Safety and efficacy of Levetiracetam and Carbamazepine monotherapy in the management of pediatric focal epilepsy: A randomized clinical trial

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Abstract

Background: Due to the limited number of studies in children with focal epilepsy and the importance of choosing the most suitable drug to control seizures in children, the administration of the most effective medication with the most negligible side effects is vital.

Objectives: This study aimed to evaluate the effectiveness and side effects of Carbamazepine vs. Levetiracetam monotherapy in children with focal seizures.

Design: A monocentric, randomized, controlled, double-blind, parallel-group clinical trial

Setting: This study was approved by the Iranian Registry of clinical trials (registration number: **IRCT20170216032603N2)** on June 19, 2020, and conducted at the neurology department of Imam Ali Hospital, Karaj, Iran, from February 2020 to March 2021

Participant: This study assessed 120 patients with recently diagnosed focal seizures aged 2 to 14.

Methods: Patients were randomly divided into two groups, who received Carbamazepine (CBZ) 15 to 20 mg/kg and Levetiracetam (LEV) 20 to 40 mg/kg daily, respectively. Both medicines were prescribed in divided doses of tablets twice daily. Patients were evaluated for improvement and complications at weeks four, 12, and 24.

Results: Totally out of 120 patients included in the study; six patients were excluded due to various complications of CBZ. The mean number of seizures at the end of the fourth, twelfth, and twenty-fourth weeks were 1.09 ± 0.75, 0.62 ± 0.27, and 0.39 ± 0.12 in the Carbamazepine group and 1.11 ± 0.63, 0.52 ± 0.21, and 0.37 ± 0.11 in the LEV group, respectively ($P>0.05$). Similarly, the number of seizure-free patients was 34, 44, and 48 in the CBZ group compared to 41, 50, and 54 in the LEV group, respectively ($P>0.05$). On the other hand, the frequency of somnolence, dermatologic complications, and agitation was considerably higher in the CBZ group ($P <0.05$).

Significance: Although both medicines were equally effective in seizure control, CBZ was associated with considerably more side effects and less patient compliance. Physicians should be aware of this difference to prevent unwanted consequences.

Introduction

Epilepsy is a significant neurological disorder from which many patients worldwide suffer. About 4–10% of children have at least one seizure during the first 16 years of their life (1). Seizures in epileptic patients with focal seizures have a higher risk of recurrence than in patients with generalized form (2). Managing focal epilepsy with an anti-epileptic drug (AED) requires concurrently considering the effectiveness, safety, tolerability, and interactions. Also, it is challenging due to the broad spectrum and critical adverse effects of AEDs. Most older AEDs are less commonly recommended for long-term monotherapy in

controlling focal seizures due to their greater risk of severe side effects and wide-spectrum drug interactions (3, 4).

The first line of treatment from older AEDs for focal epilepsy is Carbamazepine (CBZ), which requires multiple daily doses (2). The CBZ action mechanism is prolonging the inactivity of the sodium channel in the postsynaptic nerve cell, which reduces its ability to perform high-frequency repetitive action potentials. It inhibits the release of the neurotransmitter from the presynaptic neuron and finally impedes total transmission (5, 6). CBZ's side effects are somnolence, nausea, vomiting, ataxia, headache, and hepatic and hematological complications. These complications are mainly dose-dependent and observed at the beginning of the treatment. Due to these adverse effects, CBZ prescription is challenging and requires close follow-ups (7).

Levetiracetam (LEV) was introduced as an effective second-generation AED in 1999. LEV has been used to manage adolescent focal seizures by adding-on previous therapies (8). Its mechanism of action is binding to neuronal vesicles 2A and inhibiting calcium release from neuronal calcium storage (9). Double-blind placebo-controlled clinical trials have proved the efficacy of LEV in adults and children (4, 10). However, its safety and effectiveness in infants must be determined (11). Single-drug or adjunctive therapy with LEV may help improve psychiatric symptoms such as depression, interpersonal sensitivity, and paranoid thoughts while reducing seizure severity and eventually improving the quality of life in adults (12, 13). The other advantages of this drug include twice a day prescription, fewer side effects and drug interactions, and no requirement to monitor its serum level. These pharmacological benefits favor LEV to be selected for the treatment of epileptic seizures (14).

