Wisconsin EMS Scope of Practice Change Request Worksheet

Use:

- To provide information which supports any proposed change in the psychomotor skills, types of medical devices, or list of medications allowed under the State of Wisconsin EMS Scope of Practice.

Objective:

- A comprehensive and standard review of proposed Scope of Practice changes will help ensure the safe and effective delivery of out-of-hospital care.

Please address the following statements as best possible (citing and attaching references when applicable):

- Provide a specific and detailed description of the skill, type of device, or medication you are proposing.

  I am proposing Levetiracetam (Keppra) should be added to the paramedic scope for the treatment of seizures.

- What intended clinical applications are you proposing for use (complaint, condition, ages, parameters)?

  Levetiracetam can be used for the treatment of or prophylaxis from many types of seizures. It can be used for pediatric as well as adult patients. This should not replace benzodiazepines as the first line management of seizures in the field however it can be added for patients who are resistant to seizures or who are at high risk for impending or recurrent seizure, such as patient with acute head injury.

- What EMS provider levels do you feel should have access through their scope of practice, and why?

  At this time, I am proposing Levetiracetam be added to the paramedic scope. Levetiracetam has a broad safety profile. Paramedics already have experience with the administration of many medications which are not IVP. Adding a medication with a slow push rate or with a specific drip rate will not place additional burden on paramedic education.

- List any examples of current usage in a patient care setting, both in and out of the hospital.

  Levetiracetam is frequently and liberally used for the treatment and prophylaxis of seizures in the emergency department. It is also used in the prehospital arena in other states. This is often the first line in seizure prevention in patients who have significant head injury as recommended by neurosurgery. In patients with status epilepticus, resistant to benzodiazapines, agents like Levetiracetam with different mechanisms of action are preferred to terminate the seizure. The safety profile of Levetiracetam is favorable since it has a very wide dosing range and very few drug drug interactions.

- Summarize the current evidence, concerning the proposed change, both for and against it, including benefits and improved effectiveness of patient care.

  Levetiracetam has a favorable safety profile given its wide dosing range and few side effects. It can easily be stored. It can be used for pediatrics and adults. It dos not cause respiratory depression at therapeutic doses unlike many of the other agents used for the treatment of seizures. It is now available in a generic form which helps reduce cost. Some prefer to administer the medication via IV drip over 15 min. This can be cumbersome vs IVP. Fortunately, most pharmacists are now recommending typical adult initial doses of 1000 - 1500mg can be administered IVP over 2-5 minutes. Levetiracetam has a favorable half life, is not dependent on hepatic metabolism, minimal binding to plasma proteins, minimal interaction with other medications, and speed crossing the blood brain barrier, make it an ideal agent.

- Do know of any current barriers or hesitations for use (laws/regulations, risks, costs, training)? How can these be addressed to allow for safe practice?

  I am not aware of any barriers to use

- Describe the training you feel would be appropriate to properly implement this change.

  Paramedics are already familiar with seizure treatment as well as medication administration. Reviewing the indications, contraindications, doses, and any special circumstances with paramedics should be all that is necessary for training.

- How do you plan to track usage and monitor patient care outcomes and patient safety events?

  Usage could be tracked via the medication report as part of the drop down menu in image trend. For the first two years, all cases where Keppra was administered will be manually reviewed by the medical director, looking for problems, side effects, effectiveness, and correct indications. This can be extended if needed based on the information learned in the first two years. Outcome data can be compiled as part of this review assuming it is available from the destination hospital.

Many other articles are available upon request however e-mail limits restrict the size of too many pdf attachments

- Please cite the references used to support your responses and attach as PDFs.

Daye Chen, Hongliang Bian & Lanlan Zhang (2019) A meta-analysis of levetiracetam for randomized placebo-controlled trials in patients with refractory epilepsy, Neuropsychiatric Disease and Treatment, , 905-917, DOI: 10.2147/NDT.S188111

Early Post-traumatic Seizure Occurrence in Pediatric Patients Receiving Levetiracetam Prophylaxis With Severe Traumatic Brain Injury
Meghan J. Kolf, PharmD; Christopher C. McPherson, PharmD; Kara S. Kniska, PharmD; Caitlyn M. Luecke, PharmD; Michael A. Lahart, PharmD; and Jose A. Pineiro-Carrero

Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study
Open Access
Jilske A. Huijben1*, Victor Volovici1,2, Maryse C. Cnossen1, Iain K. Haitsma2, Nino Stocchetti3,4, Andrew I. R. Maas5, David K. Menon6, Ari Ercole6, Giuseppe Citerio7,8, David Nelson9, Suzanne Polinder1, Ewout W. Steyerberg1,10, Hester F. Lingsma1, and Mathieu van der Jagt11 CENTER-TBI investigators and participants

Name of person completing request for State of Wisconsin Scope of Practice change:

Mark Schultz, DO, FACEP, FAEMS — 8-15-24

Name — Signature/Date

Medical Director attestation of involvement and support for requested State of Wisconsin Scope of Practice change:

Mark Schultz, DO, FACEP, FAEMS — 8-15-24

Name — Signature/Date

All requests for change in State of Wisconsin Scope of Practice will be addressed by the EMS Office via a thorough decision-making framework. Interested parties are welcome to attend open EMS Board and Committee meetings to hear discussion on the proposed change. Proposals will be handled in the order of greatest perceived importance to WI EMS.

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A meta-analysis of levetiracetam for randomized placebo-controlled trials in patients with refractory epilepsy

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REVIEW

A meta-analysis of levetiracetam for randomized placebo-controlled trials in patients with refractory epilepsy

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Neuropsychiatric Disease and Treatment

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Objective: The objective of this study was to investigate the efficacy and safety profile of levetiracetam as add-on therapy in patients with refractory epilepsy.

Methods: Web of Science, MEDLINE (Ovid and PubMed), Cochrane Library, EMBASE, and Google Scholar were systematically searched to identify potential eligible randomized controlled trials by two reviewers independently. Pooled estimates of risk ratios (RRs) for 50%, 75%, and 100% reduction from baseline were calculated using the fixed-effect model or random-effect model. Quality of included studies was assessed with the Cochrane Collaboration's Risk of Bias tool. Serious adverse events and withdrawals induced by interventions and the most common side effects were analyzed.

Results: Seventeen trials with a total of 3,205 participants were included in this meta-analysis, including 14 trials for adulthood and three trials for children. Pooled estimates suggested that levetiracetam was an effective anti-epileptic drug at 1,000–3,000 mg/day (RR =2.00 for 1,000 mg/day, RR =2.68 for 2,000 mg/day, RR =2.18 for 3,000 mg/day) for adults and 60 mg/kg/day (RR =2.00) for children compared to placebo in terms of 50% reduction from baseline. Likewise, as for seizure freedom rate, levetiracetam had an advantage over placebo at 1,000–3,000 mg/day (RR =5.84 for 1,000 mg/day, RR =4.55 for 2,000 mg/day, RR =4.57 for 3,000 mg/day, respectively) for adults and 60 mg/kg/day (RR =4.52) for children. Regarding safety profile, patients treated with levetiracetam had significantly higher occurrence than placebo for somnolence, asthenia, dizziness, infection, nasopharyngitis, anxiety, and irritability; however, most studies reported that these adverse events were mild and transient.

Conclusion: Levetiracetam is an effective anti-epileptic drug for both adults and children with generalized or partial-onset refractory seizures at 1,000–3,000 or 60 mg/kg/day, with a favorable adverse event profile.

Keywords: levetiracetam, adjunctive, refractory epilepsy, placebo

Introduction

Epilepsy is a serious neurological disorder, with the prevalence of ~0.5%–1% in developed countries,[1] and it rises up to 7.4% in developing countries because of inferior health care and a higher proportion of children.[2,3] Maintaining seizure freedom by using a tolerated anti-epileptic drug (AED) schedule is the goal of epilepsy treatment. However, of the 50 million people who suffer epilepsy, nearly one third were treated with available AEDs but due to lack of favorable effect, they still have onsets; this is regarded as "drug-resistant" or "refractory."[4] Besides, side effects induced by AEDs leading to failed adequate seizure control account for 20%–30% of the patients.[5]

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As a broad-spectrum AED, levetiracetam ((S)-α-ethyl-2-*oxo*-1-pyrrolidine acetamide) has unique mechanisms of action that differs from other AEDs. A study published recently revealed that through binding, levetiracetam modulates the activity of synaptic vesicle protein 2A in brain neurons to maintain a normal level, and as a result seizures reduce.[6] Compared to other AEDs, levetiracetam has a favorable pharmacokinetic profile in both adulthood and childhood. After oral administration, levetiracetam will be rapidly and almost 100% absorbed in a few hours; the peak serum concentration is achieved in ~1 hour (0.6–1.3 hours). Mean half-life of levetiracetam is about 6–8 hours in young adulthood and increases to 10–11 hours in elderly patients, and within 24–48 hours, the dose-proportional pharmacokinetic maintains a steady state serum level. One favorable characteristic of levetiracetam is that to date, there are few reports concerning pharmacokinetic drug interactions with levetiracetam in adults and children alike.[7,8] In comparison with adulthood, body clearance of levetiracetam in childhood is higher of about 30%–40%, and therefore, the recommended dose for children is about 130%–140% of that of adulthood, equivalent to 20–60 mg/kg/day, but should be adjusted according to body weight.[9] Moreover, studies revealed that the pharmacokinetic profile of single-dose levetiracetam in children aged 2–46 months is similar to those aged >4 years, suggesting that levetiracetam could be used in infants and young children.[10] Since introduced in the market in 2000, levetiracetam has become first-line and one of the most commonly prescribed AED and is recommended as add-on agent for partial seizures, benign childhood epilepsy with centrotemporal spikes, and myoclonic epilepsy.[11] This meta-analysis aimed to investigate the effects of levetiracetam as adjunctive therapy for patients suffering from refractory generalized or partial-onset epilepsy.

Materials and methods

This meta-analysis was performed and reported in accordance with the PRISMA.[12] Responder rate (50% reduction from baseline) and seizure freedom (100% reduction from baseline) were the primary outcomes for this meta-analysis. Serious adverse events (SAEs) during treatment induced by interventions and premature termination related to interventions were regarded as the secondary outcomes.

Search strategy and selection criteria

For this systematic review and meta-analysis, following databases were searched from inception up to May 31, 2018: EMBASE, MEDLINE, Web of Science, Cochrane Library PubMed, and Google Scholar, as well as Chinese National Knowledge Infrastructure and Wanfang Data databases. A combination of relevant keywords, abbreviations, and synonyms for levetiracetam and refractory partial epilepsy are as follows: (*levetiracetam*) and ([*refractory*] or [*uncontrolled*] or [*drug-resistant*]) and ([*onset**] or [*seizure**] or [*epilepsy*]). Database search was supplemented by manual screening of the references of relevant articles and reviews, and there was no restriction on publication language. Two reviewers (Chen and Bian) assessed the eligible articles independently, disagreements were resolved via discussion and, if necessary, arbitrated by the third reviewer (Zhang).

Inclusion criteria

Studies were included only if they meet all the following criteria: 1) involved refractory epilepsy, regardless of age and gender, 2) must be randomized controlled trials (RCTs) that involved levetiracetam, 3) reported at least one efficacy of responder or seize freedom rate, and 4) detailed adverse events (AEs) including dropouts owing to AEs and SAEs were reported.

Exclusion criteria

Studies were excluded if they meet any of the following criteria: 1) non-RCT studies such as retrospective and observational studies, 2) compared to other AEDs rather than placebo, 3) not for refractory epilepsy but other diseases such as migraine or autism, 4) not reported detailed efficacy of responder and/or seizure freedom and adverse profile, and 5) conference abstracts, guidelines, editorials, letters, and reviews.

