Reviewer 1

Comments and Suggestions for Authors

* I find it hard to understand the purpose of this research, when there is no correlation between the drug levels and reduction of seizure control. There is a lot of arbitrariness in the research design. But most of all, it does not provide us with any new information, contribute to the body of scientific knowledge or have any potential of modifying the clinical practice around management of seizures.

Author`s comments

Thank you for your constructive comments.

In this study, we were able to find a correlation between the dose of lacosamide (LCM) and its blood level, but we could not demonstrate a correlation between the blood level and the reduction in the epileptic seizure rate (RR). As mentioned in the text, we thought the reason for this was that there were a certain number of cases whose treatment was highly effective even with low blood levels. Since our goal was to set the clinically useful target level for LCM treatment, we confirmed that the therapeutic blood level could not be achieved, and we examined the significant difference between two groups by the RR. We demonstrated that LCM blood levels were significantly higher in the effective group (RR≥50%) than in the other group. As mentioned above, even if there were cases with low blood levels that were effective, we did identify the optimal range, focusing on the fact that 50% or more of seizures can be reliably suppressed. Therefore, we thought that new information as a standard for seizure management was provided in this study. We hope that clinicians, aware of this optimal range, will measure LCM blood levels regularly. Confirming that the actual blood levels of their patients are within this range and that their seizure frequency is reduced will change clinical practice for seizure management.

Other detailed corrections were made in accordance with the comments of Reviewer 2 as follows.

* Please indicate a specific purpose for your research.

The goal of the present study was to set the clinical targets for the blood levels. More specifically, the purpose was to determine the optimal LCM range. First, we demonstrated the correlation between the LCM blood level and dose. Next, since no correlation was found between the blood level and RR, we compared the blood level of the patient group with RR≥50% and the blood level of the other group and found a significant difference. Based on these two points, we determined the target blood level to suppress seizures by adjusting the LCM dose. Moreover, we considered the optimal range for the actual blood sampling point and the optimal ideal ranges for the peak and trough levels. Finally, we were able to set the optimal range for an arbitrary blood sampling point and trough level (Fig. 7). The text has been revised from “The aim was to evaluate the efficacy of lacosamide (LCM) and the usefulness of measuring its blood levels in patients with focal epilepsy and to analyze the optimal range of LCM blood levels.” to “The aim was to analyze clinical targets for lacosamide (LCM) blood levels in patients with focal epilepsy. Referring to the LCM optimal range will motivate us to think about the importance and usefulness of measuring its blood levels.” in the Objectives section of the Abstract on Page 1.

* How can be explained that in patients with FBTCS, the blood levels were significantly higher in effective cases than in ineffective cases.

Because the attending physician frequently fine-tunes the prescribed dose based on detailed reports of seizure frequency from the parents, we thought that the blood levels in FBTCS were significantly higher than the optimal range of the whole population, which resulted in less overlap between the effective group and the other groups.

In the text, we have revised the sentence in the latter half of 4. Discussion on Page 10 to "The target range in FBTCS was slightly higher than the optimal range mentioned above. It was expected that the dosage would be adjusted proactively because the patients and their families want the seizures to be completely suppressed, because the seizures in FBTCS are easily identified by the families and have large impacts on daily life. Therefore, doctors would likely make frequent and sensitive adjustments to the LCM dose based on parental reports of detailed seizures. We thought that the optimal ranges in FBTCS would be higher than the optimal range of all cases, and there would be less overlap between the effective group and the other group."

In addition, we added "As mentioned above, there were cases in which low LCM blood levels were effective (# in Figs. 5 and 6), and we thought that the presence of these cases was one of the reasons. Furthermore, it was also considered that these cases were more numerous than the ineffective cases with higher LCM levels ($ in Figs. 5 and 6)." following "There have been very few reports that advocated a range lower than the optimal range of the present study [21]."

* How did you come to the conclusion that the effect and required dose of lacosamide may vary depending on the type of seizure, despite there being no significant difference in the blood levels of lacosamide in the 3 groups?

The text that you noted, "possibility which the dose may differ depending on the type of seizure," was poorly stated. When we planned this study, we inferred the relationship between seizure type and the dose (the blood level) of ASM based on the following papers.

29. Asadi-Pooya AA, Farazdaghi M. Idiopathic generalized epilepsies: Which seizure type is more difficult to control? J Clin Neurosci. 2023 Aug;114:93-96. doi: 10.1016/j.jocn.2023.06.011. PMID: 37348286.

