operator's mouth. In a review of 179 cases of post dural puncture meningitis, only 9% followed diagnostic LP; most followed either spinal or epidural anaesthesia (Baer, 2006). Iatrogenic meningitis was not analysed in this study.

In rare cases, severe complications such as spinal abscess, and subdural hematoma have been reported (Sudlow & Warlow, 2001). Dizziness and reversible hearing loss are fairly

common. During lumbar puncture, needle contact with the sensory roots causing transient electric shocks or dysesthesias occurs in about 13% of patients. Permanent motor and sensory loss rarely occur (Evans, 2006).

2.3 Complications of sedation

Lumbar puncture is a painful procedure, and thus all patient, regardless of age group should receive some form of analgesia. Lidocaine infiltration is commonly use in older patient, other alternative includes topical mixture like EMLA. For younger age group, intravenous sedation is the best option. Ketamine is a well-established anaesthetic drug that has been in use for around 50 years (Domino, 1965). It produces a spectrum of anaesthetic effects that results in a type of anaesthesia that has an obviously different feel qualitatively as compared to more traditional volatile based anaesthesia. This state of so-called "dissociative anaesthesia" has been well described including: (a) hypnosis which includes psychotomimetic effects at low concentrations, followed by increasing sedation and unconsciousness at higher doses; (b) intense analgesia (or more accurately anti-nociception); (c) increased sympathetic activity; and (d) maintenance of airway tone and respiration. Ketamine has been demonstrated to be a safe and effective dissociative anaesthetic agent in a variety of hospital settings (Dailey, 1979). However, ketamine can result in unpleasant hallucinations and dreams that occur during the recovery period. These phenomena can be reduced or eliminated with the concomitant administration of benzodiazepines. (White, 1982). Several studies have attempted to identify risk factors for adverse events associated with procedural sedation and analgesia in children. A retrospective study conducted in paediatric emergency department observed several complications in the use of ketamine in their setting. Ketamine cause oxygen desaturation below 85%, apnea, transient stridor, hypertension, tachycardia, hypersalivation, vomiting, hallucinatory emergence reaction and rash. In their study, there was no adverse

outcomes attributable to the use of combination IV ketamine and midazolam (Karapinar, 2005).

2.4 Parental consent refusal for lumbar puncture

Obtaining consent for a procedure involves an interaction between parents' beliefs, perception or understanding of their child's illness, and doctors' skills at convincing them of the necessity of the procedure. A balance must be struck between the robustness of the indication and the advantages versus the risks of performing that procedure or not. Even though lumbar puncture (LP) is a common and safe procedure but yet some parents still have fears of having it performed on their child and refuse consent not only in paediatric oncology patient but also in general paediatric population. There were several factors identified to be associated with parental refusal for lumbar puncture.

2.4.1 Patient or parental knowledge

- In a previous prospective study of children whose parents refused to give consent for a diagnostic LP, undertaken in the emergency and the inpatient paediatric ward, from a total of 55 families who were asked to give consent for an LP on their child, 24 (44%) refused to give consent. Seven families (29%) had no previous knowledge of the indications for LP (Narchi et al,2001)

- Borhani et al found the high prevalence of LP refusal due to poor of knowledge (92.6%) and negative attitude (63%) towards LP. The reason behind this respond was directly related to lack of information given, lower socioeconomic status, lower educational level, and residence in rural areas (Borhani, 2009)

- In a descriptive cross sectional, questionnaire-based study, King et al found that reason for LP refusal, majority was due to fear of pain and patient also associate LP with death and paralysis (King et al, 2014).

2.4.2 Perception towards lumbar puncture

75% of parents fear of LP complications and 21% of them had a perception that LP was unnecessary and distrust of the motives behind the request for consent (Narchi, 2001). A local cross-sectional study done in Hospital University Sains Malaysia reported that, 54% of parents refused LP (Malik, 2000). They reported several factors which did not play a statistically significant role in decision-making to give consent which includes patient age, parental age, gender and education and family monthly income (Malik, 2000). On the other hand, factors that positively influenced the decision to give consent included knowledge about the purpose of LP and underlying disease (Malik, 2000). In an exploratory descriptive study for children with ALL, out of 159 patients who was diagnosed with ALL, 40 parents (25%) refused or abandoned therapy (Sitaresmi, 2009). There was limited data reported on the lumbar puncture refusal specifically for ALL children who received their intrathecal chemotherapy.

CHAPTER 3: OBJECTIVES

3.1 OBJECTIVES

3.1.1 Primary Objective

To audit the success rate of performing lumbar puncture by single attempt in children undergoing treatment for ALL in UMMC

3.1.2 Secondary Objectives

1) To describe risk factor that contribute to a successful lumbar puncture eg. operator seniority, patient BMI, adequacy of sedation and patient ethnicity

2) To describe complications related to LP and/or sedation used

3) To compare adverse events in those who received IV ketamine with or without IV Midazolam

4) To identify the prevalence of parental refusal in giving consent for LP and the reason for it

5) To identify the prevalence of parental need for repeat consenting and re-explanation for subsequent lumbar puncture procedure

5) To identify any association between parental psychosocial factor with reluctance to give consent for first lumbar puncture and the need for repeated explanation for subsequent LP

6) To validate an 'in-house' formula for ideal depth of needle insertion for successful lumbar puncture

3.2 HYPOTHESIS

3.2.1 Research hypothesis

Lumbar punctures are performed successfully in children undergoing therapy for ALL in UMMC if lumbar punctures are performed in single attempt

CHAPTER 4 : METHODOLOGY

4.1 STUDY DESIGN

This is a prospective, cross sectional study mixed with an observation and interview based. Patients were recruited from July 2017 until September 2017 in the Paediatric Oncology Unit in University Malaya Medical Centre (UMMC).

4.2 RECRUITMENT

4.2.1 Inclusion Criteria:

- Patients with de novo acute lymphoblastic leukaemia
- Aged 3 - 18 years old
- Underwent lumbar puncture in Ward 5PA or PDC, UMMC
- For diagnostic as well as for IT MTX administration as per their chemotherapy protocol.

4.2.2 Exclusion criteria:

- ALL patients with CNS involvement
- ALL relapse
- Chronic headache
- History of venous thrombosis or anticoagulant use

