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COMPARATIVE STUDY OF TIME ECHO VARIATIONS IN THE METABOLITE VALUES MR BRAIN SPECTROSCOPY

STUDI PERBANDINGAN VARIASI TIME ECHO PADA NILAI METABOLIT MR SPECTROSCOPY OTAK

Original Research Article
Penelitian

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ABSTRACT

Background: *MR spectroscopy is an additional sequence to evaluate lesion characteristics in the brain. Time Echo (TE) is crucial for analyzing MR spectroscopy metabolite.* ***Purpose:*** *This study aims to evaluate the best TE variations during MR spectroscopy examinations in brain lesions.* ***Method:*** *This research is an experimental quantitative study. Researchers used five samples focusing on the results of head multi-voxel spectroscopy charts with clinical lesions or masses that had been taken twice using TE 35 and TE 144. At each TE in each sample, three voxel areas were measured, namely normal, perilesional, and lesion. Each spectroscopy data result is processed individually through READY View software, automatically producing a spectroscopy graph pattern. The required data in this study is the value of each head spectroscopy metabolism: N-Acetyl Aspartate (NAA), Choline (Cho), Creatine (Cr), Myo-Inositol (MI), Lipids Lactate (LL). All statistical tests used the SPSS v.26 application.* ***Result:*** *Based on Paired T test results, NAA, Cho, Cr, and MI metabolites have p-values of 0.779 > 0.05; 0.179 > 0.05; 0.581 > 0.05; and 0.057 > 0.05. Based on the Wilcoxon sign rank test, the LL metabolite showed a p-value of 0.460 > 0.05.* ***Conclusion:*** *There is no significant difference between TE 35 ms and TE 144 ms during MR spectroscopy examinations.*

ABSTRAK

Latar belakang: MR *spectroscopy* merupakan salah satu tambahan sekuen untuk mengevaluasi karakteristik suatu lesi pada otak. *Time Echo* (TE) adalah parameter yang berperan penting dalam menganalisa metabolik MR *spectroscopy*. **Tujuan:** Penelitian ini bertujuan untuk mengetahui variasi TE terbaik dalam MR *spectroscopy* pada lesi otak. **Metode:** Jenis penelitian ini adalah kuantitaif eksperimental. Peneliti menggunakan 5 sampel dengan fokus pada hasil grafik multi-voxel *spectroscopy* kepala dengan klinis lesi atau massa yang sudah dilakukan dua kali pengambilan *spectroscopy* menggunakan TE 35 dan TE 144. Pada setiap TE disetiap sampel dilakukan pengukuran 3 area voxel yaitu normal, perilesi, dan lesi. Masing-masing hasil data *spectroscopy* diproses satu persatu melalui *software READY View* yang secara otomatis akan menghasilkan pola grafik *spectroscopy*. Data yang dibutuhkan pada penelitian ini adalah nilai pada setiap metabolisme *spectroscopy* kepala yaitu: *N-Acetyl Aspartate* (NAA), *Choline* (Cho), *Creatine* (Cr), *Myo-Inositol* (MI), *Lipids Lactate* (LL). Seluruh pengujian statistik menggunakan aplikasi SPSS v.26. **Hasil:** Berdasarkan hasil uji statistik *Paired T test*, NAA, Cho, Cr, dan MI metabolit memiliki *p-value* 0.779 > 0.05; 0.179 > 0.05; 0.581 > 0.05; dan 0.057 > 0.05. Sedangkan berdasarkan uji *Wilcoxon sign rank test* metabolit LL menunjukkan *p-value* 0.460 > 0.05. **Kesimpulan:** Tidak ada perbedaan yang signifikan antara TE 35 dan TE 144 pada MR *spectroscopy*.