Several studies have focused on LEV monotherapy in managing children's epilepsies (either focal or general) (15). Some of them with lower population numbers had effectively switched their treatment from adjunctive therapy to monotherapy (16, 17). Only a few randomized clinical trials (RCTs) with a limited sample size in children with focal seizures compared LEV's efficacy and side effects with CBZ. In these trials, LEV monotherapy's efficacy in children is almost equally comparable to other AEDs, specially CBZ as first-line therapy. Also, they recommended conducting RCTs with larger sample sizes to compare the efficacy and adverse effects of LEV monotherapy in children more accurately (18, 19). Due to the limited number of comparing trials on LEV and CBZ monotherapy and the importance of choosing a suitable drug for controlling pediatric focal seizures, this randomized clinical trial was conducted in children with focal epilepsy to investigate and evaluate the efficacy and side effects of both therapies.

Methods and materials

Trial design

A monocentric, randomized, controlled, double-blind, parallel-group clinical trial was designed. This clinical trial was conducted among recently diagnosed children with focal epilepsy referred to the neurology department of Imam Ali Hospital, Karaj, Iran, from February 2020 to March 2021.

Alborz University of Medical Sciences Research Ethics Committee approved the study by the ID: (**IR.ABZUMS.REC.1398.208**) on June 19, 2020, and written informed consent was obtained from the parents of patients. Also, the Iranian Registry of clinical trials approved the trial by the registration number: **IRCT20170216032603N2**.

Participants

One hundred and twenty patients "between the ages of 2 to 14 years, diagnosed with focal epilepsy, were enrolled in the study. Seizures should have occurred at least twice with an interval of more than 24 hours. Other inclusion criteria were new cases and a diagnosis confirmation by electroencephalogram (EEG). Exclusion criteria were: patients who did not fall into the category of focal seizures according to the definition, seizures in patients with a history of brain injury in the last three months, history of renal, hepatic, and hematologic disorders, history of receiving anticonvulsant and psychiatric medication, and parents' reluctance to participate.

Interventions

Patients were selected based on their history and clinical examination and, if desired, entered the study after signing the informed consent by their parents. A pediatric neurologist identified participants with non-provoked seizures after a neurological examination and electroencephalography (EEG). A questionnaire containing demographic and specific information (seizure characteristics, number of seizures, duration of episodes, side effects) was prepared and completed at the beginning of the study. Finally, tests including Electroencephalogram (EEG), Complete Blood Count (CBC), Liver Function Tests (LFT), Creatinine (Cr), and Blood Urine Nitrogen (BUN) were performed for all patients.

Patients admitted with the above criteria were randomly divided into two groups: LEV and CBZ. The prescribed medications for both groups were in the form of tablets twice a day. In the CBZ group, the medicine started with a dose of 5 mg/kg of body weight per day, increased by 5 mg/kg per week, and finally reached the usual dose of 15 mg/kg per day; and then it continued with the same dose. On the other hand, the drug started with 10 mg/kg per day in the LEV group and increased by 10 mg/kg per week to reach the usual 30 mg/kg per day (20). The overall therapeutic approach was to titrate the anti-epileptic drug dose until participants were seizure-free.

The expected adverse effects had been taught to parents, and they were asked to record all of their child's seizure-related data in a seizure diary; this information included the seizure characteristics, number of seizures, duration of episodes, drug compliance, and any side effects such as somnolence and agitation, nausea, and dermatologic complications. In addition to our scheduled visits, parents were asked to report the severe side effects immediately.