4.3 DATA COLLECTION:

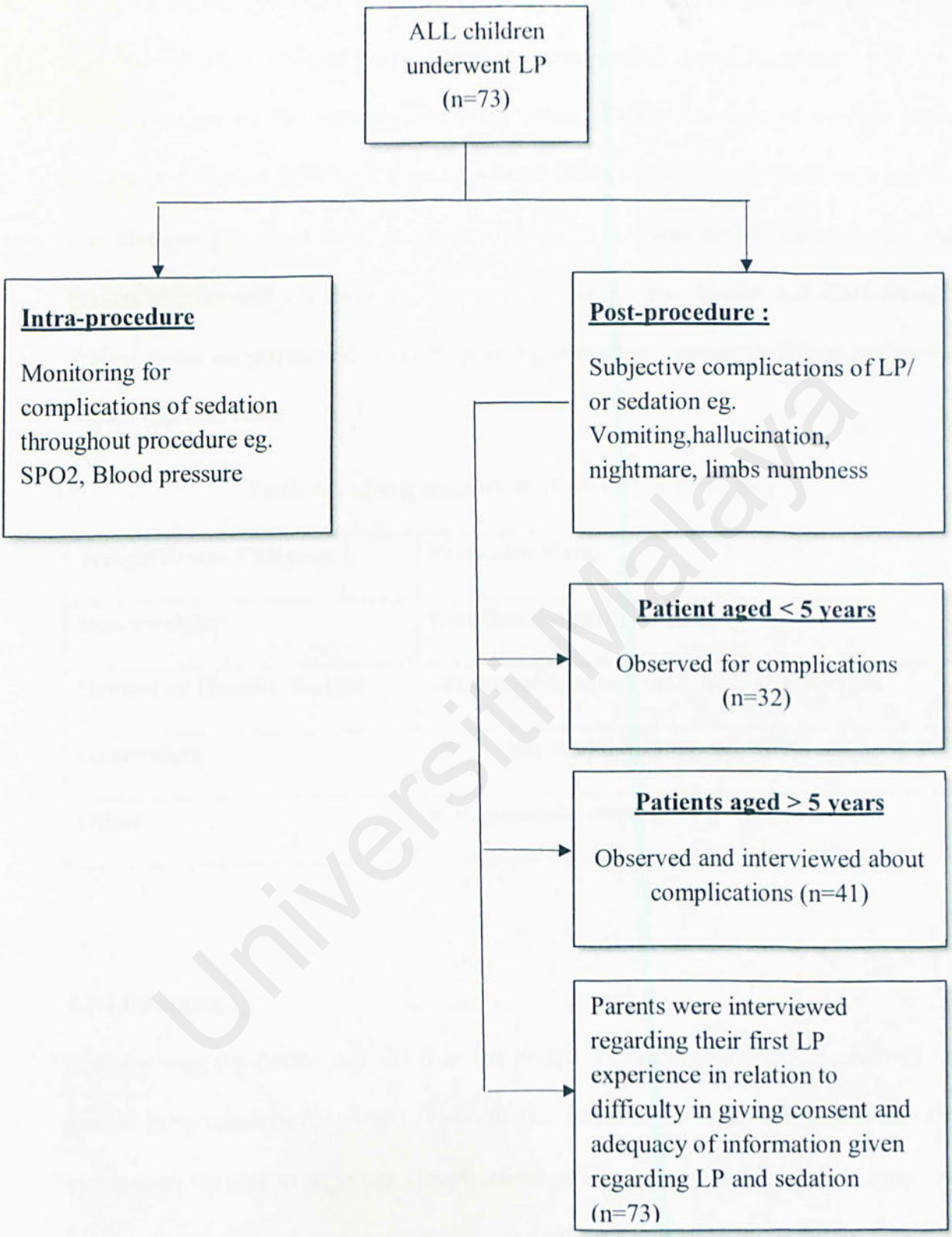


Figure 4.1 : Flow chart for data collection

4.3.1 Patient's demographic data:

Patient's demographic data, including name, age, hospital registration number, and My Kid identification number were obtained from patient hospital sticker and was counterchecked by the operator and staff nurses. Patient's weight and height were measured, BMI and BSA were then calculated. Patient's current chemotherapy regime was checked prior to lumbar puncture. The CDC (Centres for Disease Control and Prevention) Growth Charts were used to measure weight, height and BMI-for-age. Weight status categories and the corresponding percentiles recommendations are shown in the following table:

Table 4.1 : Body mass index (BMI) for age category

Weight Status Category	**Percentile Range**
Underweight	Less than the 5th percentile
Normal or Healthy Weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obese	95th percentile or greater

4.3.2 Operator :

Operator was the doctor that filled in the patient's demographic data, performed the lumbar puncture, monitored and observed the patients for complications. They also interviewed the patient regarding complications of LP and parental experience regarding LP in relation for reluctance in giving consent and adequacy of information given regarding LP and sedation used.

These operators were:

- Specialist: Oncology Unit consultant or trainee lecturer that working in the Paediatric Oncology Unit including ward and paediatric day care.
- Medical Officer: Doctor that was posted to Paediatric Oncology ward/ clinic or day care rotation for 3 months as part of their post-graduate paediatric clinical master programme with more than 2 years' experience in paediatric.
- House officer: Doctor that had less than 2 years working experience after graduation from medical school, that was posted to paediatric department UMMC as part of their housemanship training programme.

4.3.3 Monitoring for complications from LP and/or sedation :

Before the patient underwent LP, blood was withdrawn from every patient and sent for full blood count (FBC) and GSH (Blood grouping, screen and hold). The platelet result was reviewed electronically via 'iPesakit', an electronic database of UMMC prior to lumbar puncture and for subjects with platelet count less than 50,000, the procedure was performed under platelet cover (10ml/kg of platelet). For subjects with low platelet count less than 50,000, the procedure was performed by specialist and/ or medical officer under supervision of specialist. For monitoring of complications related to intravenous sedation particularly IV Ketamine and IV Midazolam, subject's blood pressure and heart rate were taken pre- and during procedure with continuous SPO2 monitoring throughout the procedure using Nellcor machine. Oxygen desaturation was defined as SPO2 less than 90% with no prior empirical oxygen supplementation given via face mask throughout procedure unless patient developed desaturation. Resuscitation equipment were available at the bedside for all patients. The blood pressure recorded will be classified as hypertension if BP > 95th percentile for age, gender and height percentiles and an increment of more than 2 percentile from baseline (pre-procedure) was considered as a

significant side effect of sedation used. Hypotension was defined as blood pressure less than 5th percentile for age and height or a drop in BP more than 2 percentile from baseline.

4.3.4 Sedations:

4.3.4.1 Intravenous sedation

Standard sedation used in oncology paediatric ward or daycare UMMC were IV Ketamine 2mg/kg/dose, IV Midazolam 0.2mg/kg/dose (maximum dose of 5mg) and IV Atropine 0.02mg/kg/dose (maximum 0.2mg). Patient was classified as inadequate sedation if they required additional IV Ketamine of more than 2mg/kg/dose. Dosage of sedation given to patient was documented in a standardized data collection form and was further counter-checked with patient's own medication cardex.

4.3.4.2 Local anaesthesia

Standard local anaesthesia used was EMLA cream (Eutectic Mixture of Local Anaesthetics), which was applied by the staff nurse onto the overlying skin of the lumbar puncture site, 30 to 45 minutes prior to procedure and covered with an occlusive dressing. The staff nurse that applied the EMLA cream ensured that LP was done within 45 minutes after EMLA application to ensure adequate local anaesthetic effect. Parents/ guardians that accompanied the patient have to remind the staff nurse in charge if EMLA was applied beyond the targeted time.

4.3.5 Lumbar puncture procedure and CSF collection

All patients were kept nil by mouth at least 6 hours prior to procedure except those who received local anaesthesia. They were given supplementation of intravenous fluid as per maintenance fluid requirement. The procedure was done at the treatment room in the oncology ward or paediatric daycare by one operator and one assistant nurse. A right-

handed operator should position the patient in the left lateral decubitus position, with the vertebrae in line in the horizontal plane and the head in a neutral position and the knees flexed. After the patient is properly positioned, any local anaesthetic cream or dressing was removed and a circular area around insertion site was cleaned. A sterile drape with eye-hole was placed on the patient's back to allow visualization of the puncture site. The spinal needle size 22 gauge was inserted with the bevel parallel to dural fibres into the desired interspaces (L3-L4 or L4-L5) that has been identified using posterior superior iliac spine bone (PSIS) as a marker. Entrance into the subarachnoid space was confirmed by a good free flow of cerebrospinal fluid. There was no opening pressure measured. A Total of 20 drops of CSF fluid were collected for each patient and the samples were sent to the lab for CSF biochemistry and microscopy examination and also to examine for existence of blast cells. Once CSF was obtained and intrathecal chemotherapy was administered, the needle was removed and the depth of needle insertion (length from needle insertion at patient's skin until tip of spinal needle) was measured (in centimetre) by operator using a ruler placed near the operator on a flat surface. The measurement of depth of needle insertion was further verified by assisting nurse. All operators were trained and informed regarding needle depth measurement beforehand to ensure consistency and accuracy inter-operator. Patient was instructed to lie in supine position for at least 4 hours post procedure and was allowed orally once they regained full consciousness.