Data extraction and quality evaluation

To standardize the data extraction process, we developed a data collection form with Excel (Office 2013; Microsoft Corporation, Redmond, WA, USA), and following data were extracted from each study: 1) study and demographic characteristics: first author, year of publication, country, sample size, patient age, and ratio of male/female and 2) clinical characteristics: dosage, follow-up period, responder and seizure freedom number, total number of AEs, premature termination owing to AEs, SAEs, and specific side effects reported by more than three trials. Risk of bias for included studies was evaluated with the Cochrane Collaboration's Risk of Bias tool, which covered seven aspects of random sequence generation, allocation concealment, blinding of outcome participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each RCT was regarded as high, low, or unclear risk

of bias for these aspects. Quality assessment was performed by two reviewers (Chen and Bian) independently; in case of disagreements, the third reviewer (Zhang) was consulted.

Data synthesis and analysis

Outcomes were reported as risk ratio (RR) with 95% CI, with fixed-effect model if there was no significant heterogeneity identified;[13] otherwise the random-effect model was used to calculate.[14] Heterogeneity across studies was assessed by Cochran's Q test and measured with inconsistency index (I^2), value of which was interpreted as follows: 1) 0%–40% was considered as not important, 2) 30%–60% was considered as moderate, 3) 50%–90% was considered as substantial, and 4) 75%–100% was regarded as considerable.[15] A funnel plot was presented to visually evaluate the publication bias, quantified by Egger regression and Begg–Mazumdar test.[16,17] All randomized participants were analyzed based on intention-to-treat patient population, namely in the treatment group they had been allocated, irrespective of the treatment that they actually received. Participants randomized but excluded from analysis were assumed non-responders. If the difference in dosage between studies was slight, then for sake of convenient calculation, we categorize them in the same group; in this case, we would make a specific declaration. Subgroup analyses based on dosage and age were performed as well. A P-value <0.05 was regarded as statistically significant. Pooled estimates of RRs and corresponding 95% CIs of 50%, 75%, and 100% of seizure reduction from baseline, along with SAEs and dropout due to interventions, were presented in the forest plots. Another measurement for epilepsy treatment is quality of life (QoL), but to date widely accepted instruments to assess it are still lacking; therefore, we did not combine the results of QoL. All analyses were performed with the STATA 14.1 (Stata Corporation, College Station, TX, USA) and the "metan" module of it.

Results

Literature search

Figure 1 describes an overview of the study selection process. The initial systematic search yielded 1,325 results, of which

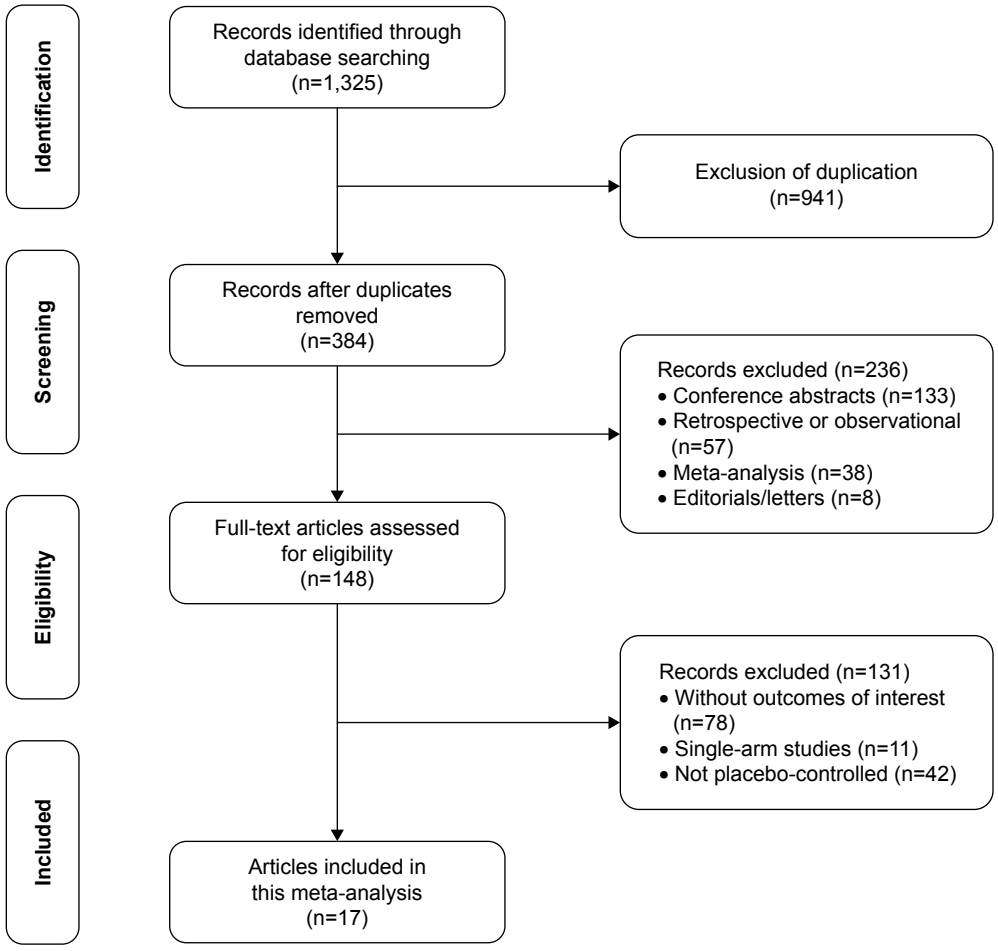

Figure 1 Study selection process for this meta-analysis.

975 were removed for duplicates. Of the remaining 384 articles, 138 were excluded for conference abstracts, 57 for retrospective or observational studies, and 38 for systematic reviews or meta-analyses. Full-text screening was performed by two reviewers independently and manually, then 128 articles were ruled out for following reasons: 75 studies did not report sufficient data for efficacy or AEs; 11 studies were single-arm trials, and 42 studies were compared to other AEDs such as oxcarbazepine, sulthiame, or carbamazepine rather than placebo. Eventually, a total of 17 RCTs with 3,205 participants were included in the current meta-analysis.[2,5,10,18–30]

Study characteristics

Details of demographic and clinical characteristics for 17 RCTs are summarized in Table 1. Sample size for these trials ranged from 24 to 351. Fourteen trials involved adult patients[2,5,18–25,27,31] and three involved children,[10,26,28] with age ranging from 1 month to 69 years. Regarding the 14 trials involving adults, the most administered dosages were 1,000, 2,000, and 3,000 mg/day. However, in the trial of Inoue et al, single-arm participants were administered at 500 mg/day.[27] Another exception was in the trial of Betts et al, in which dosage reached 4,000 mg/day.[5] Of the three trials involving children, two used the maximum dosage of 60 mg/kg/day,[26,28] the remaining one used slightly less, at a maximum of 50 mg/kg/day.[27] In nearly all the included trials, levetiracetam was administered orally twice-daily; the only exception was trial of Peltola et al, in which levetiracetam was administered 1,000 mg/day once daily.[18] Most of the trials lasted at least 16 weeks; however, the trial of Piña-Garza et al only lasted 7 days, which may bring about potential risk of bias for outcomes.[10] Of the 17 RCTs, 15 involved patients with refractory partial-onset seizures, whereas the two others were designed to assess the efficacy for patients with uncontrolled idiopathic generalized epilepsy.[29,30]

Quality assessment of included studies

Details of risk of bias for each RCT are presented in Figure 2. Ten trials were considered as low risk of bias, because sequence generation and allocation method were described.[2,5,18–21,25,26,29,30] The remaining seven trials were regarded as risk of selection bias, mainly because insufficient information for random list generation and allocation concealment were not reported.[10,22–24,27,28,31] All trials were reported to be double-blind trials; however, six trials did not describe the details of approaches applied to blind participants and personnel, then regarded as unclear for risk of bias.[19,27–31] Most of the trials were viewed as low risk of bias concerning incomplete outcome data biases; nevertheless, three trials were considered as high risk of bias, for the number of patients reported after treatment was not consistent with the initial number.[5,10,31] In general, the quality assessment for all included RCTs was not very high.

50% reduction from baseline

50% reduction from baseline was reported by all RCTs. Pooled estimates suggested that patients treated with levetiracetam had substantial higher responder rate than those with placebo (RR =2.17, 95% CI 1.93–2.43, $P<0.05$), and heterogeneity test showed that there was no significant different (I^2=12.9%, P=0.28). Subgroup analysis based on dosage showed that pooled estimates from five trials at 2,000 mg/day possessed the optimal efficacy of the responders (RR =2.68, 95% CI 1.99–3.61),[2,5,19,21,27] and for other dosages of 1,000, 3,000, and 60 mg/kg/day, they had comparable efficacy (RR =2.00 with 95% CI 1.56–2.57; RR =2.18 with 95% CI 1.84–2.58; and RR =2.00 with 95% CI 1.50–2.67, respectively). Moreover, results suggested that regarding these four dosages, levetiracetam had a considerable advantage over placebo ($P<0.05$). One trial involved a dosage of 500 mg/day and one involved 4,000 mg/day, and the results suggested that the efficacy was not as good as the other dosages (RR =1.63, 95% CI 0.72–3.68, P=0.24 and RR =1.64, 95% CI 0.59–4.57, P=0.34). Subgroup analysis based on age (<16 years vs >16 years) showed that adult patients treated with levetiracetam had a slightly better efficacy of responder rate than children (RR =2.08, 95% CI 1.83–2.34 and RR =1.94, 95% CI 1.46–2.57). Subgroup analysis according to epilepsy type (generalized vs partial) showed that levetiracetam had a better efficacy of responder rate in patients with partial epilepsy (for partial-onset, RR =2.14, and for generalized epilepsy, RR =1.75). However, there was no statistically significant difference between them (P=0.14). Figure 3 presents the details of responder rate based on dosage.

Seizure freedom from baseline

All RCTs reported details regarding seizure freedom within the treatment period, and pooled estimates demonstrated that levetiracetam behaved considerably better than placebo overall (RR =4.68, 95% CI 3.19–6.85). According to subgroup analysis, dosage of 1,000 mg/day had the best efficacy compared to placebo (RR =5.84, 95% CI 2.28–14.97, $P<0.05$), followed by the dosages of 2,000, 3,000, and 60 mg/kg/day with minute difference among these three doses (RR =4.55, 95% CI 1.75–11.87; RR =4.57, 95% CI 2.50–8.35;

Table 1 Demographic characteristics of included trials

Study	Country	Year	Type	Age, years (mean ± SD, range)	Gender (M/F)	Number (LEV/PBO)	Dosage (mg/day, maximum)	Concomitant AEDs	Follow-up (weeks)
Wu et al[24]	China	2009	Partial	32.8±11.9 32.7±13.4	105/97	102/100	3,000	CBZ/VPA/TPM/GBP/PHT	16
Tsai et al[21]	Taiwan	2006	Partial	32.8±10.5 31.7±8.2	42/52	47/47	2,000	CBZ/LTG/VGB/VPA/TPM	18
Shorvon[2]	Multicenter	2000	Partial	37±11 (16–69)	157/167	106/106/112	1,000/2,000	CBZ/PHT/VPA/VGB/LTG	28
Peltola et al[18]	Multicenter	2009	Partial	33.97±13.4 32.38±12.6	99/59	79/79	1,000	NR	12
Inoue et al[27]	Japan	2015	Partial	32.9±11.2	171/180	71/70/70/70/70	500/1,000/2,000/3,000	NR	16
Cereghino et al[20]	USA	2000	Partial	38±11	178/116	98/101/95	1,000/3,000	CBZ/PHT/GBP/VPA/PB	18
Berkovic et al[30]	Multicenter	2007	Generalized	26.9±11.2/30.6±12.1	73/91	80/84	3,000*	VPA/LTG/CBZ/TPM/PHT	24
Piña-Garza et al[10]	USA	2009	Partial	1 month to 4 years	57/59	60/56	50 mg/kg/day	VPA/PB/TPM/OXC/VGB	7 days
Levisohn et al[28]	USA	2009	Partial	10.6±3.5 10.3±3.7	56/42	64/34 46/27	60 mg/kg/day	OXC/LTG/VPA/CBZ/TPM	18
Zheng et al[31]	China	2009	Partial	16–65	NR	18/9	3,000	NR	16
Glauser et al[26]	North America	2006	Partial	10.4 (4–17) 9.7 (3–17)	100/98	101/97	60 mg/kg/day	CBZ/TPM/VPA/LTG/OXC	14
Betts et al[5]	UK	2000	Partial	39±13/40±12 35±12	73/46	42/38/39	2,000/4,000	NR	24
Ben-Menachem and Falter[25]	Sweden	2000	Partial	36±12	137/149	181/105	3,000	NR	16
Boon et al[19]	Europe	2002	Partial	37±11	157/167	324	1,000/2,000	NR	16
Xiao et al[22]	China	2009	Partial	32.8±11.2 32.5±11.2	24/32	28/28	3,000	TPM/CBZ/VPA/GBP	16
Noachtar et al[29]	Multicenter	2008	Generalized	25.0±7.4/26.8±9.5	44/77	61/60	3,000	VPA/LTG/PB/TPM/CBZ	16
Zhou et al[23]	China	2008	Partial	28.2±11.1 31.3±9.8	13/11	13/11	3,000	NR	16

Note: *For patients <16 years of age, the dosage was 60 mg/kg/day.