Every visit, patients underwent a physical exam (to investigate any side effects), EEG, and routine tests (cell blood count, liver, and kidney function). Their seizure diary was analyzed at the end of each session, and its critical data was extracted. In case of any side effects requiring termination of treatment, or the physician's decision, the patients were excluded from the study.

After the 24th -week visit, the incidence of side effects was compared between the two treatment groups based on the dosage at the initiation of the severe adverse event and the period from the onset of the drug usage to the reported side effect.

Outcomes

The primary outcome measures included seizure characteristics, the number of seizures, duration of episodes, and side effects, measured at the start and end of treatment and weeks 4, 12, and 24 follow-ups. Secondary outcomes were seizure freedom, defined as having no seizures during the three months immediately prior to the 6-month follow-up point.

Sample size

Based on the study of Perry et al. (14), considering $\alpha = 0.05$ and $\beta = 0.2$ and the effectiveness of epilepsy control in the two groups, according to the estimation formula and ratio calculated by PASS 2021 sample size software. The sample size in each group was 60.

Randomization and blinding

Patients admitted with the inclusion criteria were divided into two groups randomly. Randomization was performed using computer-generated, stratified sequences matched based on age and gender. The data collection was single-blind, and the data recorder was unsighted to the drug prescription.

Statistical methods

Statistical analysis was performed on intention to treatment (ITT) and per-protocol basis (PP). For the ITT analysis, the last observation carried forward approach was used for patients who dropped out during the study. Data were analyzed using SPSS software version 24. The Kolmogorov-Smirnov test was used to determine quantitative data's normal or non-normal distribution. An Independent T-test was applied to compare the mean of data with normal distribution. Moreover, qualitative data were compared using the Chi-square test and Fisher's exact test '. A P-value < 0.05 was considered significant.

Results

A total of 128 children underwent screening; 3 were ineligible, and 125 met the inclusion criteria. Two patients did not return for the follow-up visits, and three of the patients' parents withdrew their consent or did not use the study medications (Fig. 1). A total of 120 patients were randomized to the CBZ group (n = 60) or the LEV group (n = 60, ITT). From the CBZ group, six patients, including one case of Stevens-Johnson syndrome, three cases with severe dermatologic complications, and two cases with severe agitation, were excluded from the study. This left 60 patients in the LEV group and 54 in the CBZ group for the PP analysis. There were no significant differences in the baseline characteristics between the two groups. Following are the summarized results.

Patient Characteristics

'Before beginning the monotherapy, patients received benzodiazepines only after a seizure, and no other AEDs were used. There was no requirement to add adjunct AEDs through the follow-up period. The demographic characteristics of the two treatment groups were comparable, and all patients were followed for six months after the initiation of monotherapy (Table 1). The mean ± SD age of patients in the CBZ group was 7.86 ± 2.96 (ITT analysis) and 8.05 ± 2.94 (PP analysis), and in the LEV group was 7.96 ± 3.09 (both PP and ITT analysis). The demographic and pretreatment seizure frequency of the population is shown in Table 1. There were no significant differences between both groups (P > 0.05).

Table 1
Characteristics of Patients on Carbamazepine and Levetiracetam Monotherapy

	Intention-to-treat analysis		Per-protocol analysis	
	Carbamazepine (n = 60)	Levetiracetam (n = 60)	Carbamazepine (n = 54)	Levetiracetam (n = 60)
Age (mean ± SD)	7.86 ± 2.96	7.96 ± 3.09	8.05 ± 2.94	7.96 ± 3.09
Gender (male:female)	36:24 (60%:40%)	32:28 (53.3%:46.7%)	31:23 57.4%:42.6%	32:28 (53.3%:46.7%)
Pretreatment seizure frequency (mean ± SD)	3.95 ± 1.41	4.32 ± 1.58	3.96 ± 1.49	4.32 ± 1.58