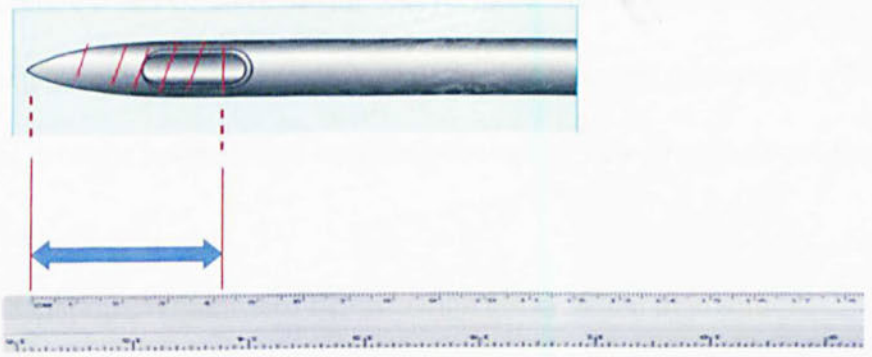


Figure 4.2: Measurement of actual depth of needle insertion (The length (in cm) between the needle tip to the start of the 'stain' on the needle body was measured using a standard ruler)

4.3.6 Monitoring of LP and/ or sedation post-procedure and interview with parents

After the procedure and once subject was fully conscious, patient and parents were interviewed by the operator regarding complications of lumbar puncture and /or sedations used. Patient were interview within 2 to 6 hours following lumbar puncture. Patients older than 5 years old were observed and interviewed in the presence of parents as a translator or guidance either English or Malay according to their preference. They were asked specifically regarding headache, backache, limb numbness, hallucination (visual or auditory) or nightmare. For subjects less than 5 years old, they were observed for symptoms related to complications of lumbar puncture and sedation effect by operator and assisting nurse or through report by parents.

Complications definition:

- Headache must be differentiated from dizziness from the effect of sedation. Headache following procedure can be generalized or localized to frontal or occipital area. The pain is exacerbated by head movement and/ or adoption of the upright posture, and relieved by lying down. If any headache was present, it will

be scored using a number scoring scale from 0 to 10 depending on the severity of headache (0 less or no headache and 10 more severe headache).

- Bleeding from the puncture site was defined as bleeding that caused a fully soaked initial dressing applied, and requiring change of new dressing over the puncture site.
- Hallucinations: any form of hallucination either visual or auditory.

4.3.7 Interview with parents

Parents were interviewed using non-validated questionnaire by operator regarding their socioeconomic backgrounds particularly their education level, occupation, total household income and their experience regarding lumbar puncture. They were asked regarding any reluctance to give consent during the first lumbar puncture, the reason for reluctance to give consent and also whether they need re-explanation regarding lumbar puncture, indication, complications of procedure and/or sedation for each LP procedure.

Parent's education level was further divided into 4 categories which were:

- No formal education
- Primary education : completed 6 years of primary education
- Secondary education: completed 5 years of secondary education and sat for common public examination, Sijil Pelajaran Malaysia (SPM)
- Tertiary education : includes vocational and training, diploma and university

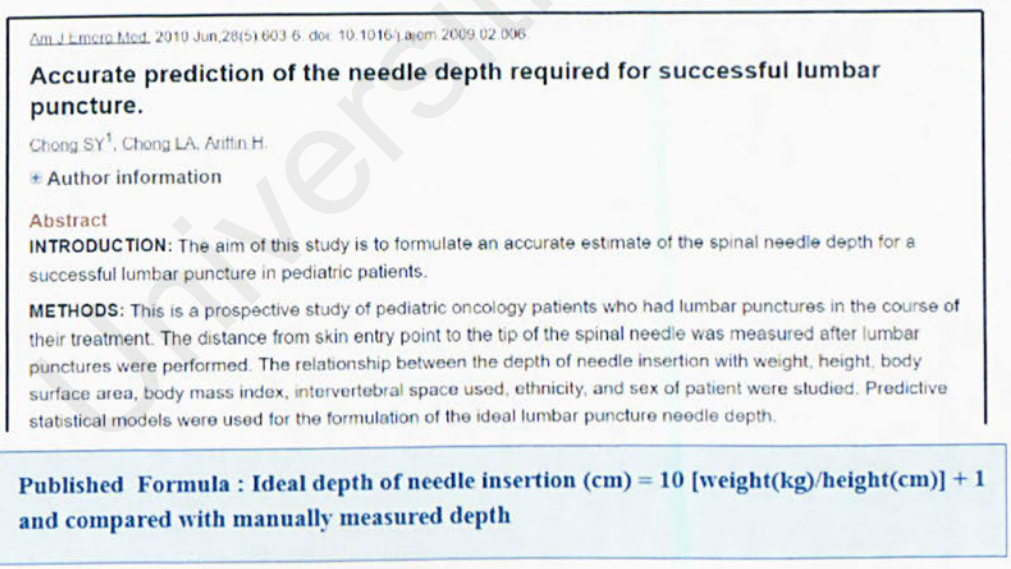
For statistical analysis, parental education was further divided into non-tertiary and tertiary education.

Parental total household incomes were divided into low income group for those with total household income less than RM5000 per month and high income group for those with total household income more than RM5000 per month.

All data collection forms from oncology ward or paediatric daycare were collected by investigator and parents were contacted if any of the information was not available or incomplete.

4.3.7 Validation of previous published formula for ideal depth of needle insertion

In order to validate the correct needle depth insertion, values from subjects with successful single attempt lumbar puncture were analysed. The first value was calculated using mathematical formula from a previous published study (Chong, 2009). The other set of value (measured in centimetres) was the actual depth of needle insertion measured by operator during procedure once a good CSF flow was obtained. Spearman correlation was used to analyse the correlation between the two value. The mathematical formula used as follow :



Am J Emerg Med. 2010 Jun;28(5):603-6. doi: 10.1016/j.ajem.2009.02.006.

Accurate prediction of the needle depth required for successful lumbar puncture.

Chong SY[1], Chong LA, Ariffin H.

+ Author information

Abstract

INTRODUCTION: The aim of this study is to formulate an accurate estimate of the spinal needle depth for a successful lumbar puncture in pediatric patients.

METHODS: This is a prospective study of pediatric oncology patients who had lumbar punctures in the course of their treatment. The distance from skin entry point to the tip of the spinal needle was measured after lumbar punctures were performed. The relationship between the depth of needle insertion with weight, height, body surface area, body mass index, intervertebral space used, ethnicity, and sex of patient were studied. Predictive statistical models were used for the formulation of the ideal lumbar puncture needle depth.

Published Formula : Ideal depth of needle insertion (cm) = 10 [weight(kg)/height(cm)] + 1 and compared with manually measured depth

Figure 4.3: Mathematical formula for ideal depth of needle insertion for successful LP

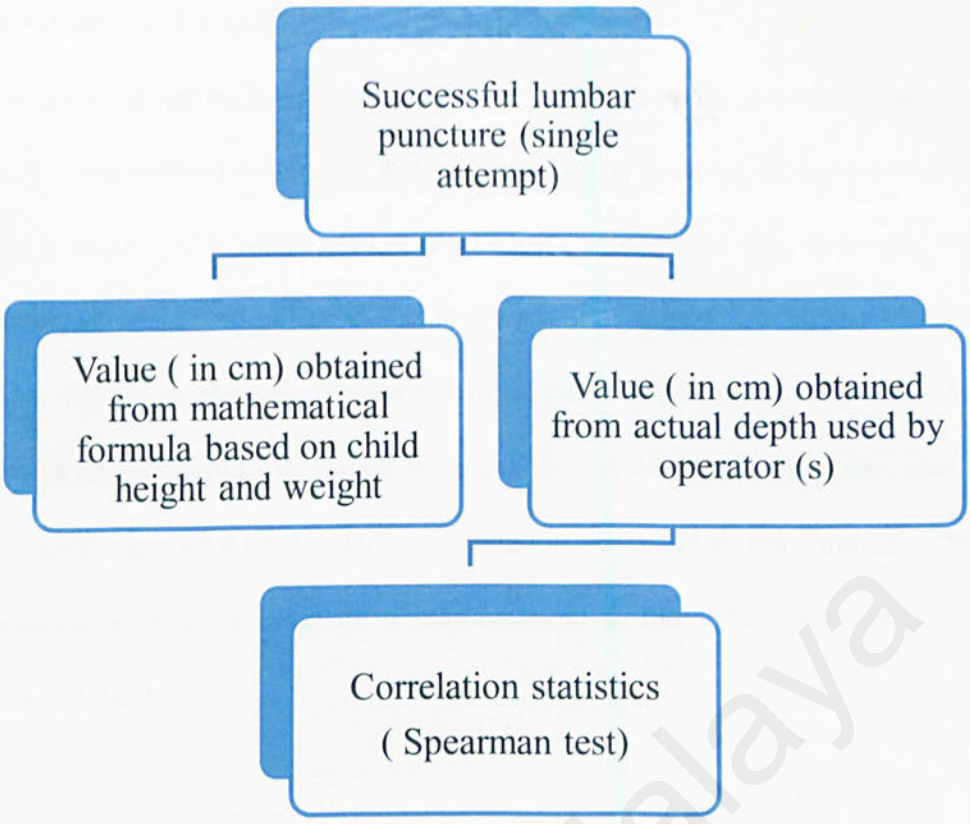


Figure 4.4: Methodology to identify correlation between calculated and measured depth of needle insertion

4.4 STATISTICAL ANALYSIS

Data was managed and analysed using the Statistical Package for Social Sciences (SPSS), Version 23. Conventional descriptive methods (means and standard deviation, medians with interquartile ranges (IQRs) were used to describe and characterise the continuous variables. The prevalence of successful LPs in this study was determined. Chi square test was used to compare dependent and independent variables, particularly to look for factors that were associated with successful LPs (single attempt). All *p*-values quoted are two-sided, with a level of significance of 0.05. Spearman correlation was used to see correlation between two variables in order to validate a mathematical formula from the previous study published in UMMC.