Abbreviations: NR, not reported; M, male; F, female; LEV, levetiracetam; PBO, placebo; CBZ, carbamazepine; GBP, gabapentin; TPM, topiramate; PHT, phenytoin; PB, phenobarbital; VGB, vigabatrin; VPA, valproic acid; LTG, lamotrigine; OXC, oxcarbazepine.

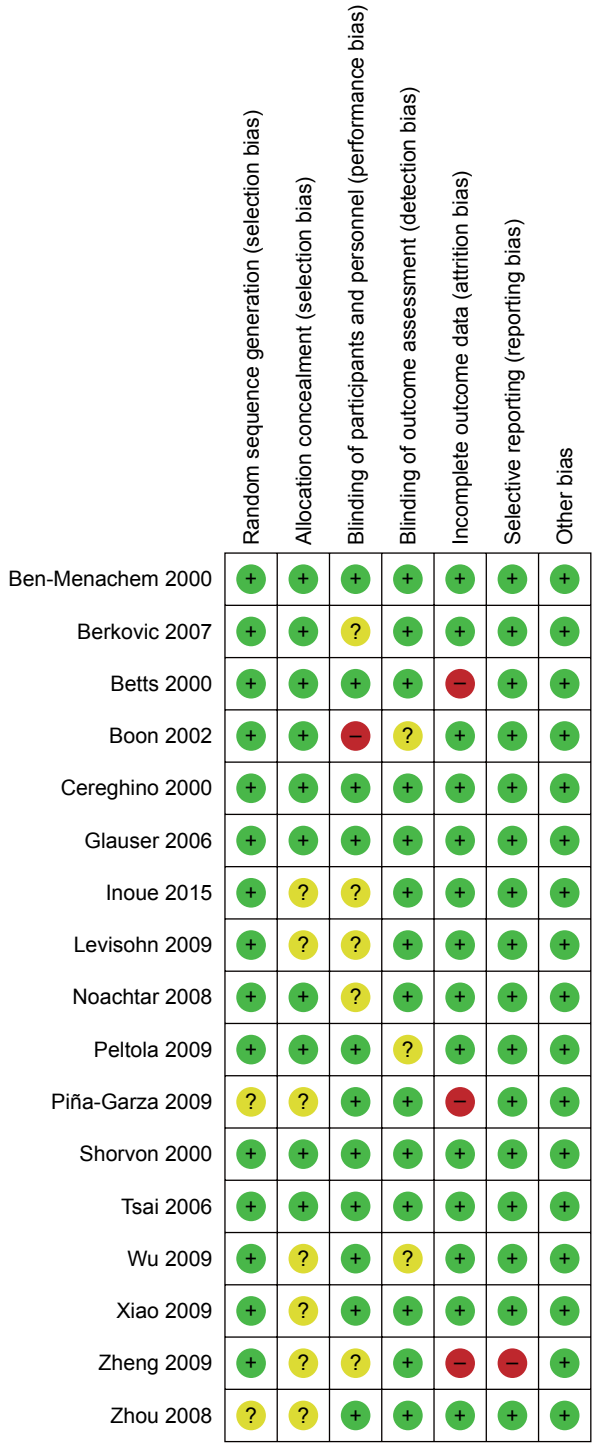

Figure 2 Risk of bias summary.
Notes: +, low; −, high; ?, unclear.

and RR =4.52, 95% CI 2.09–9.77, respectively). For all of the four dosages, levetiracetam behaved substantially better than placebo ($P<0.05$). However, on the other hand, at a dose of 4,000 mg/day, a RR value of 2.05 (95% CI 0.19–21.71) suggested that the efficacy was not substantial ($P=0.55$). Subgroup analysis showed that there was no statistically significant difference between groups of age, with RR =4.14 for adulthood (95% CI 2.65–6.48) and RR =4.31 for children (95% CI 1.99–9.32). Heterogeneity test suggested that there was no significant difference ($P=0.93$) across trials. Analysis according to epilepsy type suggested that compared to refractory generalized epilepsy, refractory partial-onset seizures had a better seizure freedom rate (RR =3.11 vs RR =4.44); however, the difference was not significant ($P=0.5$). Figure 4 shows the details of seizure freedom from baseline compared to placebo.

75% reduction from baseline

Besides responder and seizure freedom rates, eight trials reported >75% reduction from baseline,[2,18–23,31] and all of them involved patients of adulthood, with dosage of 1,000, 2,000, and 3,000 mg/day. Overall pooled estimates showed that for 75% reduction from baseline, levetiracetam had a substantial advantage over placebo (RR =4.45, 95% CI 3.16–6.26, $P<0.05$). Subgroup analysis based on dosage showed that 2,000 and 3,000 mg had comparable efficacy, calculated RRs were 5.87 (95% CI 3.15–10.94) and 5.33 (95% CI 2.37–6.26), respectively. However, heterogeneity test in 3,000 mg group showed higher inconsistency ($I^2=52.2\%$, $P=0.10$) than 2,000 mg/day group ($I^2=0.0\%$, $P=0.67$), but it did not reach statistical significance. At a dosage of 1,000 mg/day, even though levetiracetam performed inferior to 2,000 and 3,000 mg/day, it is still significantly better than placebo (RR =3.37, 95% CI 2.08–5.44, $P<0.05$). Details are presented in Figure 5.

SAE and side effects leading to withdrawal

Almost all studies reported SAEs and withdrawals induced by interventions. As for SAEs, regardless of age and dosage, pooled estimates of RR =0.87 (95% CI 0.67–1.11, $P=0.37$) suggested that there was no statistically significant difference between levetiracetam and placebo, and heterogeneity test of $P=0.56$ showed there was no significant heterogeneity was observed across included trials. Our subgroup analysis suggested that there was no statistically significant difference among dosages excepted at 4,000 mg/day, in which RR =0.21 (95% CI 0.03–1.68, $P=0.14$). Subgroup analysis based on age showed no statistically significant difference between children (RR =0.86, 95% CI 0.36–2.05) and adults (RR =0.89, 95% CI 0.66–1.15), with $P=0.95$. Analysis according to epilepsy type showed that for partial-onset, RR =0.90 (95% CI 0.68–1.17), and for generalized epilepsy, RR =0.72 (95% CI 0.24–2.19), and difference between them was not significant ($P=0.71$). Details of SAEs are demonstrated in Figure 6.

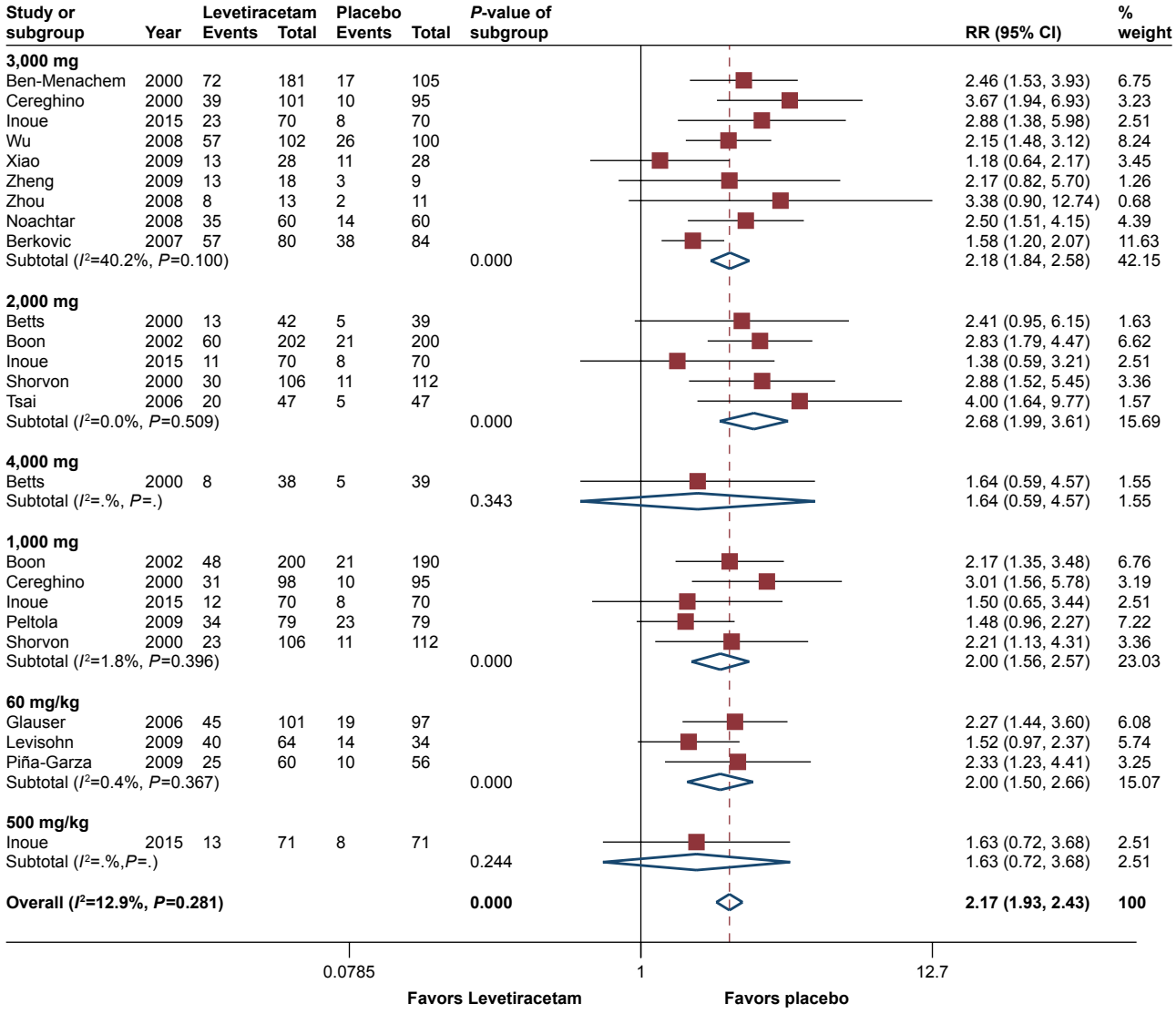

Figure 3 Forest plot of seizure frequency reduction >50% from baseline, levetiracetam vs placebo.
Abbreviation: RR, risk ratio.