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INTRODUCTION

Over the past two decades, *MR spectroscopy* (MRS) has become an advanced examination used clinically in many hospitals worldwide to evaluate brain tumors (Horská and Barker, 2010). MRS can distinguish between neoplastic and non-neoplastic tumors with sensitivity, and higher accuracy than conventional MRI, which accounted for 78% and 66%, respectively (Hellström *et al*., 2018). MRS can also monitor response to therapy and predict recurrence (Galijasevic *et al*., 2022). Based on theory, MRS aims to evaluate the metabolite in the human body with a non-invasive approach to biochemical processes in the body. MRS applications include studies of body fluids and perfused organs at high magnetic field strengths (Tognarelli *et al*., 2015), such as *N-Acetyl Aspartate* (NAA 2.02 ppm), *Choline* (Cho 3.22 ppm), *Lactate* and *Lipids* (LL 0.9 and 1.3 ppm), *Myo-Inositol* (MI 3.55 - 4.06 ppm), *Creatine* (Cr 3.03 ppm), *Glutamate* (Glx 2.1 - 2.5 ppm), and *γ-aminobutyric acid* (GABA 2.3 ppm) (Buonocore and Maddock, 2015; Ricci *et al*., 2007; Yildirim *et al*., 2014). In brain tumor cases, there are specific metabolite changes such as enhancement of Cho metabolite and decline in NAA metabolite (Law, 2004; Li *et al*., 2015).

Besides a non-invasive examination, MRS aims to give further information on metabolism processes such as energy metabolism, neuron integrity, cell proliferation, degradation, and necrotic tissue changes through the MR spectrum (Ulmer *et al*., 2016). The signals used by MRS to make the MR spectrum emerge from the nucleus in individual molecule atoms from the tissue network. Two techniques for the acquisition spectrum MR are single-voxel spectroscopy and multi-voxel spectroscopy. In this research, the authors used pulse sequence 2D/3D *Chemical Shift Imaging* (CSI) (multi-voxel spectroscopy) because in the CSI, all MR spectra are reconstructed in each voxel (Bertholdo *et al*., 2013).

The aims of MRS imaging are to get many voxels at the same time and spatial distribution from metabolite in a sequencing cycle. This MRS technique uses a phase-encoding gradient for translating spatial information after RF pulse and slice selection gradient. After that, the MRS images can be obtained with signals that will produce metabolite spectra with different frequencies. The metabolite signal correlates well with the *Time Echo* (TE) parameter. Tivaskar *et al*. (2021) explained that TE is a crucial parameter that can significantly contribute to MRS result quality. In addition, determining appropriate TE can help analyzing pathology diagnostics more accurately. Based on the literature, there are three kinds of TE: short TE (20 - 40 ms), intermediate TE (136 - 144 ms), and long TE (270 - 288 ms) (Law, 2004).

There are also pros and cons to using these three kinds of TE. Short TE is suitable for low signal metabolite interpretation such as MI, Glx, and lipid. This metabolite can demonstrate the tumor characteristics and evaluation after therapy. However, short TE is not optimal while capturing higher signal metabolites such as NAA. Meanwhile, intermediate TE is optimal when metabolite value is accurate with long relaxation such as NAA, Cho, and lipid with little contamination from water residual and fat tissue without baseline distortion (Naser *et al*., 2016). However, it can not be maximal to demonstrate the lipid value. The last one is long TE and T2 decay from metabolite. Therefore, signals such as NAA, Cho, and Cr can not be maximal. As a result, the noise is lower than short and intermediate TE.

Considering the strengths and weaknesses of three kinds of TE, most TE values used for brain tumor examinations range from short TE to intermediate TE (Naser *et al*., 2016; Tivaskar *et al*., 2021). Nowadays, most TE values used for brain tumor examinations range from short TE to intermediate TE (Naser *et al*., 2016). The use of TE value is still under further discussion among scientists. Thus, this research aims to prove the differentiation between short TE (35 ms) and intermediate TE (144 ms) in brain tumor cases.

MATERIAL AND METHOD

This research was quantitative experimental. The subjects obtained 15 brain MR spectroscopy examinations at Dr. Moewardi Hospital, Surakarta, Central Java, from September 2022 to October 2022. From all of these brain MR spectroscopy examinations, a selection was made according to the research inclusion criteria (Figure 1) based on The American College of Radiology (2008), which are patients who do not move during the examination process, especially in TE 35 and TE 144 acquisition data collection, tumor positions that are not adjacent to bone, blood, air, and fluid. Patients must be examined using contrast media to determine the boundaries of voxel placement that should not be exposed to bone, blood, fluid, and air around the tumor. Based on this, only five samples can be used in this study.