4.5 SAMPLE DATA CALCULATION

In this study, to determine sample size power study was used. Power of study is a very useful and frequently used tool in medical research to prove the sample size adequacy. The prevalence of a successful single attempt LPs for children is 81.0 (Procter et al., 2016). Since our population size is unknown, to obtain an appropriate sample size from this population, in this study the following formula was used :

$$n = \frac{(Z_{1-\beta})^2 [p(1-p)]}{d^2}$$

Where,

n = required sample size

$Z_{1-\beta}$ = Z value at power 1-β (at power 80% this value is 0.84)

p = referred prevalence for the study (0.810)

d = margin of error (ideal value is 0.05)

Considering 80% power of test, 5% marginal error and 0.810 prevalence rate, the formula gave us a sample size of 43.

In practice we may need to enrol more participants to account for potential missing sample or level error (Sakpal, 2010). The formula of adjustment sample size is

$n_1 = n/(1-d)$

n = required sample size as per formula

n_1 = is adjusted sample size

d = is the dropout rate

Considering 10 percent potential missing sample or level error, the adjusted sample size is 47.7. This is the minimum sample size that was calculated, finally, the targeted sample size for this study will be 48.

4.6 ETHICAL APPROVAL

Ethical approval for this study was obtained from the Ethnical Review Committee of UMMC (MECID. No : 2017710-5401).

CHAPTER 5 : RESULTS

5.1 Patient demographic characteristics

A total of 73 subject who underwent LPs were analysed. Their age range was between 3 to 13 years old (median, 6.4 years). Median body weight was 19.4kg (range 10.9 – 77.4kg) and median height was 106.6cm (range 84.5 – 165 cm. Our study population consisted of 56 male and 17 female. The main ethnic groups were Malays 71%, followed by Chinese 25%, Indians 3% and Bumiputra/ others 1%. 47(64.4%) subject had normal BMI for age and the rest of the subjects were overweight or obese. There were total of 24 operators involved from different groups of seniority. There were only 2 subjects whom underwent their first LP and the rest underwent their subsequent LP as per chemotherapy protocol. Median duration from diagnosis made until time subjects were interviewed was 9.6 months (range from 0 until 23 months). There were 3 subjects who received local anaesthesia while the rest of the subjects received intravenous sedation as per UMMC paediatric oncology guideline (Table 5.1). Majority of subjects (95.9%) received IV sedation, either Ketamine alone (50.7%) or a combination of IV Ketamine and Midazolam (45.2%). 12 (16.4%) out of 73 subjects required additional IV Ketamine during LPs (defined as inadequate sedation) (Table 5.2)