Regarding premature withdrawal, the situation was a little different. The pooled estimates of RR =1.34 (95% CI 1.05–1.71, *P*=0.02) indicated that discontinuation occurred in patients with levetiracetam and was substantially more common than placebo. Subgroup analysis showed dosages of 1,000, 3,000, and 60 mg/kg/day had comparable RRs, and there was no statistically significant difference between levetiracetam and placebo (Figure 7). However, for the dosage of 2,000 mg/day, calculated RR reached 1.92 (95% CI 1.28–2.90), and a *P*-value of 0.002 showed that withdrawal was significantly more common in patients treated with levetiracetam. Since 2,000 mg/day was the significant factor affected the heterogeneity, it could also explain the discrepancy between children and adults, and the subgroup analysis according to age show that RR for children was 0.89 (95% CI 0.39–2.00, *P*=0.77), and for adults, it was 1.39 (95% CI 1.07–1.81, *P*=0.01).

Most common AEs

Eleven AEs were reported by more than four studies, as demonstrated in Table 2. The most common side effect was somnolence, reported by 13 studies, including all the three trials related to children; RR =1.67 (95% CI 1.37–2.04) and $P<0.05$ suggested that the occurrence of this side effect was significantly higher in patients treated with levetiracetam. Subgroup analysis based on dosage showed that incidences in dosages of 1,000, 2,000, and 60 mg/kg/day were significantly more common in levetiracetam ($P<0.05$). With regard to age, the analysis suggested that there was no statistically significant difference (*P*=0.31) between children and adults

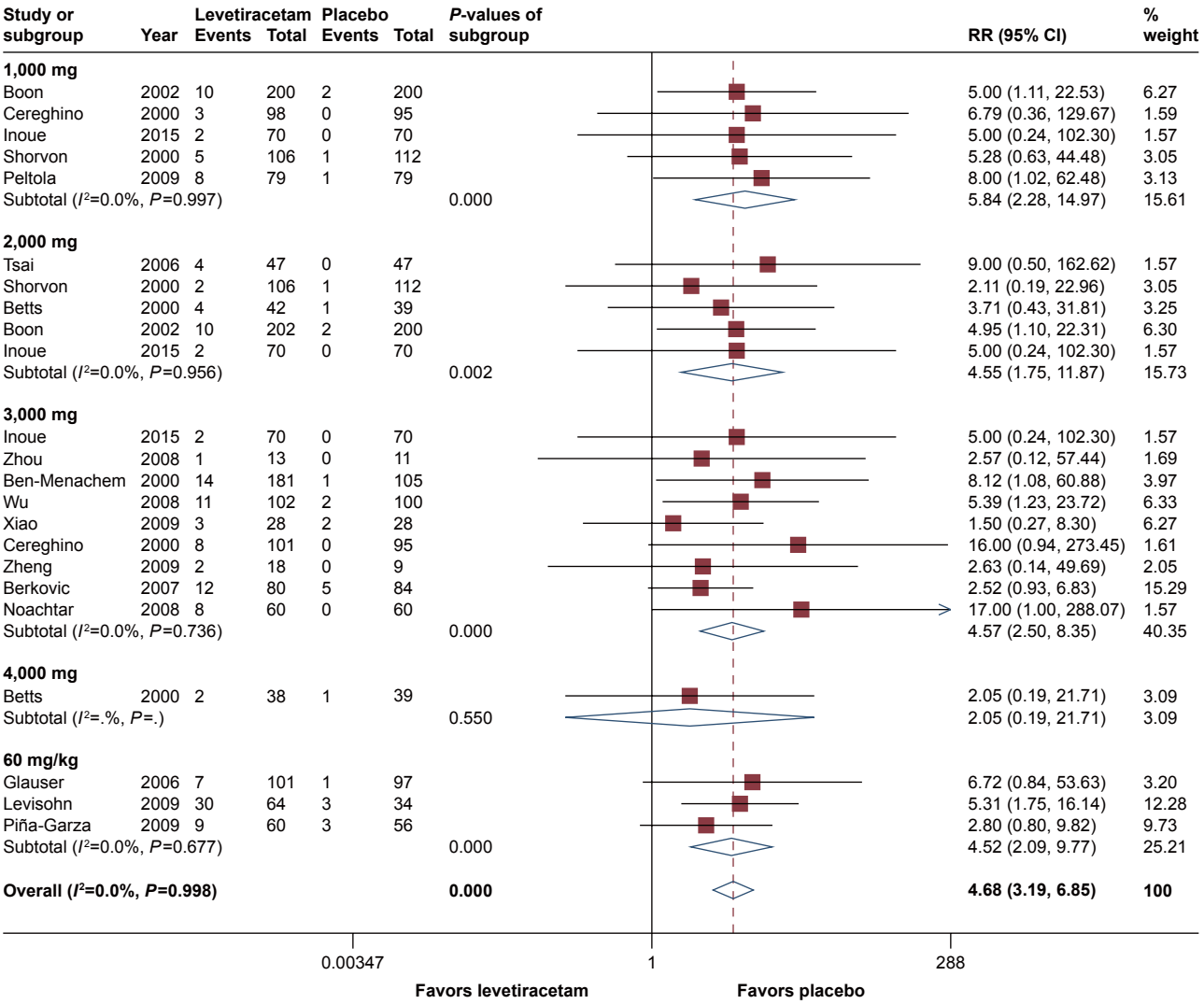

Figure 4 Forest plot of seizure freedom from baseline, levetiracetam vs placebo.
Abbreviation: RR, risk ratio.

for this AE, even though children had a higher occurrence of AE than adults (RR =2.11 vs RR =1.54). Asthenia (fatigue) was also more frequent in patients with levetiracetam, and calculated RR =1.38 (95% CI 1.05–1.81, P=0.02) suggested that the statistical difference between levetiracetam and placebo was significant. Subgroup analysis according to dosage suggested that 2,000 mg/day was the most effective dose (RR =1.80); however, the occurrence of AE in levetiracetam group was not significantly higher than in placebo group (P=0.05). Analysis based on age showed that this AE was more common in children (RR =1.74) than in adulthood (RR =1.41), but the differences between them did not reach statistical significance (P=0.05). Another side effect that was widely reported was dizziness (RR =1.50, 95% CI 1.13–2.00, $P<0.05$). Subgroup analysis suggested that dosage of 1,000 and 2,000 mg/day had the highest occurrence (RR =1.72 and 1.66, respectively); however, none of them reached statistically significant difference (P=0.09 and P=0.10, respectively) compared to placebo. With respect to infection, pooled estimates of RR was 1.56 (95% CI 1.16–2.10, $P<0.05$) which suggested that there was significant difference between levetiracetam and placebo, and the results from subgroup analysis showed that this side effect was more common for 1,000 mg/day (RR =1.94, $P<0.05$) and 3,000 mg/day (RR =2.05, $P<0.05$). Nasopharyngitis was also a widely reported AE, by nine trials, and RR values through dosages ranged from 1.07 (2,000 mg/day) to 1.62 (3,000 mg/day). Though there was no single dosage substantially higher than placebo, pooled estimates of RR =1.37 (95% CI 1.07–1.77, $P<0.05$) suggested that occurrence of AE in levetiracetam group was significantly more common. Another AE of nausea was described by seven trials; nevertheless, pooled

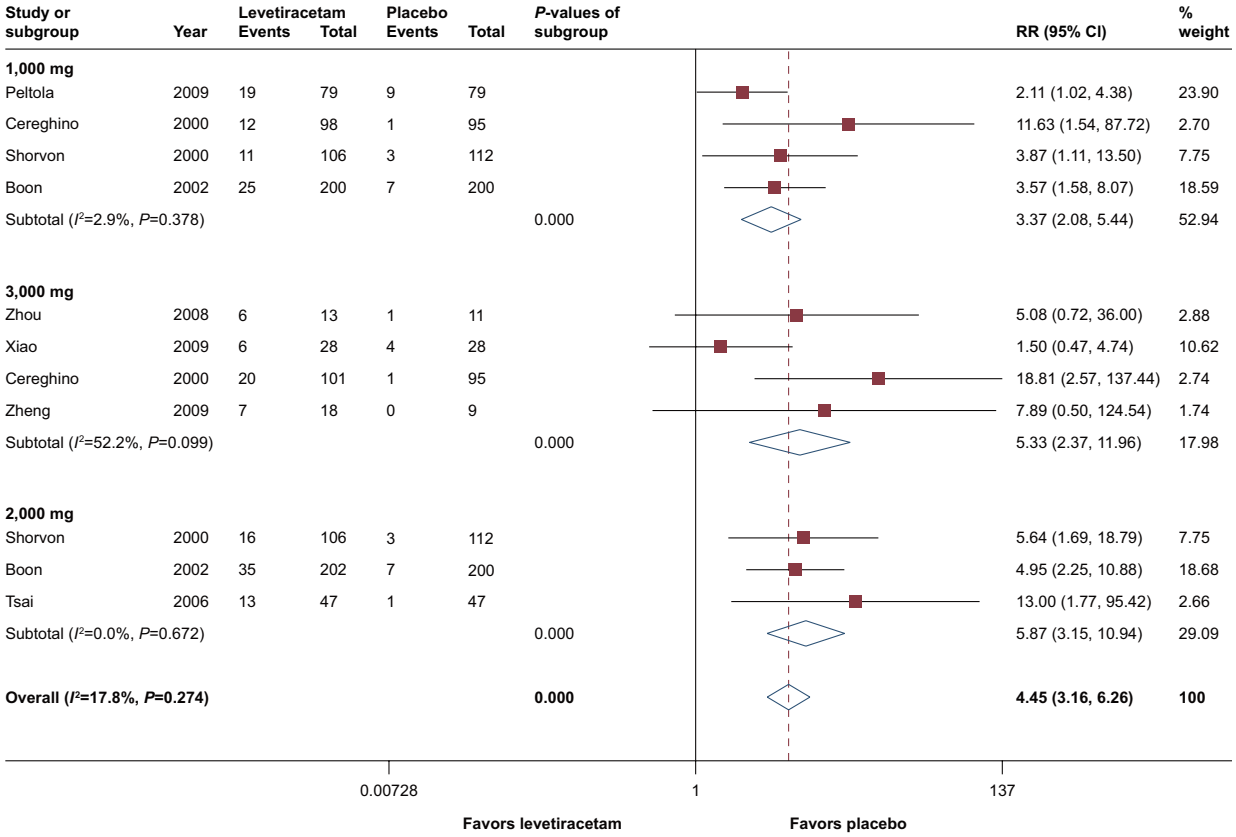

Figure 5 Forest plot of seizure frequency reduction >75% from baseline, levetiracetam vs placebo.
Abbreviation: RR, risk ratio.

estimates of RR =1.09 (95% CI 0.72–1.63, *P*=0.7) suggested that there was no significant difference between levetiracetam and placebo.

QoL

Apart from efficacy and safety profile, four trials used the 31-item QoL in epilepsy questionnaire[34] to evaluate the improvement of the QoL.[20,23,29,30] Cereghino et al found that for the overall health-related QoL, there was no significant improvement; however, concerning three of seven items of seizure worry, cognitive functioning, and overall QoL, the effect was obvious.[20] Berkovic et al reported in terms of total score; 38.3% of patients treated with levetiracetam had obvious improvement in overall QoL since the start of the study, by contrast, only 28.6% of patients with placebo showed improvement.[30] In the trial of Noachtar et al, except for the social functioning, all of the other subscale scores were higher in the levetiracetam group than in the placebo group.[29] Zhou et al also reported that patients benefited from levetiracetam with regard to QoL according to their study.[23] Levisohn et al explored the cognitive effect by using the Leiter International Performance Scale-revised attention and memory (Leiter-R AM),[35] Wide Range Assessment of Memory and Learning (second edition, WRAML-2),[36] and neither Leiter-R AM nor WRAML-2 showed statistically significant differences between the levetiracetam and placebo groups in changes from baseline to the end of the evaluation period in any of the index scores.[28]

Publication bias

Publication bias evaluation revealed that there was no potential bias across included studies, with Egger's test of *P*=0.81 and Begg's test of *P*=0.6.