Furthermore, in each TE, all samples were measured voxel in three different areas: normal, lesion, and perilesional (Durmo *et al*., 2018). For the samples data, the authors used MRI Signa HDxt 1.5 T GE *HealthCare System* using multi-voxel CSI technique approach because its capable to capture a few voxel areas, thus can reach out wider anatomy of the human brain for the sample data. The authors used MRI Signa HDxt 1.5 T *GE HealthCare System* using a multi-voxxel CSI technique approach because it can capture a few voxel areas, thus reaching out to the broader anatomy of the human brain for the processing data. The authors used *Ready View* software in post-processing advanced workstation volume share 7 GE medical system. The ethics committee has been approved, and informed consent was given with the ethical number 732/V/HREC /2023. The patient's data were kept confidential and only used for research purposes.

Each spectroscopy data was processed through *Ready View* software. The required data for this research were value for each brain metabolite: NAA, Cho, Cr, MI, LL, and the samples were conducted voxel measurement in three areas: normal, perilesional, and lesion (Figure 2). In each metabolite, statistical tests were carried out between the two TEs with SPSS ver. 26 software. A normality test with the *One-sample kolmogorov smirnov* test to determine the normality of the data. If the normality test results are *p-value* > 0.05 with normal data distribution, then proceed with a *Paired T* test, but if the normality test results are *p-value* < 0.05, then it will be continued with the *Wilcoxon sign rank* test.