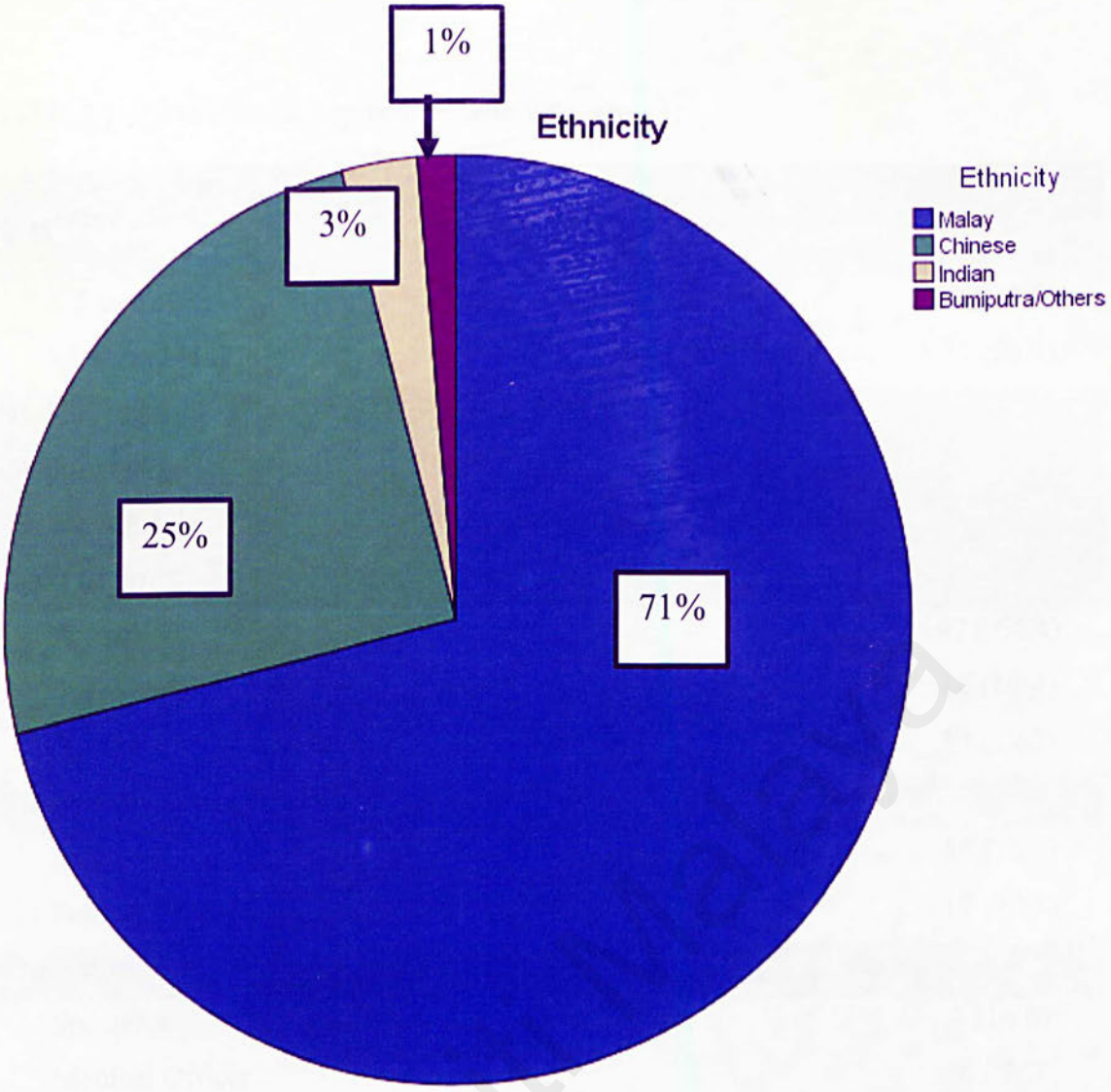


Figure 5.1: Study population based on ethnicity

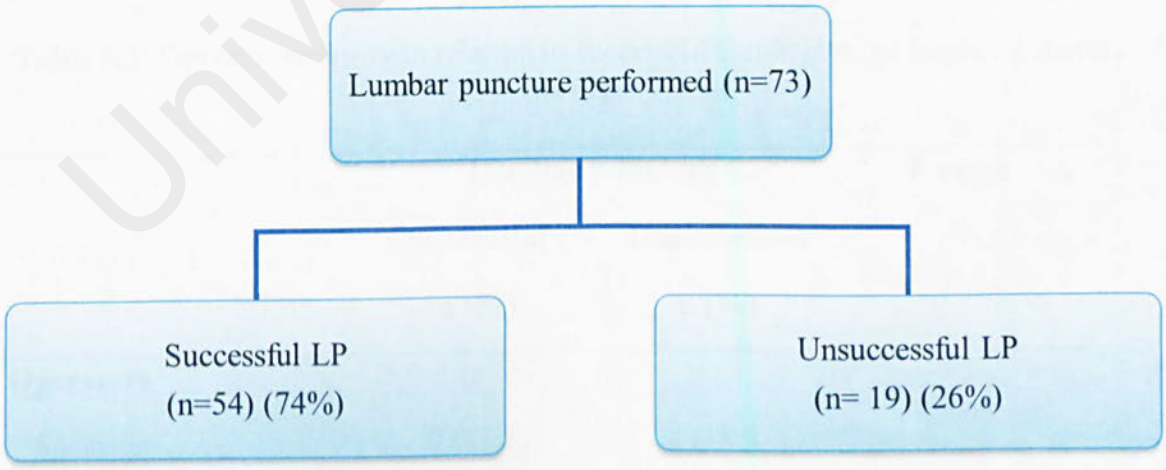
Table 5.1: Patient Demographic Characteristics (n=73)

Characteristics	Median (IQR)	Range	n (%)
Age (years)	6.49 (3.21)	3-13	
< 5 years old			32 (43.8)
>5 years old			41 (56.2)
Height (cm)	106.60 (32.05)	84.50-165.00	
Weight (kg)	19.40 (13.25)	10.9-77.4	
BSA (m^2)	0.75 (0.34)	0.50-1.87	
BMI (kg/m^2)	16.4 (3.80)	11.7-29.2	
Normal			47 (64.4)
Overweight			12 (16.4)
Obesity			14 (19.2)
Gender			
Male			56 (76.7)
Female			17 (23.3)
Operators			
Specialist			4 (16.6)
Medical Officer			6 (25)
House officer			14 (58.3)
Lumbar puncture performed			
First LP			2 (2.73)
Subsequent LP			71 (97.2)
Duration from diagnosis made (months)	9.62 (7.274)	0-23	
Sedation used			
IV sedation		70 (95.9)	
Local anaesthesia		3 (4.1)	

Table 5.2 : Procedure details

Characteristics	Frequency (n)	Percentage (%)
Platelet level		
< 50000	2	2.7
50000 and above	71	97.3
IV sedation		
Ketamine only	37	50.7
Midazolam only	0	0.00
Both ketamine and midazolam	33	45.2
Additional IV sedation required		
Yes	12	16.4
No	61	83.6
CSF result		
No cells seen	66	90.4
Few red cells	5	6.8
No result/sample not sent	2	2.7

5.2 Prevalence of successful LP in ALL children in UMMC



Lumbar puncture was performed successfully in 74% of subject who underwent lumbar puncture in paediatric oncology unit UMMC. Successful lumbar puncture in this study was defined as lumbar puncture performed with only single attempt.

5.3 Risk factors associated with successful lumbar puncture

There were four risk factors analysed in this study which were operator seniority, patient's BMI, adequacy of sedation and patient ethnicity. When compared for three operator groups based on seniority, LPs done by specialist had higher success rate (81.1%), followed by house officer (75%) and medical officer (70%) (Table 5.3). House officer success rate is higher compared to the more senior operator probably due to patient who are considered to be more difficult (history of multiple attempt LP performed before) will be selected to have their LP performed by more senior operator. However, operator seniority was not related to a successful LPs with P value of 0.735. Even though patient's BMI (p=0.072 RR 1.314 (95% CI 0.941-1.835)) (Table 5.4) and adequacy of sedation (p= 0.067, RR 1.574 (95% CI 0.881-2.813)) (Table 5.5) in relation to a successful single attempt LP were not statistically significant, a trend toward successful LP were observed in these two factors. There was no significant difference was found in the proportion of successful LPs between Malay or non-Malay ethnicity (p= 0.146, RR 0.808 (95% CI 0.628-1.039)) (Table 5.6).

Table 5.3: Operator seniority in relation to successful single attempt lumbar puncture (n=73)

	Lumbar puncture		**P value**
	Successful	**Unsuccessful**	
	n (%)	**n (%)**	
Operators			
Specialist	9 (81.1)	2 (18.2)	
Medical Officer	21 (70)	9 (30)	0.735
House officer	24 (75)	8 (25)	

Table 5.4: Patient BMI in relation to a successful single attempt LP (n=73)

	Lumbar puncture		P value	RR (95% CI)
	Successful n (%)	Unsuccessful n (%)		
BMI for age				
Normal	38 (80.9)	9 (19.1)	0.072	1.314
Overweight/ obesity	16 (61.5)	10 (38.5)		(0.941-1.835)

Table 5.5: Adequacy of sedation in relation to a successful single attempt LP (n=73)

	Lumbar puncture		P value	RR (95% CI)
	Successful n (%)	Unsuccessful n (%)		
Sedation required				
Adequate	48 (78.8)	13 (21.3)	0.067	1.574
Additional sedation required	6 (50)	6 (50)		(0.881-2.813)

Table 5.6 : Patient ethnicity in relation to a successful single attempt LP (n=73)

	Lumbar puncture		P value	RR (95% CI)
	Successful n (%)	Unsuccessful n (%)		
Ethnicity group				
Malay	36 (69.2)	16 (30.8)	0.146	0.808
Non-Malay	18 (85.7)	3 (14.3)		(0.628-1.039)

5.4 Complications of lumbar puncture and sedations

This study showed that out of 73 subjects, 26 (35.6%) developed vomiting and 3 (4.1%) subjects developed bleeding from LPs site (Table 5.7). For subjects more than 5 years old (n=41), 15 (36.6%) had headache, 8 (19.5%) had backache and 6 (14.6%) had limb numbness (Table 5.8).

Table 5.7 : Complications of lumbar puncture for all age group (n = 73)

Characteristics	Frequency (n)	Percentage (%)
Vomiting		
Yes	26	35.6
No	47	64.4
Bleeding from puncture site		
Yes	3	4.1
No	70	95.9

Table 5.8: Complications of lumbar puncture for patient aged more than 5 years (n=41)

Characteristics	Frequency (n)	Percentage (%)
Headache		
Yes	15	36.6
No	26	63.4
Backache		
Yes	8	19.5
No	33	80.5
Limbs numbness		
Yes	6	14.6
No	35	85.4

Majority of the subjects received intravenous sedation in particular ketamine, midazolam and atropine. There were only 3 of them who received local anaesthesia as sedation for the procedure. IV ketamine is known to cause hypertension, which were observed in 19

(27%) subjects who received IV sedation (n=70). As mentioned, IV midazolam is known to cause hypotension and oxygen desaturation, but none of these complications were observed in this study (Table 5.9). For subjects more than 5 years old whom received IV sedation (n=38), 14(36.8%) had hallucination and 6(15.7%) had nightmare (Table 5.10). When compared between 2 different groups of subjects with age more than 5 years who received either a combination of intravenous ketamine and midazolam (n=14) or intravenous ketamine alone (n=24) subjects who received combination of intravenous ketamine and midazolam reported lower percentage of complications compared to those that received IV ketamine alone. Similarly, for all subject whom received iv sedation (n=70) vomiting was observed more in subject whom received iv ketamine alone compared with whom received combination of ketamine and midazolam(Table 5.11 & Table 5.12). The results are as followed (Figure 5.2) :

- Hallucination [5 (35.7%) vs 9 (37.5%)]
- Nightmare [2(14.3%) vs 4 (16.7%)]
- Vomiting [10(30.3) vs 16 (43.2%)]

Table 5.9: Complications of intravenous sedation used for all age group (n= 70)

Characteristics	Frequency (n)	Percentage (%)
Hypertension		
Yes	19	27
No	51	73
Hypotension		
Yes	0	0
No	70	100
Desaturation (SPO2 <90%)		
Yes	0	0
No	70	100