Treatment Efficacy

The incidence of seizures between the follow-up visits was compared with each other in the two groups at the end of weeks 4, 12, and 24 (Table 2). PP-analysis indicated that despite a lower incidence of seizure in the LEV group, there is no significant difference (P > 0.05). Similar data was seen in the seizure freedom (P = 0.54, 0.57, and 0.85 in 0–4, 4–12, and 12–24 weeks, respectively). The ITT analysis demonstrated that there was no significant difference in any period despite the seizure incidence in 0–4 weeks being 20 and 19 in the LEV and CBZ groups. In contrast, the seizure freedom in the LEV group is lower than in the CBZ group, but this difference was only significant between 12 and 24 weeks (P-value: 0.047, F: 18.20).

Table 2
Results of treatment outcome measures

	Intention-to-treat analysis				Per-protocol analysis			
	CBZ (n = 60)	LEV (n = 60)	p-value	OR (95%CI), or F	CBZ (n = 54)	LEV (n = 60)	p-value	OR (95%CI), or F
Seizure freedom (%)								
Week 0–4	34 (56.6)	41(68.3)	0.19	1.65 (0.78–3.47)	34 (62.9)	41(68.3)	0.54	1.26 (0.58–2.57)
Week 4–12	44 (73.3)	50(83.3)	0.19	1.81 (0.74–4.41)	44 (81.4)	50(83.3)	0.80	1.14 (0.43–2.98)
Week 12–24	48 (80)	54(90)	0.13	2.25 (0.78–6.56)	48 (88.8)	54(90)	0.84	1.12 (0.34–3.72)
Seizure frequency (mean ± SD)								
Week 0–4	1.43 ± 1.08	1.12 ± 0.63	0.057	8.13	1.09 ± 0.75	1.12 ± 0.63	0.54	0.37
Week 4–12	0.79 ± 0.45	0.52 ± 0.22	0.059	16.58	0.63 ± 0.28	0.52 ± 0.22	0.57	1.42
Week 12–24	0.67 ± 0.31	0.37 ± 0.12	0.047	18.20	0.39 ± 0.13	0.37 ± 0.12	0.85	0.12

Treatment Side Effects

The frequency of side effects in both groups is shown in (Table 3). There were no hematologic and renal complications reported in any group. Also, there was no difference between the two groups in terms of nausea and the frequency of somnolence, dermatologic complications, and agitation in the CBZ group was significantly higher than in the LEV group (P: 0.022,0.027,0.036).

Table 3
Frequency of Side effects of Levetiracetam and Carbamazepine monotherapy

	Carbamazepine (n = 60)	Levetiracetam (n = 60)	*P*-Value
Somnolence	0(0%)	0(0%)	NC
Agitation	6(10%)	1(1.7%)	0.036
Nausea	2(3.7%)	3(5%)	1.000
Hematologic complications	0(0%)	0(0%)	NC
Renal complications	0(0%)	0(0%)	NC
Hepatic complications	2(3.7%)	0(0%)	0.292
Dermatologic complications	6(10%)	0(0%)	0.027
NC: not calculatable			

These severe side effects developed in less than four weeks, and it was impossible to examine any of these patients during the 4th-week visit. Stevens-Johnson syndrome developed 20 days after starting 15mg/kg/day CBZ and was treated with intravenous immunoglobulin. Of the other three skin conditions, two were generalized erythroderma, 14 and 11 days after CBZ initiation, and one was maculopapular lesions of the trunk and limbs, which occurred nine days after the start of treatment. These three complications occurred following the initial dose of 15 mg/kg CBZ and disappeared after the drug's termination and application of topical medications. Two cases of severe agitation developed in the second month of the treatment after increasing the dose to 20 mg/kg/day. Due to the minimal number of excluded patients compared to the total population and the lack of a clear characteristic difference between included and excluded patients, no further analysis was performed.