Discussion

In this meta-analysis, we explored the efficacy, tolerability, and safety profile of levetiracetam based on 17 RCTs. Pooled estimates suggested that levetiracetam had a favorable efficacy for 50%, 75%, and 100% seizure reduction from baseline. For 50% reduction from baseline, dosages of 60 mg/kg/day, 1,000, 2,000, and 3,000 mg/day performed substantially better than placebo; furthermore, the difference was statistically significant. Four trials reported responder rate among levetiracetam group to be substantially higher at

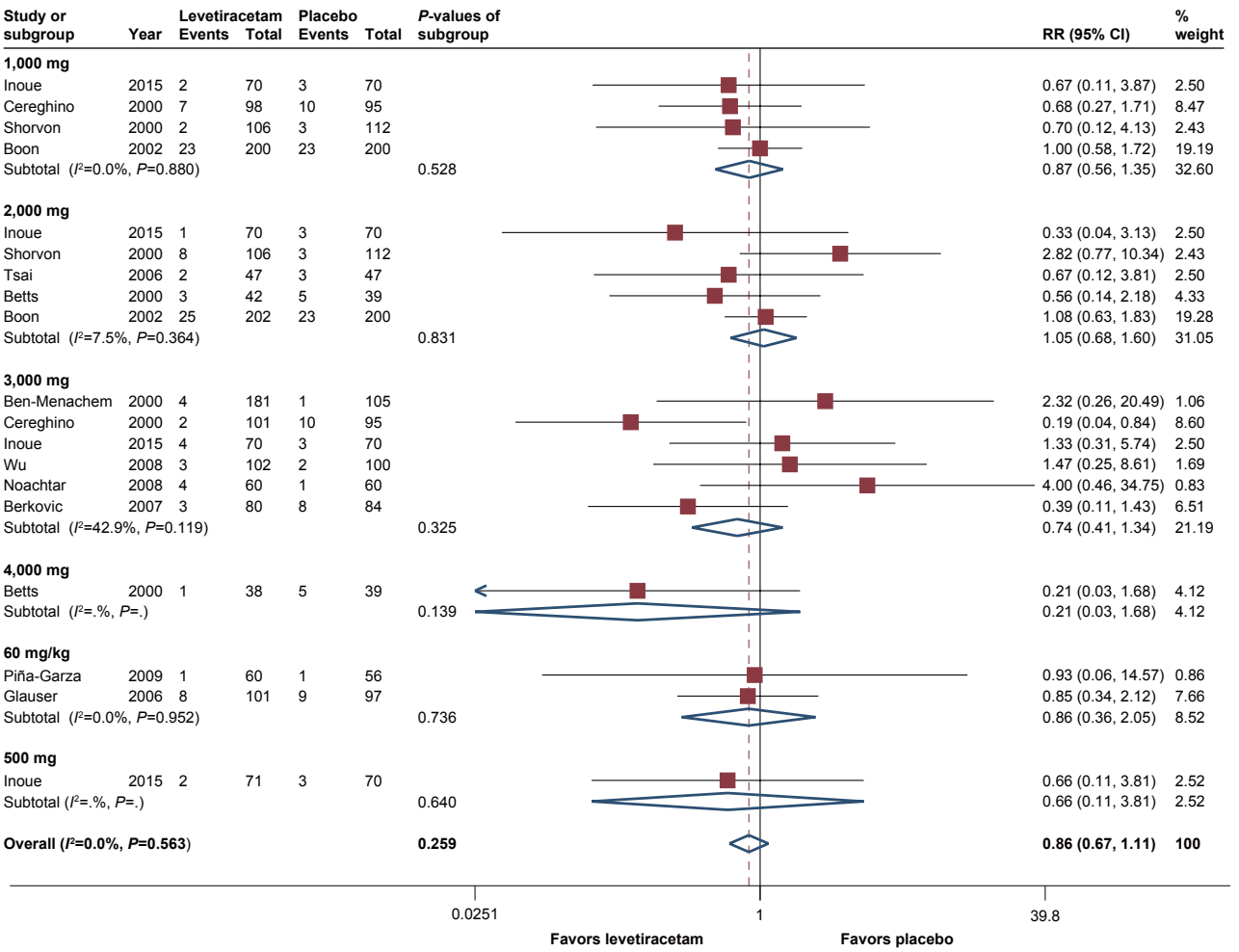

Figure 6 Forest plot of serious adverse events, levetiracetam vs placebo.
Abbreviation: RR, risk ratio.

1,000 mg/day,[2,18–20] while only one trial reported no statistically significant difference when compared to placebo.[27] As for dosage of 3,000 mg/day, more than half RCTs reported significant improvement in patients treated with levetiracetam,[20,24,25,27] whereas only two trials observed no significant difference between levetiracetam and placebo.[22,31] Regarding efficacy among children, two of three trials described favorable responder rate at a dose of 60 mg/kg/day, which was equivalent to 3,000 mg/day for adults.[10,26] According to our analysis, it seemed 1,000 mg/day was the optimal dosage for responder rate in most RCTs. In trial conducted by Boon et al, however, patients treated with 2,000 mg/day had significantly greater responder rate than those treated with 1,000 mg/day (P=0.018).[19] For seizure freedom rate, patients treated with levetiracetam at 60 mg/kg/day, 1,000, 2,000, and 3,000 mg/day performed significantly better than with placebo, and there were three of six trials at 3,000 mg/day[20,24,25] and one of three trials[28] involving children observed that levetiracetam had significant greater seizure freedom rate.

As for the adverse profile, it seemed that somnolence, asthenia, dizziness, infection, nasopharyngitis, anxiety, and irritability were more common in patients treated with levetiracetam and significantly higher than patients with placebo. However, according to the description of studies, most of these AEs were mild or moderate and did not affect the treatment. Regarding the other six side effects reported by more than three trials of abdominal pain, accident injury, headache, flu syndrome, rash, and diarrhea, results from our analysis suggested that they were more common among patients with placebo than levetiracetam. In most studies, SAE was any AE that was fatal, life-threatening, or permanently or severely disabling or incapacitating, which resulted in prolonged hospitalization. SAEs were not substantially higher in patients treated with levetiracetam, in fact it was even lower (RR =0.87), and subgroup analysis suggested

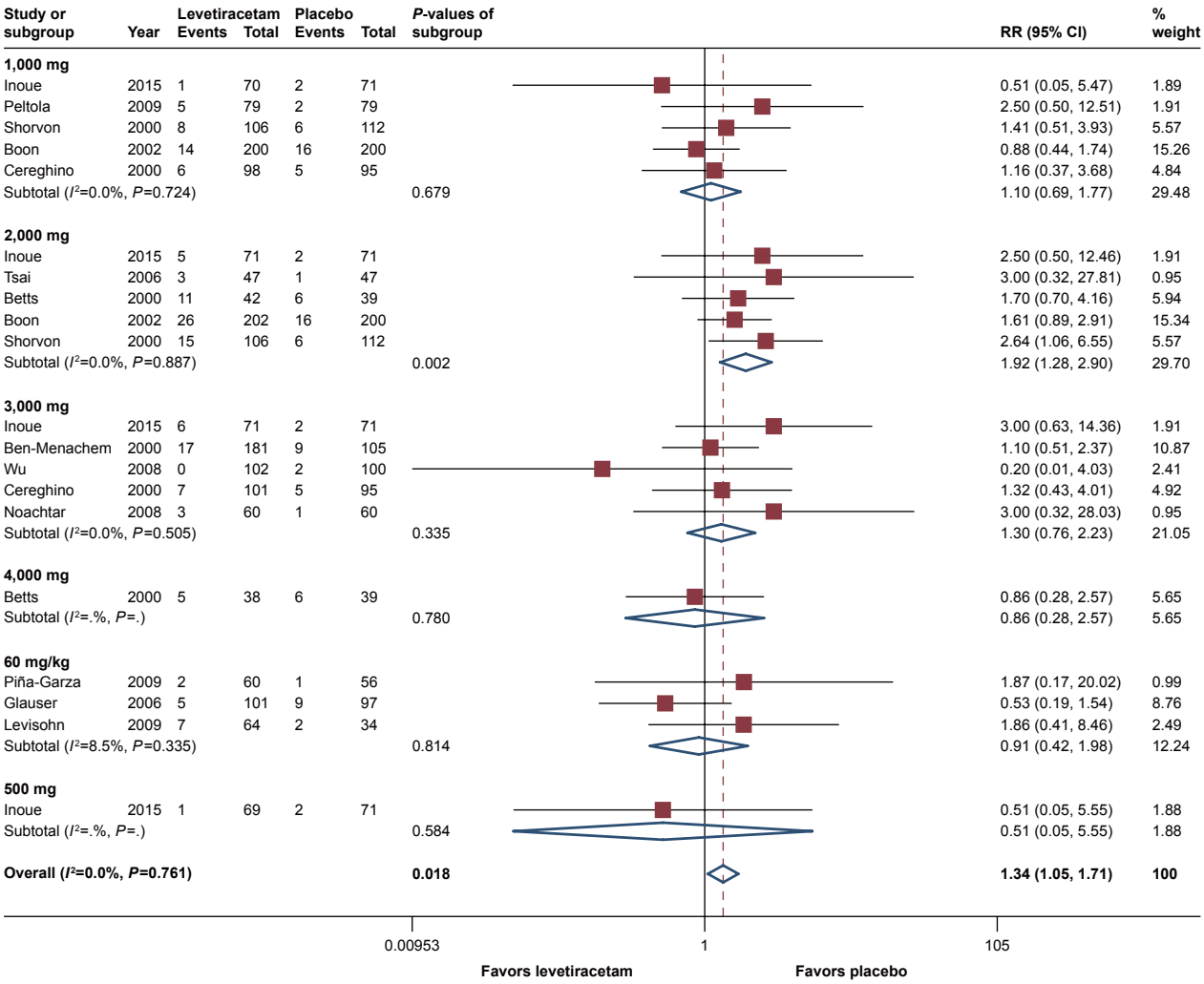

Figure 7 Forest plot of premature discontinuations, levetiracetam vs placebo.
Abbreviation: RR, risk ratio.

Table 2 Most common adverse events reported among included RCTs

System	Adverse event	Events		RR	95% CI	*P*-value
		Levetiracetam	Placebo			
Behavioral	Anxiety	13	1	5.79	1.33–25.13	0.019
	Irritability	17	2	6.09	1.80–20.64	0.004
Nervous	Dizziness	110	70	1.50	1.13–2.00	0.005
	Headache	137	149	0.85	0.69–1.06	0.142
	Somnolence	228	130	1.67	1.37–2.04	0.000
Gastrointestinal	Diarrhea	31	42	0.73	0.47–1.13	0.159
	Nausea	47	40	1.09	0.72–1.63	0.695
Others	Flu syndrome	31	39	0.80	0.50–1.21	0.332
	Abdominal pain	29	37	0.68	0.42–6.51	0.119
	Infection	103	57	1.56	1.16–2.10	0.004
	Accident injury	77	100	0.74	0.56–0.96	0.026
	Asthenia	123	79	1.38	1.05–1.81	0.02
Respiratory	Nasopharyngitis	130	90	1.37	1.07–1.77	0.013
Skin	Rash	6	5	0.89	0.29–2.71	0.841

Abbreviations: RR, risk ratio; RCT, randomized controlled trial.

that the results were comparable through different dosages. Withdrawal induced by AEs was significantly higher in levetiracetam (RR =1.92, $P<0.05$), and subgroup analysis showed that except 2,000 mg/day, for all of the other dosages, there was no statistically significant difference between levetiracetam and placebo. Some studies reported that compared to adults, children are prone to suffer from behavioral side effects such as aggression hostility and nervousness;[11,32,33] however, because only two trials involved children (the other involved children <4 years, and lasted a period of 7 days; it was difficult to observe behavior-related side effects), we did not perform comparison between children and adults.