Table 5.10: Complications of IV sedation used for patient aged more than 5 years (n=38)

Characteristics	Frequency (n)	Percentage (%)
Hallucination		
Yes	14	36.8
No	24	63.2
Nightmare		
Yes	6	15.7
No	32	84.3

Table 5.11: Comparison of complications of sedation used in those received IV ketamine alone and those received combination of IV Ketamine and IV Midazolam, in subjects aged more than 5 (n=38)

	Hallucination n (%)	P value	Nightmares n (%)	P value
IV Sedation				
Ketamine alone (n=24)	9 (37.5)	0.912	4 (16.7)	1.00
Ketamine&Midazolam (n=14)	5 (35.7)		2 (14.3)	

Table 5.12: Comparison of complication from sedation used in subjects who received IV ketamine alone and those received combination of IV Ketamine and IV Midazolam for all subject (n=70)

	Vomiting n (%)	P value
IV Sedation		
Ketamine alone (n=37)	16 (43.2)	0.263
Ketamine & Midazolam (n=33)	10 (30.3)	

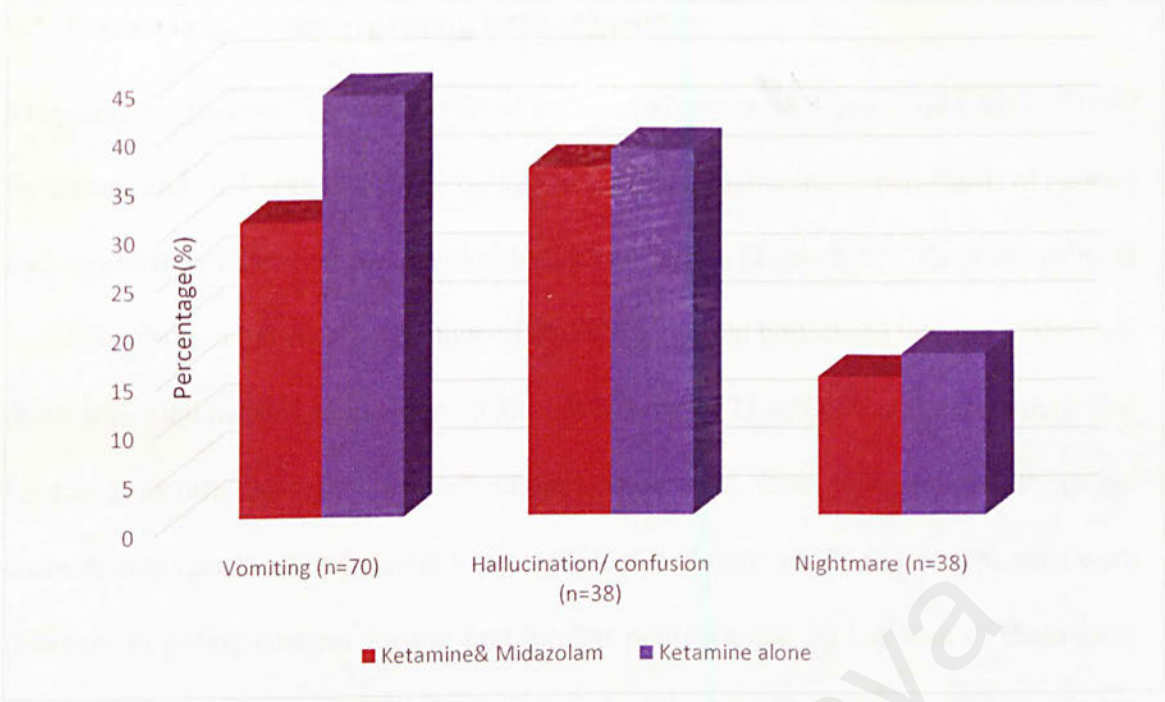


Figure 5.2: Comparison of complications from sedation used in subjects who received combination of IV Ketamine and Midazolam and those received IV ketamine alone

5.5 Parental experience regarding lumbar puncture

Mean age for parents that were involved in this study were 38.4 years old (SD ± 6.060) for fathers and 36.7 years old (SD ± 6.352) for mothers. In this study, two-thirds of parents had non-tertiary education compared to tertiary education (Table 5.12). There was almost equal distribution between percentage of parents with total household income <5000 and those with total household income > 5000. Only 2 out of 73 subjects underwent their first lumbar puncture, and the rest of subjects underwent their subsequent LP as per chemotherapy protocol at different treatment block and timeline. 23 (31.5%) parents were reluctant in giving consent for the first lumbar puncture and 20 (86.9%) of them gave reason due to concern towards the procedure itself and 3 (13.1%) were due to concern toward the effects of sedation. 15 (20.5%) parents needed re-explanation regarding lumbar puncture, complications from the procedure and sedation used for each and subsequent LP despite adequate explanation given beforehand at the time of diagnosis made (Table 5.13). For those that required re-explanation, the reason was due to long interval between the previous LP and current LP and some of them needed re-education regarding their child's disease, treatment protocol and procedures done.

Table 5.13: Parents socioeconomic background (n=73)

Characteristics	Frequency (n)	Percentage (%)
Father's education level		
Non-tertiary	45	61.6
Tertiary education	28	38.4
Mother's education level		
Non-tertiary	40	54.7
Tertiary education	33	45.3
Total monthly household income		
< 5000	37	50.6
>5000	36	49.4
Father's age (mean ± SD)	38.47 ± 6.06	
Mother's age (mean ± SD)	36.70 ± 6.35	

Table 5.14: Parental LP experience regarding the reluctance in giving consent and the need for re-explanation for subsequent and each LP (n=73)

Characteristic	Frequency (n)	Percentage (%)
Reluctance in giving consent for first lumbar puncture		
Yes	23	31.5
No	50	68.5
Reason for difficult consent		
Concern regarding procedure	20	86.9
Side effects of sedation	3	13.1
Need for re-explanation/ re-education for each LP		
Yes	15	20.5
No	58	79.5

5.5.1 Parental total household income and education level in relation to reluctance in giving consent during first LP and the need for re-explanation/ re-education for subsequent and each LP procedure

Parental education level is one of the surrogate marker for parental understanding and perception towards lumbar puncture other than total parental income. Parental psychosocial background particularly father's education level and parental total household income were statistically significant with parental reluctance in giving first LP consent (p = 0.048 and 0.029 respectively) (Table 5.14). This study showed that 15 (20.5%) parents still needed re-explanation regarding LP, its complication and complications of sedation used for each LP and father education level was associated with it (p = 0.02) (Table 5.15).

Table 5.15 : Parental reluctance in giving consent for LP in relation to parental total household income and educational level (n=73)

	Reluctance in giving consent (during first LP)		**P value**
	Reluctant (n=23) n (%)	**Not reluctant(n=50) n (%)**	
Total household income			
<5000	16 (69.6)	21 (42)	0.029
>5000	7 (30.4)	29 (58)	
Father's education level			
Non-tertiary	18 (78.2)	27 (54)	0.048
Tertiary education	5 (21.7)	23 (46)	
Mother's education level			
Non-tertiary	13 (56.5)	27 (54)	0.841
Tertiary education	10 (43.5)	23 (46)	

Table 5.16: Parental need for re-explanation/ re-education regarding LPs in relation to parental psychosocial factor (n=73)

	Parental need for re-explanation		P value
	Yes (n=15) n (%)	No (n=58) n (%)	
Total household income			
<5000	5 (33.3)	32 (55.2)	0.132
>5000	10 (66.7)	26 (44.8)	
Father's education level			
Non-tertiary	4 (26.7)	41 (70.7)	0.002
Tertiary education	11 (73.3)	17 (29.3)	
Mother's education level			
Non-tertiary	7 (46.7)	33 (56.9)	0.478
Tertiary education	8 (53.3)	25 (43.1)	