The hepatic complication included raising the liver enzymes to more than three times the normal level during the first month. The liver function enzymes returned to normal one week after discontinuing the drug.

Discussion

Many studies have shown the efficacy of LEV as adjunctive therapy in adults and children. In contrast, a small number of clinical trials have specifically reviewed LEV monotherapy in children with recently diagnosed focal epilepsy (15, 21). Due to the complexities in recruiting patients caused by legal and ethical considerations, it is not easy to plan clinical trials on LEV monotherapy for focal seizures in children (22). Therefore clinical trials are required to show each AED's benefits and disadvantages in controlling seizures (23). To our knowledge, this study is one of the few randomized clinical trials with a more considerable sample size that concentrates on comparing LEV and CBZ monotherapy.

We investigated the efficacy and side effects of LEV compared to CBZ in the 2-14-year-old patients recently diagnosed with focal epilepsy. The results indicated that the effectiveness of CBZ monotherapy compared to Levetiracetam in controlling focal seizures was similar. In line with our study outcomes, a 2008 study by Perry et al. showed that monotherapy with LEV and CBZ has similar efficacy for treating focal epilepsy in children and is well tolerated (14).

For comparing the effectiveness, a measurable indicator is needed. So, our research stated both indexes of seizure freedom and seizure frequency of each patient in different periods. One reason for using both indicators is the response of some patients with focal epilepsy to anti-epileptic therapies. Studies have shown that focal seizures in some patients are not entirely cured even with appropriate medication. The presence of refractory patients in each of the LEV and CBZ groups may affect the number of patients with seizures, so this study also evaluated the mean number of seizures per person.

Ninety percent of patients (54 of 60 participants) treated with LEV experienced seizure freedom on the 24th of follow-up. Similar results have been seen in the patients of the CBZ group (89.9%, 48 of 54 participants). Also, in the study of Jung et al. in 2015 (24), similar results were obtained, confirming the present study's results. In contrast, a study by Akhondian et al., Conducted in 2020, indicated that Levetiracetam was more effective in controlling focal epilepsy in children, which contradicts the present study's findings. This conflict can be attributed to the limitation of sample size and lack of continuous examination of patients in their study design (18). Also, an adult randomized clinical trial confirms no differences in efficacy between LEV and CBZ in managing focal seizures. Compared to children, adults' frequency of seizure freedom was higher in a faster period of follow-ups. These higher and quicker responses to treatment might be due to adults' different metabolic rates and types (8).

Ben-Menachem et al. showed that shifting from the LEV adjunctive treatment to monotherapy at a suitable dosage reduced the seizure episodes successfully (21). Moreover, based on adult and children population study reports, LEV monotherapy has the same efficacy at relatively lower dosages (25, 26). According to the mentioned reports, lower dosages of LEV monotherapy could effectively control focal seizures. We initiated the LEV dosage at 20 mg/kg daily, titrated until participants were seizure-free, met the maximum dose of 40 mg/kg daily, or severe side effects appeared. According to our findings, no patients with severe complications were required to discontinue LEV.

In our study, no long-lasting neurological effects were seen in the two groups; in the study of Jung et al., similar results were obtained as well (24). In our population, the incidence of agitation as a side effect was significantly higher in the CBZ group vs. the LEV group (10% vs. 1.7%, P = 0.036), which was in contrast to the Akhondian et al. study (18). Their findings suggested that agitation was the only complication significantly higher in the LEV group vs. the CBZ group (28% vs. 0%, P = 0,003). Moreover, the frequency of patients with somnolence in the CBZ-treated group was significantly higher than those treated with LEV, consistent with the two articles of Perry et al. and Akhondian et al. (14, 18). Four patients with dermatologic complications and two participants with severe agitation from the CBZ group were excluded from our study. Dermatologic complications and agitation were similarly the most