Regarding QoL, different measurements used across studies made it difficult to combine the data and to perform a meta-analysis. However, according to studies, it seemed that levetiracetam has some positive effects on QoL, but it is difficult to be sure of the real-life impact of these changes; thus, these conclusions remain to be validated in future.

Two meta-analyses on levetiracetam for refractory partial-onset seizures were published earlier. One by Mbizvo et al included 11 RCTs,[32] in which comprised nine for adults and two for children and subgroup analyses were performed based on dosage. The difference between the present meta-analysis and theirs was that we analyzed the 75% and 100% reduction from baseline, after all, the goal of treatment for epilepsy is to achieve seizure freedom. Another difference was that other than the most common side effects and premature discontinuations that were reported, we analyzed SAEs. Besides, our meta-analysis included more trials than previous studies. In summary, our analyses revealed that levetiracetam was an effective anti-epileptic drug, and significantly superior to placebo regarding responder rate at 1000, 2000, and 3000 mg/day for adults and 60 mg/day for children, this was consistent with two earlier meta-analyses. Mbizvo et al found that doses of 2,000 and 4,000 mg/day levetiracetam had higher withdrawal rates,[32] and our analysis suggested that at 2,000 mg/day, levetiracetam had statistically significant higher dropout rate than placebo. Another meta-analysis by Costa et al involved levetiracetam for the treatment of refractory partial-onset seizures,[37] which primarily concentrated on comparison among several AEDs, and not only involved levetiracetam. Moreover, they did not provide subgroup analyses as well as detailed description regarding adverse events.

Limitations

Several limitations existed in the current meta-analysis. First, there were only three trials that involved children and one of them had a study period of only 7 days; hence, the results for children should be regarded with caution. Second, for the treatment of refractory generalized epilepsy, only two trials were included in this meta-analysis, and the results of analyses and comparison were susceptible to one of them. Third, several trials reported detailed efficacy for subtypes, but owing to insufficient data, it was difficult to perform analysis or comparison. Finally, all the included trials were placebo-controlled, thus our meta-analysis lacked comparison with other AEDs.

Conclusion

In summary, findings from the current meta-analysis suggested that levetiracetam at 1,000–3,000 mg/day (for children 60 mg/kg/day) is an effective AED for patients with refractory partial or generalized epilepsy, even in very young children. Moreover, levetiracetam has a favorable safety profile, and most of the AEs are mild or moderate. However, it seems that levetiracetam has a limited improvement in patients' QoL.

Disclosure

The authors report no conflicts of interest in this work.

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JPPT | Clinical Investigation

Early Post-traumatic Seizure Occurrence in Pediatric Patients Receiving Levetiracetam Prophylaxis With Severe Traumatic Brain Injury

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OBJECTIVE Although levetiracetam is used for the prevention of early Post-traumatic seizures (EPTS) after traumatic brain injury (TBI), limited data exist describing the incidence of seizures in pediatric patients receiving levetiracetam prophylaxis. The objective of this research is to evaluate the prevalence of EPTS in children given prophylactic levetiracetam after severe TBI.

METHODS This study was conducted at a Level 1 pediatric trauma center and included pediatric patients with severe TBI who received levetiracetam for EPTS prophylaxis. Demographics and clinical information were retrospectively collected and evaluated. The primary outcome was prevalence of clinical or electrographic seizures within 7 days of initial injury as noted in the EMR.

RESULTS In 4 of 44 patients (9%), seizures developed despite levetiracetam prophylaxis. Concurrent use of other medications with antiepileptic properties was common (91%). There were no differences in demographic or baseline clinical characteristics between the group of patients experiencing seizures and those who did not. However, craniotomy was significantly more common in the seizure group (75% vs. 18%, p = 0.03).

CONCLUSIONS Children receiving prophylaxis with levetiracetam after severe TBI had a lower incidence of seizures (9%) than had previously been reported in the literature (18%). Given the limited literature available supporting the use of levetiracetam for the prevention of EPTS in children experiencing severe TBI, further study is needed to support routine use.

ABBREVIATIONS EEG, electroencephalogram; EMR, electronic medical record; EPTS, early post-traumatic seizures; FDA, US Food and Drug Administration; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IV, intravenous; PICU, pediatric intensive care unit; TBI, traumatic brain injury

KEYWORDS anticonvulsants; head injury; levetiracetam; pediatrics; prophylaxis; seizures; traumatic brain injury

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Introduction

The incidence of traumatic brain injury (TBI) has steadily increased in the United States over the last decade and remains a major cause of morbidity and mortality among pediatric patients. Just under half a million children younger than 15 years of age are evaluated annually in the emergency department for TBI.[1] There are a number of mechanisms of injury associated with TBI that can be particularly problematic in the developing pediatric patient. Early post-traumatic seizures (EPTS) occurring after TBI have the ability to perpetuate ongoing neurological damage and affect the long-term quality of life and developmental outcomes of pediatric patients.[2,3]

Due to the potential lasting sequelae from EPTS, some institutions have begun using antiepileptic therapy prophylactically for prevention of EPTS. However, due to lack of data and ambiguous recommendations in the guidelines, practice is highly variable.[4] Historically, prophylactic phenytoin has been used for the prevention of EPTS after TBI. A large randomized controlled trial in adult patients with TBI support its use.[5] The second edition of the pediatric TBI guidelines published in 2012 included a level III recommendation that phenytoin specifically be considered for the prevention of EPTS.[4] In a retrospective study, children with severe TBI who received prophylactic phenytoin had a 15% prevalence of EPTS compared with 53% in children who received no antiepileptic medications.[6] Additionally, a more recent study found antiepileptic drugs, including phenytoin, fosphenytoin, and phenobarbital, protective against EPTS.[7] However, because of many adverse effects, a narrow therapeutic index, and highly variable

pharmacokinetic properties in critically ill children, many institutions avoid phenytoin use.[8]

In 2006, levetiracetam was FDA approved as an IV antiepileptic agent with less documented adverse effects when compared with older antiepileptic agents like phenytoin.[9] Additionally, no significant drug interactions have been reported, and it does not cause enzymatic induction or inhibition. Consequently, in both pediatric and adult populations, there has been an increase in the use of levetiracetam in place of phenytoin for the prevention of EPTS.[10–12] Despite this general shift in practice, there are sparse data examining the efficacy of levetiracetam for this indication in the pediatric population. The updated third edition of the guidelines for the management of severe TBI published in 2019 continue to recommend EPTS prophylaxis but no longer specifically recommend phenytoin. There was also a statement added to the guidelines stating that levetiracetam could not be recommended over phenytoin based on either efficacy or toxicity.[7,13–15]

To date, there has been 1 prospective study examining the incidence of EPTS in patients who received prophylaxis with levetiracetam after TBI. A group of 34 pediatric patients with moderate to severe TBI were evaluated; 6 patients experienced EPTS despite levetiracetam prophylaxis, resulting in a seizure incidence of 17.6%.[14] Based on historically reported lower seizure incidence in patients receiving phenytoin prophylaxis (2%–15%) compared with their described incidence with levetiracetam prophylaxis, the authors concluded that levetiracetam may not be an equally efficacious agent when compared with phenytoin for the prevention of EPTS after TBI.

Despite this concern, levetiracetam continues to be used in clinical practice. Based on the gap between current literature and clinical practice, there is the need for further evaluation of levetiracetam for the prevention of EPTS. To address limitations of previous studies, mainly the inclusion of multiple injury severities, we conducted a retrospective study in which the primary objective was to report the incidence of EPTS in pediatric patients given prophylactic levetiracetam after severe TBI.

Materials and Methods

A retrospective study was conducted at St. Louis Children's Hospital in St. Louis, MO, a pediatric Level 1 trauma center. Patients admitted to the PICU with severe TBI from October 2006 to August 2017 and receiving levetiracetam for EPTS prophylaxis were identified from an internal Virtual PICU Systems database with subsequent chart reviews conducted for inclusion and exclusion criteria. EPTS was defined as the occurrence of clinical or electrographic (subclinical) seizures in the first 7 days after TBI. Severe TBI was defined as an initial recorded or admission Glasgow Coma Scale (GCS) score of ≤ 8.[4,13] Initial GCS scores were defined as the first GCS score recorded in the field or upon admission to the emergency department, and admission GCS score was defined as the first GCS score recorded upon admission to the PICU. Patients were excluded if they experienced a seizure prior to the initiation of levetiracetam, if they had a history of seizures or a seizure disorder, or if they were declared brain dead or expired < 48 hours after admission.

Management of TBI was at the discretion of the medical team and was guided by the institutional TBI protocol and published pediatric TBI guidelines. Of note, continuous EEG monitoring is not a standard of care and was initiated if there was concern for subclinical seizures, if patients were receiving neuromuscular blockade, or if pentobarbital was used for intracranial pressure (ICP) management.

Demographic information including age, gender, and mechanism of injury were recorded. Clinical or electrographic seizures in the first 7 days after injury were recorded based on documentation in the EMR by an intensivist or consulting neurologist. Dosing of levetiracetam was recorded in addition to the use of other medications with antiepileptic properties (including pentobarbital, diazepam, midazolam, and lorazepam) during the 7 days after initial injury. Presence or absence of fever, defined as temperature greater than or equal to 38°C, and nadir sodium level during PICU stay was collected because of associated seizure risk. Data related to severity of injury, including the use of additional monitoring methods, hyperosmolar agents, and the need for surgical interventions, were also collected.

Statistical analysis was performed using SPSS 19 (SPSS, Inc, Chicago, IL). Descriptive statistics were used to describe the overall seizure incidence rate. Patients who experienced EPTS and those who did not were compared using Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. A p value of < 0.05 was used to define statistical significance.

Results

A total of 275 patients admitted to the PICU with TBI were identified. One-hundred fifty-two patients were excluded for an initial or admission GCS of > 8. Fifty-six patients were excluded for prior seizure activity. Twenty-three patients were excluded because they did not receive any seizure prophylaxis. Baseline demographic data of the remaining 44 patients included in the study can be found in the Table.

Seizures were noted in 4 of the 44 children who received prophylaxis with levetiracetam. One patient presented clinically and was confirmed with EEG; subclinical seizures in 3 patients were detected by continuous EEG, which was used because of the presence of a pentobarbital coma, a coma from injury, and use of

Table. Patient Demographic Data and Comparison of Clinical Information for Patients With Seizures and Without Seizures

Patient Characteristic	All Patients (N = 44)	Patients Without Seizures (n = 40)	Patients With Seizures (n = 4)	p value
Age, yr, median (IQR)	7.5 (2–12)	7.5 (2–12)	7.5 (4–12)	0.89
Sex, male, n (%)	25 (57)	24 (60)	1 (25)	0.30
GCS score				
Earliest score, median (IQR)	5 (3–7)	4.5 (3–6.8)	7.5 (4–8)	0.22
Admit score, median (IQR)	5.5 (3–6)	6 (3–6)	3 (3–7.5)	0.37
Mechanism of injury—abusive head trauma, n (%)	7 (16)	5 (13)	0 (0)	0.71
Test/procedure				
ICP monitor, n (%)	25 (57)	22 (55)	3 (75)	0.62
Continuous EEG monitor, n (%)	27 (61)	23 (58)	4 (100)	0.15
Febrile on PICU admission, n (%)	35 (80)	31 (78)	4 (100)	0.57
Nadir sodium level, median (IQR)	139 (137–142)	139 (137–141)	141 (135–144)	0.49
Management				
Craniotomy, n (%)	10 (23)	7 (18)	3 (75)	0.03
Hypertonic saline, n (%)	30 (68)	27 (68)	3 (75)	1
Mannitol, n (%)	25 (57)	22 (55)	3 (75)	0.62
Levetiracetam, mg/kg/dose	10 (5–20)*	10 (5–30)†	10 (10–12)†	0.60
Other medications with antiepileptic properties, n (%)	40 (91)	36 (90)	4 (100)	0.18
Barbiturates	3 (7)	2 (5)	1 (25)	
Benzodiazepines	27 (61)	26 (65)	1 (25)	
Barbiturate and benzodiazepine	10 (23)	8 (20)	2 (50)	
Survived, n (%)	39 (89)	36/40 (90)	3/4 (75)	0.39

* Median (IQR).
† Median (range).

a paralytic for ventilator synchrony. This resulted in an overall seizure incidence rate of 9%. Overall, 91% of the patients included had received other medications with antiepileptic properties ranging from low dose benzodiazepines for sedation to barbiturate-induced comas for refractory elevated ICP.