5.6 Validation of previous published mathematical formula for correct depth of needle insertion.

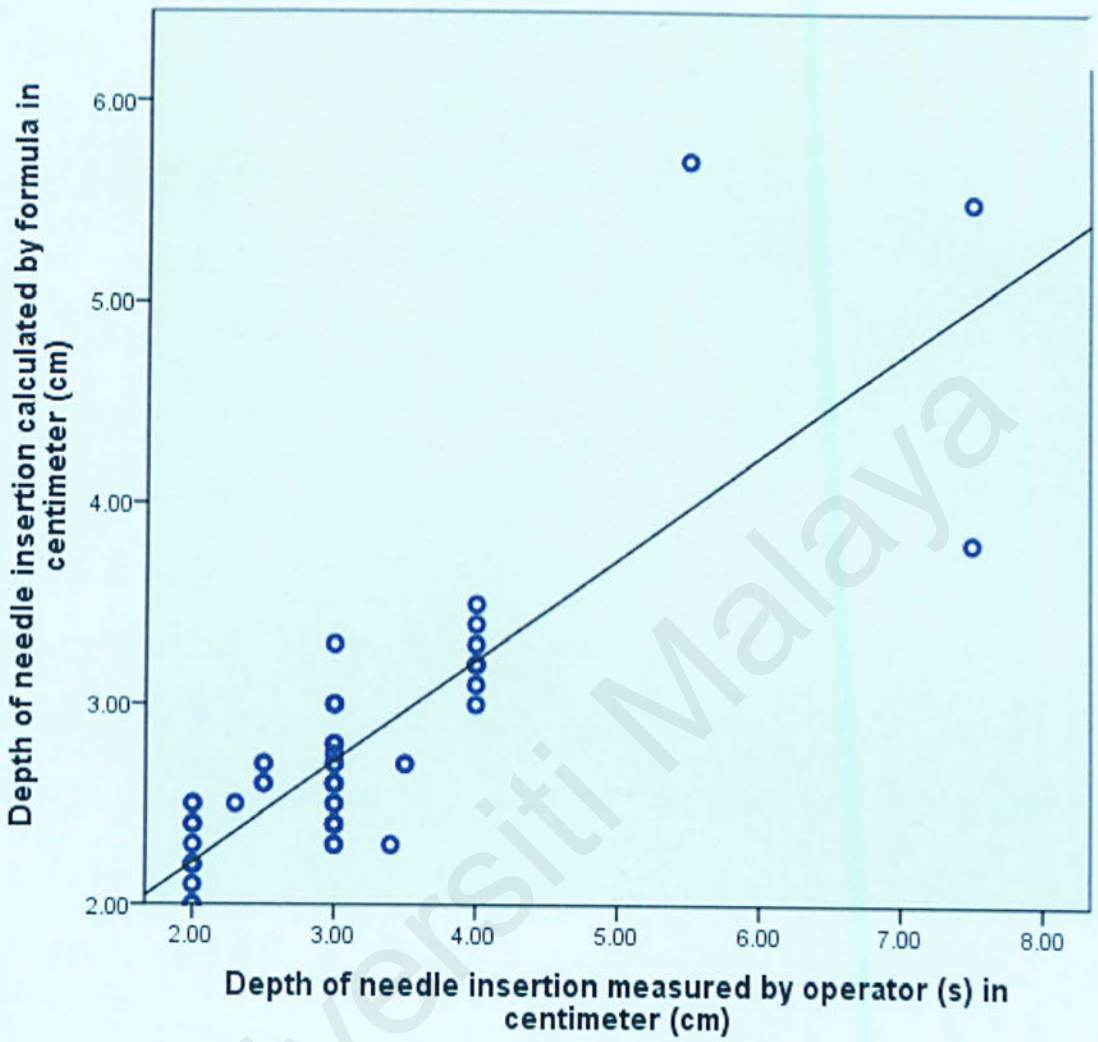


Figure 5.3 : Correlation between actual depth of needle insertion measured by operator and calculated depth of needle insertion based on mathematical formula (n=54)

Subjects with successful single attempt LP (n=54) were analysed in order to validate the previous published formula for a correct/ideal depth of needle insertion. Spearman's correlation test was done to analyse the actual depth of needle insertion compared to calculated depth for needle insertion. The result was correlation co-efficient of r = 0.761, showing good correlation between the two variables. Therefore, the mathematical

formula derived from previous study published by Chong et al, 2009 can be accepted as a valid tool to estimate the depth of needle insertion and can be used as a guide for a more successful LP especially for a less senior operator.

CHAPTER 6 : DISCUSSIONS

6.1 Prevalence of successful lumbar puncture

This cross sectional, observational study provides information on the risk factor for a successful LP in ALL children of all races in UMMC. We also able to give information on its prevalence in our department. The higher rate of successful single attempt LP reported by Procter et al.(Procter et al., 2016) compared in this study. This maybe due to large study population in the previous study which involve general paediatric population for a diagnostic purposes eg. neonatal sepsis, meningitis or fever of unknown origin. The higher prevalence of successful single attempt LP in general children compared to paediatric oncology patient partly due to majority of LP performed is for some diagnostic purposes compared to for therapeutic purposes in oncology patient in which they have to underwent multiple LP as per their chemotherapy protocol. Based on daily practice, oncology patient who already had multiple LP done before was observed to develop tolerance towards sedation given. Therefore, patient was not fully sedated throughout the procedure and will move and this lead to unsuccessful or multiple attempt LP.

6.2 Risk factors associated with successful LP

6.2.1 Operator experience

Even though previous study showed less experience practitioner was one of the risk factor for a traumatic or unsuccessful LP in paediatric oncology patients (Howard et al, 2002) which was totally different in this study, in this study success rate of single attempt LP was higher in more senior operator group compared to the less senior operator group even though it did not show statistically significant. Howard et al divided operator category based on number of LP performed by operator before compared to this study. In this study, operator was categorised according to their seniority. In practice, more senior

operator especially fellow in the oncology department known to have a higher success in performing LP with only single attempt because they have been doing more LP compared to medical officer and house officer which have less experience. Whereas, in the other previous study, year of residents training was not give significant predictors for a successful LP (Baxter 2006).

6.2.2 Adequacy of sedation

Previous study showed procedural analgo-sedation might help to reduce the child's pain and discomfort, and prevent the child's movements, reducing the risk of traumatic lumbar puncture(Howard, Gajjar & Chong, 2001-2007). Even though result shown in this study was totally different, this study showed a trend toward successful LP in patient whom received adequate sedation. In practice, to achieve a successful LP, patient must be fully sedated, placed and hold in a correct position by assiting nurse, and a calm operator to perform the procedure.

6.2.3 Patient BMI

The result in regard to look at patient BMI and a successful LP in this study was totally different compared with previous study. In this study, the result showed no statistical significant between patient BMI and a successful LP. The difference may be due to the previous study was a retrospective study with involved larger number of subject (Edward et al., 2005). In this study, the number of subject was limited as short study duration and subjects were only recruited if they came for their chemotherapy. In general practice, obesity is a known to cause difficulty in palpating the anatomical landmark for LP due to increase in the depth of fat and subcutaneous tissue which leads to unsuccessful LP. In this study result showed a trend towards successful LP in patients with normal BMI even though statistically was not significant.

6.2.4 Patient ethnicity

In previous study, patients' ethnicity had shown to affect the success of LP (Howard, 2002). In our study, patients' ethnicity did not give significant value in successful LP. Larger study population are needed to identify the significance of patients' ethnic group and a successful LP.

6.3 Complications of LP

Higher prevalence (36.6%) of PLPH observed in this study compared with previous study which showed only 27% prevalence of PLPH in children and adolescent in their 12 months prospective study (Ebinger et al,2004). The reason for the difference in result is maybe due to invalid questionnaire used. Therefore, a validated questionnaire is required and a retrospective study is recommended in order to see the complications related to PLPH.

Backache was reported in 19.5% of subject in this study. The incidence is lower compared to previous study that showed 40% of their subject developed backache (Ebinger, 2004). The difference may be due to the complications observed is subjective for every subject. Percentage of limb numbness reported in this study was almost similar in previous study, 14.6% and 13% respectively (Evans, 2006).