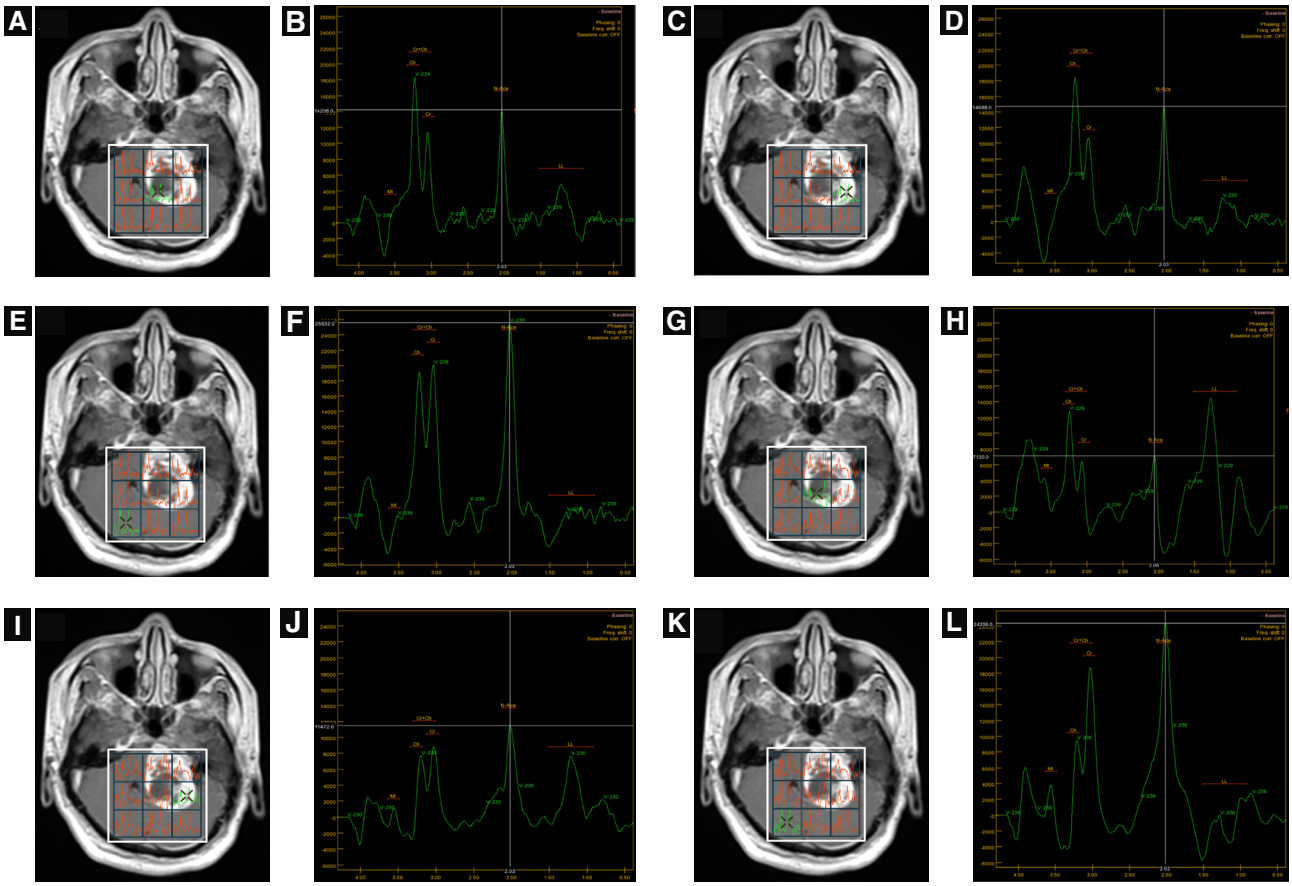

Figure 1. One of the inclusion criteria samples on *N-Acetyl Aspartate* (NAA) metabolites. (A - F) Shows 35 ms TE image and graph, (A - B) Lesion area with NAA value of 14208, (C- D) Perilesional area with NAA value of 14688, (E - F) Normal area with NAA value of 25632, (G - L) Shows images and graphs of TE 144 ms, (G - H) Lesion area with value 7120, (I - J) Perilesional area with value 11472, (K - L) normal area with NAA value 24336

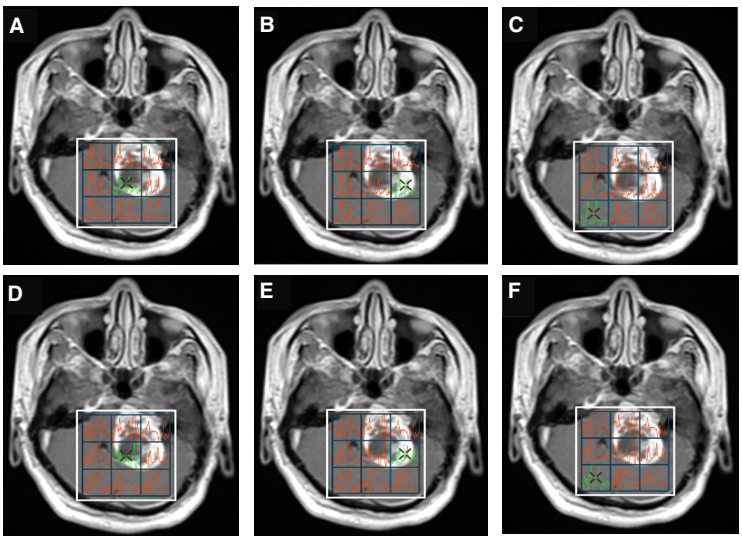

Figure 2. Examples of voxel measurement positions in the *N-Acetyl Aspartate* (NAA) metabolite data collection process. (A - C) At TE 35 ms. (A) Lesion area, (B) Perilesional area, (C) Normal area. (D - F) At TE 144 ms. (C) Lesion area, (D) Perilesional area, (F) Normal area