When comparing patients who experienced seizures to those who did not, there were no statistically significant differences found in baseline demographics (Table). There were also no significant differences in the initial or admission GCS scores or dose of levetiracetam between the groups. Continuous EEG monitoring was common and not significantly different between groups. There were significantly more craniotomies in children experiencing seizures. Notably, there was not a significant difference found between the 2 groups when the mechanism of injury was abusive head trauma. The use of other antiepileptic medications was not found to be significantly different between patients experiencing seizures and seizure-free patients.

Discussion

In our cohort, patients receiving levetiracetam after severe TBI experienced seizures at a rate of 9% despite prophylaxis. These patients were more likely to have had craniotomies and many were placed on continuous EEG monitoring, potentially alluding to clinical concern for a significant degree of brain damage. There were no significant differences in baseline demographics for patients experiencing seizures compared with patients who did not seize.

To our knowledge, this is the largest study focusing on the prevalence of seizures after severe TBI in pediatric patients receiving levetiracetam prophylaxis. A seizure incidence of 9% is lower than historically reported incidence rates for patients receiving no prophylaxis (20%–53%) and is within range for patients receiving phenytoin prophylaxis (2%–15%).[6,14] In contrast to a previous study, the seizure incidence in this cohort did not suggest that prophylaxis with levetiracetam was less efficacious than phenytoin in the prevention of

EPTS in pediatric patients with severe TBI.[14] Collectively, these data support the conclusion that levetiracetam use was associated with a lower seizure incidence when compared with patients receiving no prophylaxis historically. However, it is important to note the overall advancements in the medical management of pediatric patients with TBI when interpreting historically reported seizure incidence rates.

Given the differing seizure incidence rates reported between our cohort and the previous study, it is important to evaluate differences in the included patient populations.[14] There were no notable differences in demographic information, including median age, between the 2 populations that would serve as a possible explanation for the difference in seizure rates. The inclusion of patients with moderate TBI in the study by Chung and O'Brien[14] resulted in a higher median GCS score, which would suggest a lower potential for seizures in their cohort. The use of other medications with antiepileptic activity, including benzodiazepines and barbiturates, represents a confounding factor that must be evaluated. The use of benzodiazepines for sedation and barbiturates for refractory elevated ICP are common in the management of TBI and are both outlined in the pediatric TBI guidelines.[4,13] Although 91% of patients receiving medications with antiseizure activity is a confounding factor in evaluating the use of levetiracetam for the prevention of EPTS, the use of these medications is a standard of care and would likely be a similar finding in future or previous studies conducted in this patient population. The use of antiepileptic medications for all patients was not included in previous studies for comparison.

In both our cohort and the cohort studied by Chung and O'Brien,[14] there was a similar percentage of patients sustaining a TBI as a result of an abusive head trauma or non-accidental trauma.[14] However, in the previous study, all of the patients experiencing breakthrough EPTS also experienced TBIs as a result of abusive head traumas. This was not the case in our patient population, in which no patient experienced EPTS from a TBI with abusive head trauma as the etiology.

Differences seen in TBI patient populations regarding the incidence of EPTS may be attributed to the fact that TBI is a dynamic disease state with multiple factors affecting subsequent sequelae, including EPTS. There are several risk factors for EPTS after TBI described in the literature, including abusive head trauma as a mechanism of injury.[7] Abusive head trauma is associated with potential repetitive injury over time and there is often uncertainty surrounding the timeline of initial injury, adding difficulty to the interpretation of true EPTS in the first 7 days after injury. Therefore, variation in the timeline and frequency of abusive head trauma may be an explanation for the observed difference in seizure incidence rate in these 2 groups of pediatric patients. This observed difference highlights the importance of looking at a significant number of patients in the pediatric TBI population when assessing the efficacy of seizure prophylaxis after TBI.

There were a number of limitations in this study. Primarily, this was a small, single-center study and may not represent the pediatric TBI population as a whole. Although still small, our sample focused on severe TBI only, including more patients with severe injury than the previous study. All patients were not placed on continuous EEG monitoring because this is not a standard of care in our PICU. Although the effect of subclinical seizures on outcome after severe TBI are still being characterized, due to a lack of EEG monitoring on all patients, there is the possibility that subclinical seizures were not captured or documented in the medical record, and the actual incidence of clinically relevant seizures may be higher than reported. Ninety-one percent of patients in this study received other medications with antiseizure properties making the effect of levetiracetam specifically less clear. Finally, this study was both retrospective and observational, prohibiting prospective attention to protocol adherence. Based on the small sample size of this study and the noted limitations, further studies are needed to assess the use of levetiracetam in the prevention of EPTS after severe TBI.

Conclusions

Breakthrough EPTS occurred in 9% of pediatric patients receiving levetiracetam prophylaxis after severe TBI in our cohort. This is a lower seizure incidence than had previously been reported with this therapy. Further studies are needed to examine the use and efficacy of levetiracetam for the prevention of EPTS in children after severe TBI.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Exempted criterion.

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Critical Care

RESEARCH Open Access

Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study

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Abstract

Background: General supportive and preventive measures in the intensive care management of traumatic brain injury (TBI) aim to prevent or limit secondary brain injury and optimize recovery. The aim of this survey was to assess and quantify variation in perceptions on intensive care unit (ICU) management of patients with TBI in European neurotrauma centers.

Methods: We performed a survey as part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. We analyzed 23 questions focused on: 1) circulatory and respiratory management; 2) fever control; 3) use of corticosteroids; 4) nutrition and glucose management; and 5) seizure prophylaxis and treatment.

Results: The survey was completed predominantly by intensivists ($n = 33$, 50%) and neurosurgeons ($n = 23$, 35%) from 66 centers (97% response rate).
The most common cerebral perfusion pressure (CPP) target was > 60 mmHg ($n = 39$, 60%) and/or an individualized target ($n = 25$, 38%). To support CPP, crystalloid fluid loading ($n = 60$, 91%) was generally preferred over albumin ($n = 15$, 23%), and vasopressors ($n = 63$, 96%) over inotropes ($n = 29$, 44%). The most commonly reported target of partial pressure of carbon dioxide in arterial blood ($PaCO_2$) was 36–40 mmHg (4.8–5.3 kPa) in case of controlled intracranial pressure (ICP) < 20 mmHg ($n = 45$, 69%) and $PaCO_2$ target of 30–35 mmHg (4–4.7 kPa) in case of raised ICP ($n = 40$, 62%). Almost all respondents indicated to generally treat fever ($n = 65$, 98%) with paracetamol ($n = 61$, 92%) and/or external cooling ($n = 49$, 74%). Conventional glucose management ($n = 43$, 66%) was preferred over tight glycemic control ($n = 18$, 28%). More than half of the respondents indicated to aim for full caloric replacement within 7 days ($n = 43$, 66%) using enteral nutrition ($n = 60$, 92%). Indications for and duration of seizure prophylaxis varied, and levetiracetam was
(Continued on next page)

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mostly reported as the agent of choice for both seizure prophylaxis ($n = 32$, 49%) and treatment ($n = 40$, 61%).

Conclusions: Practice preferences vary substantially regarding general supportive and preventive measures in TBI patients at ICUs of European neurotrauma centers. These results provide an opportunity for future comparative effectiveness research, since a more evidence-based uniformity in good practices in general ICU management could have a major impact on TBI outcome.

Keywords: Intensive care unit, Traumatic brain injury, Glucose, Nutrition, Fever, Ventilation, Blood pressure, Seizure, Survey, Europe

Background

Traumatic brain injury (TBI) is one of the major causes of trauma-related death and hospital admissions in Europe [1]. TBI is recognized as a complex heterogeneous syndrome [2]. The higher vulnerability of this population is reflected by higher mortality rates in patients with TBI compared with non-head injured trauma patients [3]. Therefore, patients with (severe) TBI require specialized neurointensive care (treatment) at an intensive care unit (ICU) [4].

Case fatality rates in severe TBI are high, ranging from 30% to 40% in unselected observational series [5]. Furthermore, substantial between-country [1] and between-center differences [3, 4, 6] in overall TBI mortality rates exist which might be partly explained by differences in treatment [7–9].

The key objectives of ICU TBI management are to maintain general physiology and prevent secondary brain injury. A number of brain-specific therapies, such as intracranial pressure (ICP)-guided treatment or, less often, brain-metabolic or cerebral vascular autoregulation-based goals are employed both clinically or as the subject of clinical research [10]. However, general support of the cardiovascular system, respiratory function, and nutritional or metabolic needs must not be overlooked and could also have a significant impact on outcome [11, 12]. Cerebral metabolic control by seizure or fever management may further contribute to better outcomes [2, 13–15]. At present, optimal strategies for general management are only partly established [16, 17]. This lack of robust evidence may ultimately result in institutional or individual variations in practice that may contribute to variances in outcome.

The aim of this survey study was to assess variation in ICU management perceptions of general supportive and preventive care policies (including, for instance, circulatory and respiratory management) in patients with TBI in European neurotrauma centers.

Methods

Participating centers

This study is part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study that collects data on patient characteristics, patient management, and outcomes in 68 centers from 20 countries across Europe and Israel [18]. All these centers were asked to complete a 'Provider Profiling Questionnaire' [19]. The questionnaire items used for this study (treatment at the intensive care) are attached as Additional file 1.

Provider profiling questionnaire

The provider profiling questionnaire was developed in several stages. First, literature was explored for evidence, including guidelines and available surveys. Second, a pilot study was conducted in 16 participating centers to receive feedback, to determine ambiguity, and to detect unexpected and missing values. Throughout all stages, experts of various disciplines (neurosurgeons, intensivists, neurologists, emergency department physicians, rehabilitation physicians, medical ethicists, health care economists, and epidemiologists) were asked for their advice on the development of the questionnaire. Details on the development, administration, and content of the complete provider profiling questionnaires have been published previously [19].

General supportive and preventive management

For the purpose of the current study, we focused on 23 questions specifically aimed at general ICU policies (Additional file 1). Specifically, we focused on circulatory and respiratory management, fever control, use of corticosteroids, glucose and nutrition management, and seizure prophylaxis and treatment. Most questions were multiple-choice, except for two questions: the aim for caloric intake in TBI patients and the use of corticosteroids for other conditions. Overall, the general policy of a center rather than the individual treatment preference of the respondent was the premise for completion of the questionnaire. General policy is defined as: 'the way the large majority of patients (> 75%) with a certain indication would be treated'.

Statistical analysis

We used descriptive statistics (frequencies and percentages) to present the data. Respondents could indicate how frequently certain management strategies were used (never 0–10%, rarely 10–30%, sometimes 30–70%,

frequently 70–90%, and always 90–100%). The combined numbers of respondents that indicated 'frequently' and 'always' were interpreted as representing the general policy of a center, in line with previous reports [20, 21]. To describe center characteristics in more detail we divided centers into higher (Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, UK, and Switzerland) versus relatively lower income countries (Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania, and Serbia), based on a 2007 report by the European Commission [22]. Differences were assessed for statistical significance using the Fisher's exact test without correction for multiple comparisons. We used Statistical Package for Social Sciences (SPSS) version 21 [23] for descriptive analyses.