Complications from sedation used was described according to age group and sedation use. From our study, those who received combination of IV Ketamine with IV Midazolam had less frequency for hallucination, nightmare and vomiting compared to those who received IV Ketamine alone. These findings are similar to previous study, Mark G et. al reported significant emergence phenomena in the paediatric ED (ie, nightmares, hallucinations and severe agitation) occurred in 7.1% of the ketamine group and in 6.2% of the combination of ketamine-midazolam group. The additional midazolam increased incidence of oxygen desaturation

Previous studies have commented on the inability of midazolam to diminish emergence reactions associated with ketamine sedation. (Wathen, 2000 & Sherwin, 2000). Wathen et al. commented further that in their cohort of 266 patients, those who received combination of ketamine and midazolam were more likely to have oxygen desaturation but less likely to vomit than those receiving ketamine alone. In this study, no comparison in regard to oxygen desaturation between these 2 groups were identified. However, none of our subject had developed desaturation.

6.4 Parental reluctance in giving consent for LP

The reason for reluctance in giving consent for first LPs in our study was mainly due to concern towards LPs complications, however no further elaboration regarding their particular concerns interviewed for each parent in these group. Compared to previous study done, seven families (29%) had no previous knowledge of the indications for LP, and 3 had the impression that LP was also therapeutic. When asked about the reasons for reluctance in giving consent, 18 (75%) said that it was because of fear of complications from the procedure: 14 (58%) feared paralysis, 4 feared pain (16%), and 1 feared development of scoliosis. (Narchi, 2012). Mostert et. al showed reported 35% of parents refused or abandoned their child treatment and incidence is higher in poor family compared to prosperous family. In our study, there were no relationship between parental total household income and education level with parental reluctance in giving consent for lumbar. There was limited previous study to compared parental total household income and education level with parental need for re-explanation and re-education for subsequent procedure. Large prospective study is needed to determine this factor in order to improve medical care towards patient and family as a whole.

6.5 Validation of mathematical formula for ideal depth of needle insertion

The result from Spearman rank correlation from this study was similar with the previous study (Chong et al). It maybe due to similar method of manual measurement by operator and calculation using the formula. Furthermore, only subject with a successful single attempt LP was included in this study.

CHAPTER 7 : LIMITATIONS

This study was limited by the short duration of study period which was 2 months; if the study duration can be lengthened, more subjects can be recruited. The other limitation was that those patient age less than 5 years could not report on complication of the LP (eg.headache, limb numbness) and sedation used (eg. Hallucination and nightmare). Therefore, they was no data can be analysed in regard to complications of LP and sedation in younger group of patient. There was also recall bias in parents in giving information as the time from diagnosis until time of interview was long and parent could not recall their experience in particular to recall their memory regarding the reluctance in giving consent for their children first LP. There was possibility of operator bias in selecting patient to perform lumbar puncture. Patients that were previously known to have difficulties, required multiple attempt LP and those overweight or obese patients were selected by more senior operators. Parents also may have requested for more senior operator to perform LP for their children. Furthermore, questionnaire used to interview parents regarding their perception and experience for LP was not validated. Therefore, to improve this, a validated questionnaire should be used as it may affect the outcome.

CHAPTER 8 : CONCLUSIONS AND RECOMMENDATIONS

Even though, this study revealed a high prevalence of a successful single attempt lumbar puncture in ALL patient in our institution, the success of LP is not only measured by the success rate but also parental psychosocial background. As there were small group of parents that had reluctance in giving consent for LP and needed re-explanation for each LP, therefore, to improve parental perception, acceptance and knowledge towards the procedure, operator (s) must re-emphasize and provide re-education to parents for each LP procedure. A mathematical formula derived from previous study published by Chong et al, 2009 can be accepted as a valid tool to estimate the depth of needle insertion and can be used as a guide for a more successful LP especially for a less senior operator.

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APPENDIX A: DATA COLLECTION FORM

Patient's sticker

I) Patient Demographic

DOB			**Age**
Gender	**Male**	**Female**	
Weight			**Height** **BSA**
Diagnosis			**Current protocol**

II) Procedure

IIa) Pre-procedure :

BP :	HR :	SPO2 : %
Platelet Level :		
Sedation : Ketamine dose : (mg/kg/dose)		Additional dose : mg
Midazolam dose : (mg/kg/dose)		Additional dose : mg

IIb) During procedure

BP :	HR :	SPO2 : % (any desaturation ?)
Depth of lumbar puncture needle inserted : cm CSF result		

Operator : Specialist ☐	Medical officer ☐	House-officer ☐

How many attempt	Single ☐	> 1 ☐
Duration : Start H	Finish : H	

IIc) Post-procedure

Any of this present?

Vomiting		**Headache**		**Backache**
Bleeding		**Numbnessof limbs**		**Failed of procedure**
Tremor		**Hallucination/ Confusion**		**Nightmares**

III) Parental experience

Father's age	Occupation	Education level
Mother's age	Occupation	Education level
First experience?	Yes ☐	No ☐ Any different in feeling compared to first experience?
Difficulty/ reluctance in giving consent for first lumbar puncture?	Yes ☐ Why?	No ☐
Adequate explanation by doctor	Yes ☐	No ☐
Indication of procedure ☐	Procedure ☐	Complication of sedation and procedure ☐

APPENDIX B:

MEDICAL RESEARCH ETHICS COMMITTEE APPROVAL FOR THESIS PROPOSAL FORM

UNIVERSITY OF MALAYA MEDICAL CENTRE
MEDICAL RESEARCH ETHICS COMMITTEE
(Formerly known as Medical Ethics Committee)
UNIVERSITY OF MALAYA MEDICAL CENTRE
ADDRESS : LEMBAH PANTAI, 50100 KUALA LUMPUR, MALAYSIA
TELEPHONE : 03-79492296/2238 FAXIMILE : 03-79492600

NAME OF ETHICS COMMITTEE/ARB Medical Research Ethics Committee, University Malaya Medical Centre	MREC ID NO: 2017710-5401
ADDRESS : LEMBAH PANTAI, 50100 KUALA LUMPUR, MALAYSIA	
PROTOCOL NO(if applicable) :	
TITLE: LUMBAR PUNCTURE EXPERIENCE IN CHILDREN WITH ACUTE LEUKAEMIA	
PRINCIPAL INVESTIGATOR : Dr Noor Hidayah Binti Sunny@Ghazali	SPONSOR -

The following item [✓] have been received and reviewed in connection with the above study to conducted by the above investigator.

[✓]	Application to Conduct Research Project(form)	Ver.No :	Ver.Date : 10-07-2017
[✓]	Study Protocol	Ver.No : 1	Ver.Date : 12-07-2017
[✓]	Patient Information Sheet	Ver.No : 1	Ver.Date : 31-08-2017
[✓]	Consent Form	Ver.No : 1	Ver.Date : 31-07-2017
[✓]	Questionnaire	Ver.No :	Ver.Date :
[✓]	Investigator's CV / GCP (Dr Noor Hidayah Binti Sunny@Ghazali,PROF DR HANY BINTI MOHD ARIFIN,)	Ver.No :	Ver.Date :
[ ]	Insurance certificate	Ver.No :	Ver.Date :
[✓]	Other documents		
	1) Lumbar Puncture in Acute lymphoblastic leukaemia	Ver.No : 1	Ver.Date : 07-12-2017

and the decision is [✓]

[ ] Approved (Full Board)
[✓] Approved (Expedited)
[ ] Rejected(reasons specified below or in accompanying letter)

Comments:

Questionaire study

The Investigators are required to:

1) *follow instructions, guidelines and requirements of the Medical Research Ethics Committee.*
2) *report any protocol deviations/violations to Medical Research Ethics Committee.*
3) *provide annual and closure report to the Medical Research Ethics Committee.*
4) *comply with International Conference on Harmonisation – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.*
5) *obtain a permission from the Director of UMMC to start research that involves recruitment of UMMC patient.*
6) *ensure that if the research is sponsored, the usage of consumable items and laboratory tests from UMMC services are not charged to the patient's hospital bills but are borne by research grant.*
7) *note that he/she can appeal to the Chairman of Medical Research Ethics Committee for studies that are rejected.*
8) *note that Medical Research Ethics Committee may audit the approved study.*
9) *ensure that the study does not take precedence over the safety of subjects.*

Date of expedited approval : 08-08-2017

This is a computer generated letter. No signature required.