30. Duy PQ, Krauss GL, Crone NE, Ma M, Johnson EL. Antiepileptic drug withdrawal and seizure severity in the epilepsy monitoring unit. Epilepsy Behav. 2020 Aug:109:107128. doi: 10.1016/j.yebeh.2020.107128. PMID: 32417383.

The results of this study demonstrated a correlation between the LCM dose and blood level, but no correlation was found between the blood level and RR in the FAS, FIAS, and FBTCS groups. Much like the comparison of LCM blood levels between the effective group and other groups in the whole population, comparisons were made between the two groups for each seizure type. However, no significant differences were found except for FBTCS. Therefore, it was not possible to compare the optimal ranges, and it was not possible to state the required LCM dose for each seizure type. Based on the above, the following text has been added to the end of 4. Discussion on Page 10. References [29] and [30] were also added to the reference list.

“This study was also conducted to determine the relationship between seizure type and LCM dose based on its blood levels [29,30], and a correlation between the LCM dose and blood level was demonstrated. However, no correlation was observed between the blood concentration and the seizure reduction rate in FAS, FIAS, and FBTCS, because there were many cases in which low doses of LCM were effective, or even high doses were insufficiently effective. Similar to the comparison of blood levels between the LCM effective group and the other groups in the whole population, the two groups were compared for each seizure type; no significant differences were observed, except for FBTCS. This might be due to inadequate medication in FAS and FIAS compared with FBTCS, due to a tendency to overlook seizures. Therefore, comparisons of the optimal ranges for each type of seizure were impossible, and the required oral dose for each type could not be stated.”

* Antiepileptic drugs are stopped due to side effects, despite their high effectiveness in treating epileptic seizures. Can you add more information about this?

As Reviewer 2 noted, the effectiveness of antiepileptic drugs is not just about suppressing seizures, but also about improving quality of life. We have also experienced some cases with side effects that led to reduction or discontinuation of oral medication. Fortunately, there were no cases in which the dose was reduced or administration was discontinued due to side effects in this study. Because the quantitative analysis required for such a statistical analysis in this study design was not possible, items related to quality of life and side effects could not be identified. We have added the following to 3.1. Details of patients’ age ranges, doses, and blood levels by timing of sampling and seizure type in 3. Results. No patients in this study dropped out due to side effects.

“… and 73.8 ± 26.4% 12 months after (*P* = 0.145). Fortunately, only a few patients experienced side effects, including temporary drowsiness, and their symptoms improved spontaneously without them having to withdraw from this study.”

* Indicate the permissible maximum doses of this drug, taking into account weight and age. Specify the criteria for discontinuation of this drug.

The description of the dosage and discontinuation criteria for LCM was insufficient. We have made corrections and additions to section 2.2 Patient selection and treatment in 2. Materials and Methods.

“…Before starting LCM treatment, patients received the same kinds and dosages of ASMs for 4 more weeks, but the drugs were insufficiently effective. LCM was started at 1-2 mg/kg/day. If the patient showed seizures, the dose was increased by 2 mg/kg/day every 2 weeks. The maintenance dose was increased to 12 mg/kg/day for patients weighing less than 30 kg, and to 8 mg/kg/day for patients weighing 30-50 kg. We considered that the dose sufficient to eliminate seizures was the maintenance dose for each patient. For patients weighing more than 50 kg, the maximum dose was set to 400 mg/day. When LCM was added to therapy, all patients were on treatment with multiple ASMs (range, 1-3). Furthermore, the discontinuation criteria for this study were: no routine sampling of blood levels; no measurement of body weight at sampling time; poor adherence; and discontinuation of treatment due to serious side effects. Nine cases experienced side effects, but since their symptoms were only temporary drowsiness and resolved without intervention, they were able to continue in the study.”

Thank you again for giving us the opportunity to strengthen our manuscript with your valuable comments. We have done our best to address your concerns and hope that you will find our responses acceptable.

Reviewer 2

Comments and Suggestions for Authors

* Move this paragraph to materials and methods: “A total of 101 patients who experienced focal seizures and were treated with LCM were investigated in this study, and the efficacy of LCM and the usefulness of its blood level measurements were evaluated. Furthermore, the optimal ranges of actual and calculated values were established as clinical targets.” Please indicate a specific purpose for your research.