common and important causes of drug discontinuation in the carbamazepine group, as reported in previous studies (27–29). These adverse effects were detected in the normal range of daily doses. Measuring serum CBZ levels was not usually accessible; therefore, we cannot clarify the impact of these dosages on serum concentrations in participants stating these side effects. Most anti-epileptic medications require long-term and sometimes lifelong use, so patient compliance with these medications is essential. One of the results of this study was the observation of low compliance of patients in the CBZ group. Apart from the tolerable side effects, six patients in the CBZ group developed severe complications that made it impossible to continue treatment with this drug. Similar results have been seen in the comparison of CBZ with other drugs. For example, a study by Gamble et al. demonstrated that lamotrigine was significantly less likely to be withdrawn than CBZ (30).

Having a more considerable and reasonable sample size based on previous studies, being one of the first randomized clinical trials in children with focal epilepsy, prescribing a uniform formulation of CBZ, using the seizure freedom index to monitor the efficacy of treatment, and homogeneity between the two groups was this study's potencies. However, the most critical limitations of the present study were the unavailability to check CBZ serum levels and the lack of measuring psychological factors (child's depression or anxiety). Several prospective studies on this subject with a larger population and longer-term follow-ups measuring psychological outcomes can help make more accurate clinical decisions.

The data of this study showed that despite a slight improvement in some parameters of patients with focal epilepsy, there was no significant difference in the treatment of patients with CBZ or LEV. The only significant difference is in the average number of seizures per person at 12 to 24 weeks. In this case, the difference between PP and ITT analysis showed that it is impossible to comment on LEV's effect due to the exclusion of some patients from the CBZ group.

Overall, our study showed that despite similar treatment outcomes in both of these drugs, the use of lev due to fewer side effects, better tolerance by patients, and a lower price is a better option for treating focal epilepsy, especially in countries with limited resources.

According to the present study's findings and in line with the previous studies, both CBZ and LEV effectively controlled focal epilepsy in children, and side effects such as dermatologic complications, somnolence, and agitation were more common in the CBZ group.

Conclusion

The present study showed that the efficacy of both CBZ and LEV in controlling focal epilepsy in children was similar. Side effects of treatment (somnolence, severe dermatologic complications, and agitation) were significantly higher in the CBZ group. Selecting an AED as initial monotherapy for children with recently diagnosed focal epilepsy requires considering the efficacy and side effects of the drug. Although LEV and CBZ have similar effectiveness, LEV is a more suitable choice due to its safety and lower side effects.

Key Points Box

1) The efficacy of both Carbamazepine and Levetiracetam in controlling focal epilepsy in children is similar.

2) Compared to Levetiracetam, the side effects of treatment were significantly higher with Carbamazepine in children.

3) Considering efficacy and side effects, Levetiracetam is a better choice for monotherapy in children with focal epilepsy.

Declarations

Ethical Publication Statement: We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Availability of data and materials: The datasets generated and analyzed during the current study are not publicly available; however, the data can be shared for research and authentication purposes upon reasonable request.

Author contributions: HM, AHMEK, and ST conceived the study and participated in study design, data collection, and data analysis. HM, AHMEK, and MT wrote the manuscript. MA, MD, and KM participated in data collection and data analysis. AHMEK, MT, MA, KM, and MD assisted with preparing the document and interpreting the results. All the authors have read and approved the final submitted manuscript.

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Ethics Approval and Consent to Participate

The Ethics Committee of Alborz University of Medical Sciences approved this study (Approval ID: **IR.ABZUMS.REC.1398.208**). The Iranian Registry of clinical trials approved the trial by the registration number: **IRCT20170216032603N2 on** June 19, 2020. Informed consent was obtained from the patient's parents.

Declaration of Interest

The authors have no conflicts of interest to declare that they are relevant to the content of this article.

Disclaimer

The full article was not posted or published elsewhere.