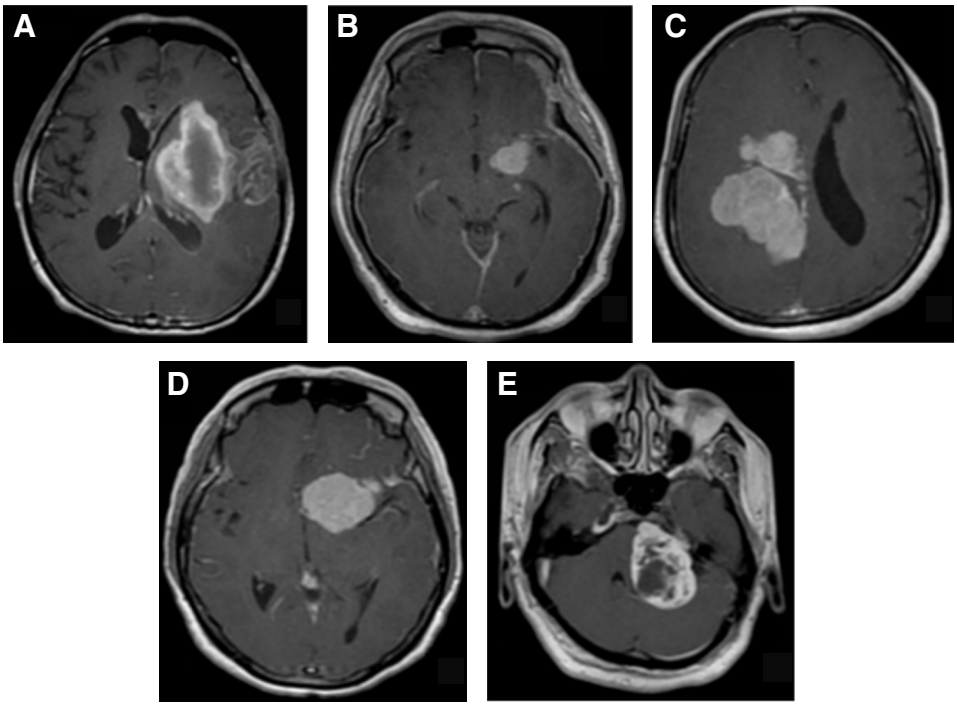

Figure 3. (A - E) Brain lesion on axial T1WI

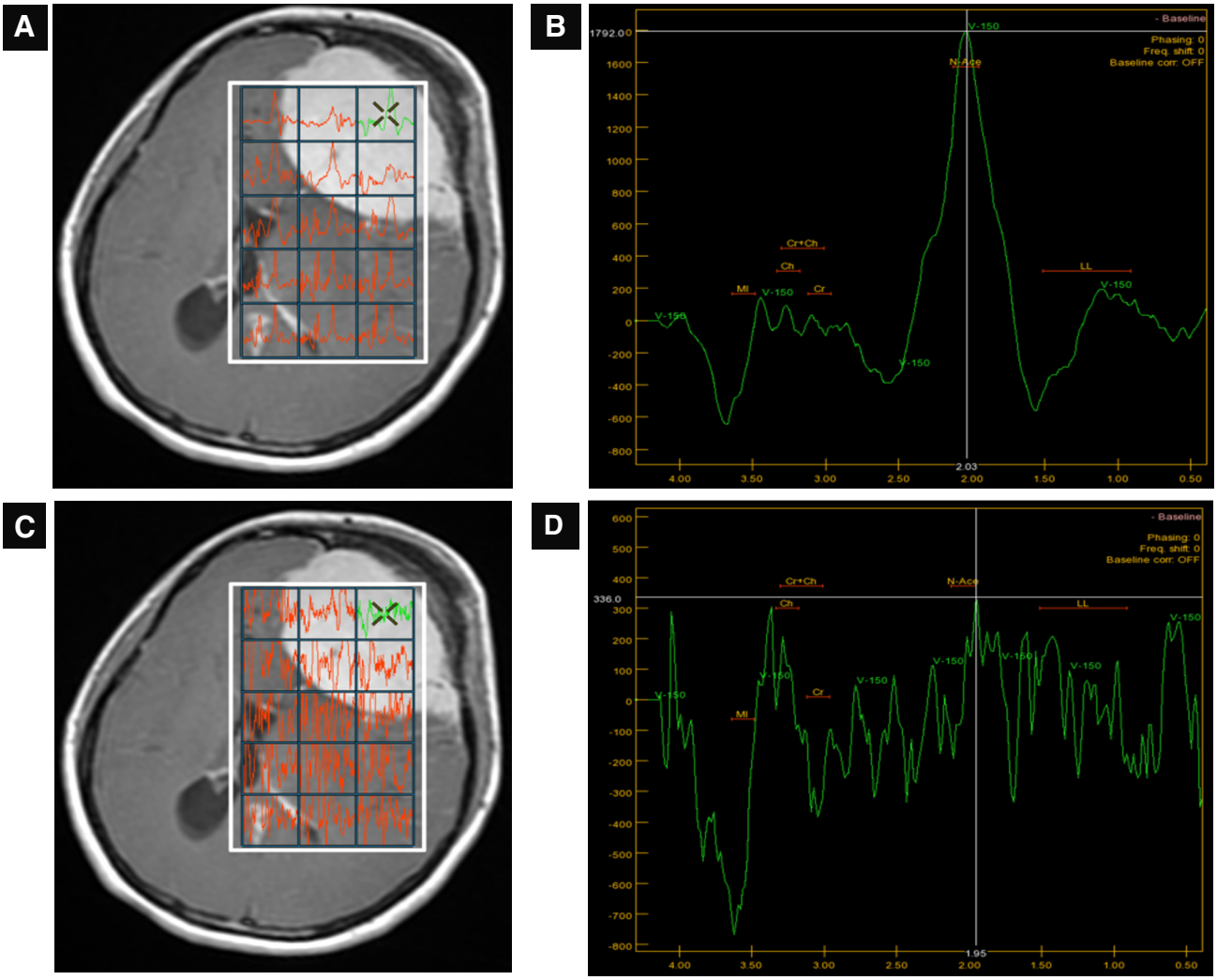

Figure 4. One of the sample exclusion criteria on *N-Acetyl Aspartate* (NAA) metabolite. (A - B) Image and graph of TE 35 ms at the lesion area with a value of 1792, (C - D) Image and graph of TE 144 ms at the lesion area with a value of 336

RESULT

Table 1 shows the sample characteristics based on gender. It shows that the percentage of male and female samples was 40% (n = 2) and 60% (n = 3), respectively. Meanwhile, the mean of *Time Echo* (TE) results in each voxel measurement is shown in Table 2. Based on Table 2, the authors conducted measurements with TE 35 ms and TE 144 ms, respectively, in five metabolites: *N-Acetyl Aspartate* (NAA), *Choline* (Cho), *Creatine* (Cr), *Myo-Inositol* (MI), and *Lipids Lactate* (LL).

These five kinds of metabolite are evaluated in three brain areas: normal, perilesional, and lesion. The first is the NAA metabolite, both short and intermediate TE are decreased in the perilesional area, and more significant in the lesion area than the normal area, suggesting that the brain is abnormal. The second is the Cho metabolite, short and intermediate TE is higher than the lesion area, and the lesion area is within the normal measurement, suggesting a non-specific abnormality in the brain. The third is the Cr metabolite, both short and intermediate TE are declined in the perilesional area, and more significant in the lesion area compared to the normal area, suggesting that the brain is abnormal. The fourth is the MI metabolite, mainly when using short TE (35 ms), there is an elevation in the perilesional and lesion area compared to the normal area. However, the perilesional area is higher than the lesion area, suggesting