Author`s comments

Thank you for your helpful comments. Our responses to your suggestions follow.

"A total of 101 patients who experienced …were established as clinical targets," which was pointed out by Reviewer 2, has been removed from “1. Introduction”. This text is a summary of the methods and objectives, and we also thought that it was inappropriate to include in the Introduction. However, similar text is already present in “2. Materials and Methods”. Moreover, we felt that it was contradictory to include the objective there. Thus, we deleted this text.

The goal of the present study was to set the clinical targets for blood levels, more specifically, to determine the optimal LCM range. First, we demonstrated the correlation between the LCM blood level and the dose. Next, since no correlation was found between the blood level and RR, we compared the blood level of the patient group with RR≥50% and the blood level of the other group to demonstrate a significant difference. Based on these two points, we estimated the target blood level to suppress seizures by adjusting the LCM dose. Moreover, we considered the optimal range for the actual blood sampling points and the optimal ideal ranges for the peak and trough levels. Finally, we were able to set the optimal range for an arbitrary blood sampling point and trough levels (Fig. 7). The text has been revised from “The aim was to evaluate the efficacy of lacosamide (LCM) and the usefulness of measuring its blood levels in patients with focal epilepsy and to analyze the optimal range of LCM blood levels.” to “The aim was to analyze clinical targets for lacosamide (LCM) blood levels in patients with focal epilepsy. Referring to the LCM optimal range will motivate us to think about the importance and usefulness of measuring its blood levels.” in the Objectives section of the Abstract on Page 1.

I think that the revision is easier for readers to understand.

* How can be explained that in patients with FBTCS, the blood levels were significantly higher in effective cases than in ineffective cases.

Because the attending physician frequently fine-tunes the prescribed dose based on detailed reports of seizure frequency from the parents, we thought that the blood levels in FBTCS were significantly higher than the optimal range of the whole population, which resulted in less overlap between the effective group and the other groups.

We have therefore revised the text in the latter half of 4. Discussion on Page 10 from "The target range in FBTCS was slightly wider than the optimal range mentioned above." to "The target range in FBTCS was slightly higher than the optimal range mentioned above. It was expected that the dosage would be adjusted proactively because the patients and their families want the seizures to be completely suppressed, because the seizures in FBTCS are easily identified by the families and have large impacts on daily life. Therefore, doctors would likely make frequent and sensitive adjustments to the LCM dose based on parental reports of detailed seizures. We thought that the optimal ranges in FBTCS would be higher than the optimal range of all cases, and there would be less overlap between the effective group and the other group."

In addition, we added "As mentioned above, there were cases in which low LCM blood levels were effective (# in Figs. 5 and 6), and we thought that the presence of these cases was one of the reasons. Furthermore, it was also considered that these cases were more numerous than the ineffective cases with higher LCM levels ($ in Figs. 5 and 6)." following "There have been very few reports that advocated a range lower than the optimal range of the present study [21].".

* How did you come to the conclusion that the effect and required dose of lacosamide may vary depending on the type of seizure, despite there being no significant difference in the blood levels of lacosamide in the 3 groups?

The text that you asked noted, "possibility which the dose may differ depending on the type of seizure," was not well stated. When we planned this study, the relationship between the seizure type and the dose (the blood level) of ASM was inferred based on the following papers.

29. Asadi-Pooya AA, Farazdaghi M. Idiopathic generalized epilepsies: Which seizure type is more difficult to control? J Clin Neurosci. 2023 Aug;114:93-96. doi: 10.1016/j.jocn.2023.06.011.

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The results of this study demonstrated the correlation between the LCM dose and blood level, but no correlation was found between the blood level and RR in the FAS, FIAS, and FBTCS groups. Much like the comparison of LCM blood levels between the effective group and other groups in the whole population, comparisons were made between the two groups for each seizure type. However, no significant differences were found except for FBTCS. Therefore, it was not possible to compare the optimal range, and it was not possible to state the required LCM dose for each seizure type. Based on the above, the following text has been added to the end of 4. Discussion on Page 10. References [29] and [30] were also added to the reference list.