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Figures

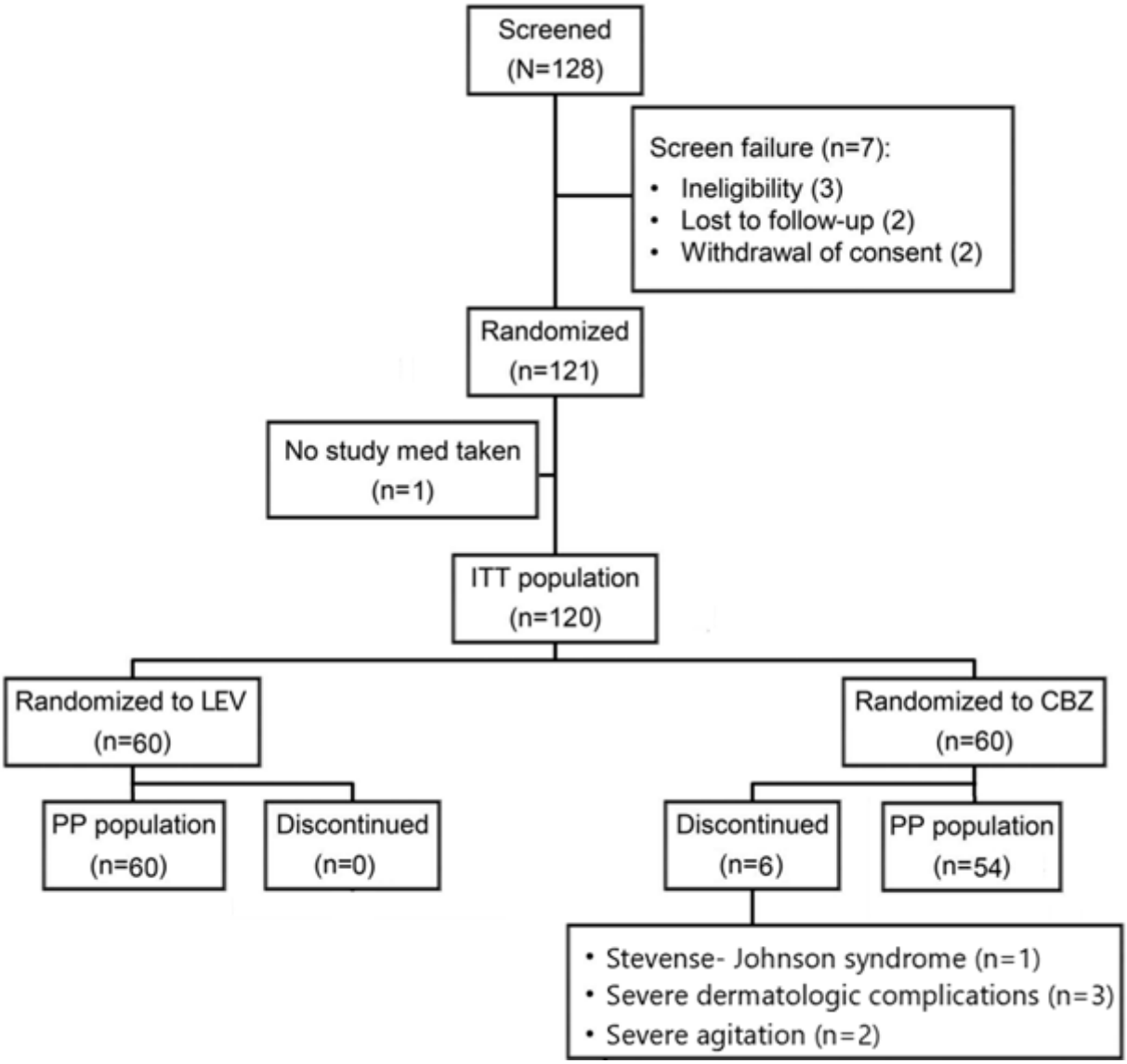

Figure 1

The trial flow diagram.