a non-specific abnormality in the brain. On the contrary, when using intermediate TE (144 ms), there is a significant decrease in the lesion area compared to the average area. The fifth is the LL metabolite, both short and intermediate TE, with an elevated lesion area compared to the average area, suggesting an abnormality in the brain, such as an abscess or necrotic in brain tissues.

Table 1. Sample characteristics based on gender

Gender	Frequency	Percentage
Male	2	40%
Female	3	60%
Total	**5**	**100%**

Table 2. Mean of voxel measurement in each metabolite

Metabolite	Mean		
	Location of voxel	TE 35	TE 144
N-Acetyl Aspartate (NAA)	Normal	18224	19889.4
	Perilesional	10598.4	13968
	Lesion	7299.2	4076.8
Choline (Cho)	Normal	7350.4	10499.2
	Perilesional	10352	12739.2
	Lesion	6128	8048
Creatine (Cr)	Normal	10400	11241
	Perilesional	8064	8217.6
	Lesion	2435.2	2729.6
Myo-Inositol (MI)	Normal	1673.6	771.2
	Perilesional	4208	665.6
	Lesion	2332.8	-12.8
Lipids Lactate (LL)	Normal	2566.4	880
	Perilesional	758.4	1481.6
	Lesion	8896	7136

Table 3. *p-value* result for each metabolite

Metabolite	*Paired T test*	*Wilcoxon sign rank test*
N-Acetyl Aspartate (NAA)	0.779	-
Choline (Cho)	0.179	-
Creatine (Cr)	0.581	-
Myo-Inositol (MI)	0.057	-
Lipids Lactate (LL)	-	0.460

A *Paired T* test was conducted for each metabolite to show whether there was a difference in the two TEs (Table 3). Based on *Paired T* test results, NAA, Cho, Cr, and MI metabolite have *p-values* of 0.779 > 0.05; 0.179 > 0.05; 0.581 > 0.05; and 0.057 > 0.05, respectively, suggesting there is no significant differentiation between short TE (35 ms) and intermediate TE (144 ms). Based on the *Wilcoxon sign rank* test, the LL metabolite test showed a *p-value* of 0.460 > 0.05, which showed no difference in the two TEs.