“This study was also conducted to determine the relationship between seizure type and LCM dose based on its blood levels [29,30], and a correlation between the LCM dose and blood level was demonstrated. However, no correlation was observed between the blood concentration and the seizure reduction rate in FAS, FIAS, and FBTCS, because there were many cases in which low doses of LCM were effective, or even high doses were insufficiently effective. Similar to the comparison of blood levels between the LCM effective group and the other groups in the whole population, the two groups were compared for each seizure type; no significant differences were observed, except for FBTCS. This might be due to inadequate medication in FAS and FIAS compared with FBTCS, due to a tendency to overlook seizures. Therefore, comparisons of the optimal ranges for each type of seizure were impossible, and the required oral dose for each type could not be stated.”

* For comparison, was used only the reduction in the frequency of epileptic seizures, although in many cases changes in the form of seizures are observed during the use of anticonvulsants. Can you add more information about that.

We know that ASMs affect not only seizure frequency, but also seizure intensity and duration, and we have evaluated these in a previous study.

Nonoda Y, Iwasaki T, Ishii M. The efficacy of gabapentin in children of partial seizures and the blood levels. Brain Dev. 2014 Mar;36(3):194-202. doi: 10.1016/j.braindev.2013.04.006. Epub 2013 May 3.

In the previous study, we compared the length and intensity of seizures between two groups. We found significant differences in the R-ratio between the shortened-disappeared group and the other groups at each evaluation point. However, there were no significant differences in seizure intensity. Furthermore, we could not quantify either the length or the intensity of seizures to examine their correlation with gabapentin blood levels. In this LCM study, we were unable to add information about the length and intensity of seizures because that information was excluded from the extraction items in the study design from the beginning.

* It is important to indicate the dynamics of quality of life and school performance against the background of lacosamide use. In many cases, antiepileptic drugs are stopped due to side effects, despite their high effectiveness in treating epileptic seizures. Сan you add more information about this?

As noted, the effectiveness of antiepileptic drugs is not just about suppressing seizures, but also about improving quality of life. We have also had some cases with side effects that led to reduction or discontinuation of oral medication. Fortunately, there were no cases in which the dose was reduced or administration was discontinued due to side effects in this study. Because the quantitative analysis required for such a statistical analysis in this study design was not possible, items related to quality of life and side effects could not be identified. We have added the following to 3.1. Details of patients’ age ranges, doses, and blood levels by timing of sampling and seizure type in 3. Results. No patients in this study dropped out due to side effects.

“… and 73.8 ± 26.4% 12 months after (*P* = 0.145). Fortunately, only a few patients experienced side effects, including temporary drowsiness, and their symptoms improved spontaneously without them having to withdraw from this study.” Moreover, we have added side effects as a discontinuation criterion in section 2.2 Patient selection and treatment of 2. Materials and Methods. We will explain this later.

* It is interesting to show the dynamics of EEG examination after treatment.

Improvement in EEG findings was not included as an evaluation item in this study, because the results are subjective and depend on the interpreting physician, and the improvement in EEG findings could not be quantified. We also encountered cases in which EEG findings improved, but we could not conduct a statistical analysis.

* Indicate the permissible maximum doses of this drug, taking into account weight and age. Specify the criteria for discontinuation of this drug.

The description of the dosage and discontinuation criteria for LCM was insufficient. The doses of ASM for children are weight dependent. Therefore, we provided details regarding the LCM dose by weight, including the maximum dose, in this study. We have also mentioned the maximum dose. In addition, we have added criteria for withdrawal from this study. With that in mind, we have made corrections and additions to section 2.2 Patient selection and treatment in 2. Materials and Methods.

“…Before starting LCM treatment, patients received the same kinds and dosages of ASMs for 4 more weeks, but the drugs were insufficiently effective. LCM was started at 1-2 mg/kg/day. If the patient showed seizures, the dose was increased by 2 mg/kg/day every 2 weeks. The maintenance dose was increased to 12 mg/kg/day for patients weighing less than 30 kg, and to 8 mg/kg/day for patients weighing 30-50 kg. We considered that the dose sufficient to eliminate seizures was the maintenance dose for each patient. For patients weighing more than 50 kg, the maximum dose was set to 400 mg/day. When LCM was added to therapy, all patients were on treatment with multiple ASMs (range, 1-3). Furthermore, the discontinuation criteria for this study were: no routine sampling of blood levels; no measurement of body weight at sampling time; poor adherence; and discontinuation of treatment due to serious side effects. Nine cases experienced side effects, but since their symptoms were only temporary drowsiness and resolved without intervention, they were able to continue in the study.”

Thank you again for giving us the opportunity to strengthen our manuscript with your valuable comments. We have done our best to address your concerns and hope that you will find our responses acceptable.