DISCUSSION

This research used five samples with non-specific lesions (Figure 3). This research used five samples with non-specific lesions that fit the inclusion criteria. The examination results of brain spectroscopy included in the exclusion criteria and are not used are patients who move so that it can cause inconsistent spectroscopy results on both TE (Figure 4), the position of the tumor is close to the bone. Hence, it is difficult to determine the voxel placement area, the patient can only stand for a short time when doing an MRI with two TEs, so it only works for one TE. The patient could not use contrast due to too high lab results, such as urea and creatinine, which exceeded the threshold as a condition for examination with contrast, voxel laying on bone, blood, other fluids, and air, and too much fluid around the tumor, which could interfere with metabolite calculation results.

MR spectroscopy in clinical non-specific lesions is beneficial in determining the following treatment method, compared to conventional MRI examinations. Hellström *et al* (2018) stated that MR spectroscopy is usually used to obtain convincing conventional MRI results. His research showed that MR spectroscopy is better (64%) for non-neoplastic tumor classification, low-grade, and high-grade tumors than conventional MRI (62%). MR spectroscopy is also better for tumor classification in other research with pediatric tumor cases, with a sensitivity of about 87% compared to conventional MRI only by 71% (Shiroishi *et al*., 2015).

MR spectroscopy is used to classify lesions, both neoplastic and non-neoplastic, based on specific metabolite changes in the lesion. Some research shows that brain tumor cases are often marked by several metabolites such as the decline of NAA signals, elevated Cho signals (Attia *et al*., 2020; Horská and Barker, 2010; Law, 2004; Naser *et al*., 2016), decreased Cr signals (Graaf, 2010), increased MI (Castillo *et al*., 2000), and increased LL (Graaf, 2010; Kim *et al*., 2006). Therefore, in this study, statistical tests were carried out on the five metabolites with TE 35 ms and TE 144 ms.

This study showed that the statistical test results of both TEs showed no significant difference in the five metabolites with *p-value* NAA 0.799 > 0.05; Cho 0.179 > 0.05; Cr 0.581 > 0.05; MI 0.057 > 0.05; and LL 0.460 > 0.05, respectively (Table 3). In their research, Kim *et al*. (2006) compared MR spectroscopy in 1.5T and 3T, respectively, stating that there is no significant difference in each metabolite ratio. However, there is an elevation from SNR for about 49 - 73% while using short TE in 3T. However, Naser *et al*. (2016) showed a difference in the results of both TEs. They explained that intermediate TE has higher diagnostic accuracy, accounting for 86% rather than short TE, which is only 75% and a combination of both TEs will generate the best accuracy (88%). However, in this research, the authors realize a discrepancy in research results because of the need for a sample.

Regarding a statistical test, there is no difference in both metabolites. However, based on Table 2, each TE has a median metabolite on the voxel measurement area. In NAA metabolite, there is a continued decline in both TE in the lesion and perilesional area compared to the average area, suggesting the brain is abnormal. (Law, 2004) stated that the function of NAA as a marker density neuronal and tissue viability has also been found in the axon. Therefore, when a decreasing NAA value always follows a decline of neuron function, an axon in the neoplastic tissue. Verma *et al*. (2016) stated that the pathology that causes axonal loss, such as malignant and benign tumors, will decrease NAA or can not be detected in MR spectroscopy.

In terms of Cho metabolite, it demonstrates the same patterns as NAA metabolite. There is a gradual decline in the lesion and perilesional area compared to the average area, suggesting it is a sign of abnormality. However, it is unmatched by some literature that malignancy in the brain area is marked by the decline of NAA and increasing Cho. The elevation of Cho in the malignancy is attributed to the function of Cho as cell membrane synthesis. The elevated membrane cell activities in tumors are aligning with increasing Cho. However, Law (2004) explained that a few malignant tumors can show the lowest Cho because of the necrosis process in the tissue area. In addition, the Cho signal will be affected by variations of intra-tumoral because of different histology values in the lesion area, such as bleeding, calcification, or necrotic radiation.

Regarding Cr metabolite, there is a significant decline in the perilesional and lesion area compared to the average area, suggesting an abnormality. Law (2004) stated that the decline of Cr correlates well with the function of Cr, energy metabolism. Because of the tumor activities that use energy metabolism, the Cr value will be decreased. However, in other journals, Cianfoni *et al*. (2011) state that the decline of Cr can happen in tumor cases with necrotic conditions. Verma *et al*. (2016) stated that glial tumors can cause the decline of Cr for about 15 - 40% of whole patients and kinds of other tumors, such as *meningotheliomatous meningioma*, which can cause the decline of Cr for about 20% of whole patients.

In terms of MI metabolite, there is a difference between both TE. In TE 35 ms, there is an elevation in the perilesional and lesion area compared to the normal area, which means there is an abnormality leading to non-specific abnormality. Castillo *et al*. (2000) explained that the enhancement of MI is attributed to some pathology, such as brain tumors. Metwally *et al*. (2014) explained that MI is related to protein C kinase activation that can produce proteolytic enzymes found in malignancy and aggressive primary tumors. It matches Verma *et al*. (2016) finding that the enhancement of MI correlates well with an elevation of glial cells. However there is a different result when using TE 144 ms, there is a gradual decline in the perilesional area compared to the average area. It is attributed to metabolite MI signals, which are more sensitive in TE 35 ms than in TE 144 ms. Metwally *et al*. (2014) also stated that MI becomes the most sensitive metabolite and can easily be detected in short TE (30 ms).

Regarding LL metabolite, there is a significant increase in the lesion area compared to the normal area, suggesting an abnormality such as malignancy or abscess. Nakamura *et al*. (2018) explained that LL has two different metabolites that are mutually continuous. Lactate is a product generated by the anaerobic glycolysis metabolite process, and it is believed to be associated with the discrepancy between the glycolysis process and oxygen stock in the human brain. In particular, pathology such as malignancy causes oxygen stock in the brain to be worsened and causes widened necrotic tissue. Therefore, the increase in LL indicates an abnormal process, such as malignancy. In another study, Umamaheswara Reddy *et al*. (2014) explain that all inflammation processes can increase LL value in spectroscopy. Chang *et al*. (1998) and Lai *et al*. (2002) stated in their research that every cystic tumor in their sample showed increased LL metabolite. The increase in lipids based on Verma *et al*. (2016) because of the cytoplasmic vesicles in the necrotic tissue, tumors, abscesses, and inflammation, thus can destroy the cell membrane in the brain. As a result, the highest malignancy in a tumor is always followed by widening deterioration of the cell membrane and elevated LL.

Table 2 shows the differentiation between LL values in the perilesional area in both TEs. While using TE 35 ms, the perilesional area has a higher value than the lesion area. While using TE 144 ms, the perilesional area was not high. It is believed that TE 144 ms can better demonstrate LL signals than TE 35 ms. A few research explained that short TE (20 - 40 ms) can demonstrate variation signals such as Glx, MI, and LL. However, Verma *et al*. (2016) stated that intermediate TE (135 - 144 ms) has the least metabolite information. But, on the other hand, offers more benefits than using short TE, such as differentiating the lactate peak from the lipid peak, which accounts for 1.3 - 1.5 ppm, better interpretation of peak NAA ranging from 2.0 - 2.05, and higher accuracy for demonstrating lipid and Cho compared to short TE.

CONCLUSION

MR spectroscopy examinations yielded beneficial additional information. Making MR spectroscopy examinations a routine part of brain MR examinations can be helpful in selected cases and may help evaluate masses and brain tumors. This research aimed to determine the best TE variation between TE 35 ms and TE 144 ms in MR Spectroscopy of brain lesions by performing statistical tests. It concluded that there was no significant difference between both TEs in MR spectroscopy examinations. Therefore, both TEs can be used during MR spectroscopy examinations. However, if there is no history examination or diagnosis, MR spectroscopy examinations with TE 35 ms can be used. Suppose there is no elevated Cho value in the lesion area compared to the average area. In that case, the authors suggest using TE 144 ms to ensure the enhancement of LL in the lesion area that can be used as a marker for the necrotic process or abscess.

The author realizes the limitations of the sample used due to limited sampling time. Statistically, a large number of samples will be closer to the existing population picture (Abadi, 2006). Based on this, it is expected that further research can be carried out with a more extended sampling period to obtain the appropriate number of samples and meet the research criteria so that the research results can be much more objective. In addition, further research can also be carried out by comparing long TE (288 ms) so that the research results can be more insightful.

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