Results

Participating centers

Of the 68 neurotrauma centers participating in this study, 66 (97%) centers completed the questions on general supportive and preventive ICU management. The questionnaire was predominantly completed by intensivists ($n = 33$, 50%) and neurosurgeons ($n = 23$, 35%). Other professionals that assisted in completion of the questionnaire were administrative staff ($n = 11$, 17%), neurologists ($n = 5$, 8%), anesthesiologists ($n = 5$, 8%), and a trauma surgeon ($n = 1$, 2%).

The majority of centers had an academic affiliation ($n = 60$, 91%). The majority of centers were designated as level I trauma centers ($n = 45$, 69%), and a minority as level II ($n = 4$, 6%), level III ($n = 1$, 2%), or no designation ($n = 15$, 23%). More than half of the centers had a dedicated neuroICU (defined as an ICU that is equipped to treat patients with neurological or neurosurgical injury) available ($n = 39$, 59%). The majority of centers adopted a 'closed' ICU organization (the intensivist is primarily responsible for the delivery of care for patients at the ICU) ($n = 43$, 65%), followed by a 'mixed' ICU organization (the admitting physician, e.g., neurosurgeon, is primarily responsible but the care is provided by a intensivist) ($n = 20$, 30%), and a minority adopted an 'open' ICU organization (the admitting physician is primarily responsible for care at the ICU) ($n = 3$, 5%). Centers indicated to treat a median of 92 (interquartile range 52–160) patients with TBI at their ICU annually. Twenty-eight centers (42%) reported to adhere to the 2007 Brain Trauma Foundation (BTF) guidelines for the management of patients with TBI at their ICU, and 21 centers (32%) reported having institutional guidelines that were based on BTF guidelines. The center characteristics and definitions are described in more detail in a previous publication [19].

Circulatory and respiratory management

As part of circulatory management, the most frequently mentioned cerebral perfusion pressure (CPP) targets were > 60 mmHg ($n = 39$, 60%) and/or "individualized" ($n = 25$, 38%). Most centers used crystalloids ($n = 60$, 91%) and/or vasopressors ($n = 63$, 96%) for CPP support; inotropes ($n = 29$, 44%) were less frequently, but still regularly, employed. Fifteen centers (23%) reported to use albumin-containing solutions for volume expansion (Additional file 2: Table S1).

In mechanically ventilated patients with TBI, initial partial pressure of oxygen in arterial blood (PaO_2) goals of > 75 mmHg (10 kPa) ($n = 29$, 45%) and > 97.5 mmHg (13 kPa) ($n = 29$, 45%) were most commonly cited as a treatment preference, with an initial arterial oxygen saturation goal of > 95% ($n = 56$, 86%). In the absence of raised ICP, most centers indicated a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) goal of 36–40 mmHg (4.8–5.3 kPa) ($n = 45$, 69%). In the presence of raised ICP this shifted towards a lower $PaCO_2$ goal of 30–35 mmHg (4.0–4.7 kPa) ($n = 40$, 62%) (Fig. 1). The timing of tracheostomy in patients with limited or slow neurological recovery varied substantially from within 1 week ($n = 13$, 20%) to between 1 and 2 weeks ($n = 36$, 55%) and more than 2 weeks ($n = 16$, 25%) (Additional file 2: Table S1).

Relatively lower income countries more frequently adopted lower oxygen saturation goals (> 90%) compared with saturation targets > 95% which were favored by higher income countries ($n = 3/11$, 27%, versus $n = 2/55$, 4%; $p = 0.037$) (Additional file 3: Table S6).

Fever control

In patients with TBI, the majority of centers indicated that they routinely treat fever ($n = 65$, 98%). One center (2%) reported they would only treat fever "sometimes". The preferred treatments were paracetamol ($n = 61$, 92%) and/or external cooling ($n = 49$, 74%). In contrast, nonsteroidal anti-inflammatory drugs (NSAIDs) were less commonly used ($n = 29$, 44%). Intravascular cooling was also rarely used ($n = 3$, 5%) (Fig. 2) (Additional file 2: Table S2).

Relatively lower income countries significantly indicated the use of NSAIDs more often than higher income countries ($n = 11/11$, 100%, versus $n = 18/55$, 33%; $p = 0.000$). Centers in higher income countries indicated the use of paracetamol significantly more frequently compared with relatively lower income countries ($n = 53/55$, 96%, versus $n = 8/11$, 73%; $p = 0.029$). Intravascular cooling was more frequently applied in the lower income group, although this difference did not reach statistical significance (Additional file 3: Table S7).

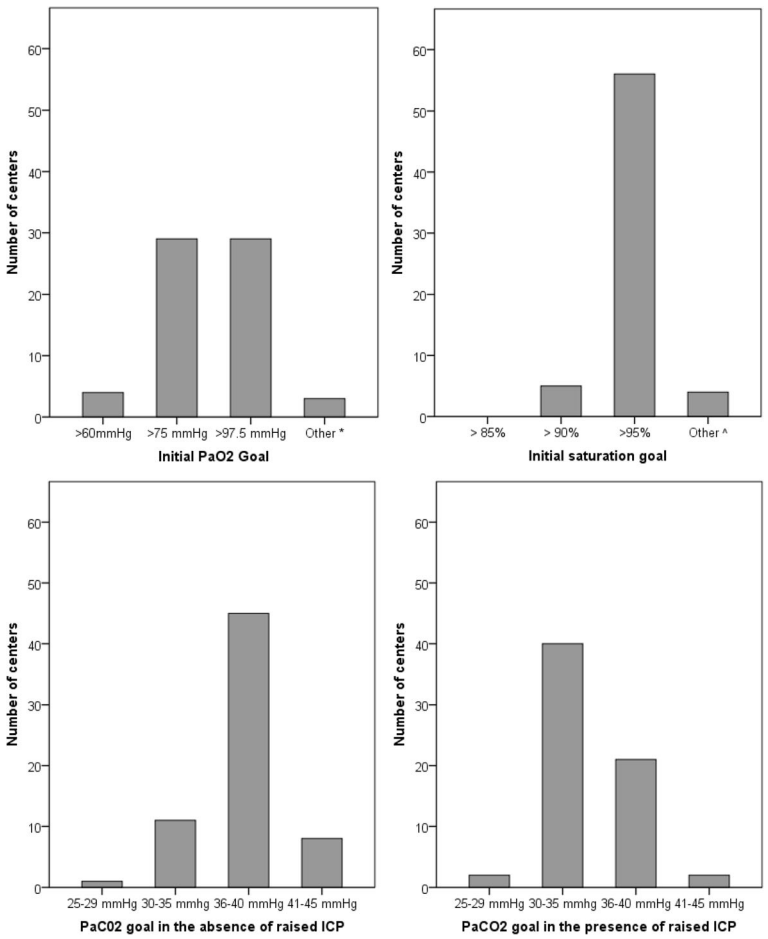

Fig. 1 Mechanical ventilation thresholds with corresponding answer frequencies; 25–29 mmHg ≈ 3.3–3.0 kPa, 30–35 mmHg ≈ 4–4.7 kPa, 36–40 mmHg ≈ 4.8–5.3 kPa, 41–45 mmHg ≈ 5.5–6 kPa, 60 mmHg = 8 kPa, 75 mmHg = 10 kPa, 100 mmHg = 13 kPa. * No specific goal ($n = 1$), > 90 mmHg ($n = 2$); ^ > 96% ($n = 2$), > 97% ($n = 1$), 92–94% ($n = 1$). PaCO2 partial pressure of carbon dioxide in arterial blood, PaO2 partial pressure of oxygen in arterial blood

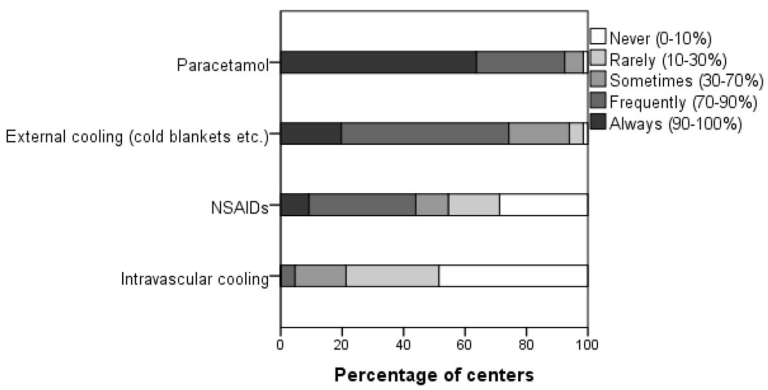

Fig. 2 Type of fever treatment and corresponding percentage of centers that indicated they use this type of fever treatment never (in 0–10% of cases), rarely (in 10–30% of cases), sometimes (in 30–70% of cases), frequently (in 70–90% of cases), or always (in 90–100% of cases). NSAID nonsteroidal anti-inflammatory drug

Use of corticosteroids

Corticosteroids were infrequently used for the primary management of brain injury, although a few respondents indicated that they used them "rarely" ($n = 5$, 8%), "sometimes" ($n = 2$, 3%), or "frequently" ($n = 1$, 2%). However, corticosteroids were specifically used for vasopressor-resistant hypotension ($n = 21$, 58%) and, to a lesser extent, sepsis ($n = 8$, 22%) (Additional file 2: Table S3).

Primary use of corticosteroids was significantly more frequently reported by lower income countries compared with higher income countries ($n = 4/11$, 36%, versus $n = 4/55$, 7%; $p = 0.023$) (Additional file 3: Table S7).

Glucose and nutrition management

The majority of centers stated that their glucose management was protocolized ($n = 50$, 77%). Most centers reported the correction of hyperglycemia as a primary aim ($n = 43$, 66%) while a smaller number implemented tight glycemic control ($n = 18$, 28%) (Additional file 2: Table S4).

Most respondents aimed for full caloric replacement within 7 days post-injury ($n = 43$, 66%). An open question on the goals for caloric intake showed a high variety in reported strategies as well as metrics used (kcal/day, kcal/kg/day, and percentages). The enteral route was preferred ($n = 60$, 92%). The timing of parenteral nutrition was highly variable: centers were equally distributed between "as soon as possible" ($n = 13$, 20%), "within 24 h post-injury" ($n = 13$, 20%), "within 72 h post-injury" ($n = 10$, 15%), "within 7 days post-injury" ($n = 17$, 26%), and "we do not have rules/guidelines for this" ($n = 12$, 19%) (Additional file 2: Table S4).

Relatively lower income countries reported using the parenteral route significantly more frequently compared with higher income countries ($n = 4/11$, 36%, versus $n = 1/55$, 2%, $p = 0.002$) (Additional file 3: Table S7).

Seizure prophylaxis and treatment

There was little consensus regarding the use of prophylactic antiepileptic drugs (for all indications). Most centers reported to use levetiracetam as the drug of choice for both seizure prophylaxis and treatment ($n = 32$, 49%, and $n = 40$, 61%), followed by phenytoin ($n = 20$, 31%, and $n = 32$, 48%) (Fig. 3). In general, both the reported duration of antiseizure prophylaxis and the criteria for initiation of antiepileptic treatment varied considerably (Additional file 2: Table S5).

The choice of agent varied with income, with levetiracetam being less commonly used for both seizure prophylaxis ($n = 0/11$ versus $n = 32/55$, 59%; $p = 0.000$) and treatment ($n = 1/11$, 9%, versus $n = 39/55$, 71%; $p = 0.000$) in the lower income group versus higher income countries, respectively. Instead, lower income countries seemed to favor valproate or phenytoin compared with higher income countries ($n = 7/11$, 64%, versus $n = 14/55$, 26%; $p = 0.029$) (Additional file 3: Table S7).

Discussion

In this survey, we found varying degrees of consensus between European neurotrauma centers with respect to general supportive and preventive ICU management in patients with TBI. Most variation was found in initial PaO_2 goals for mechanically ventilated patients, CPP

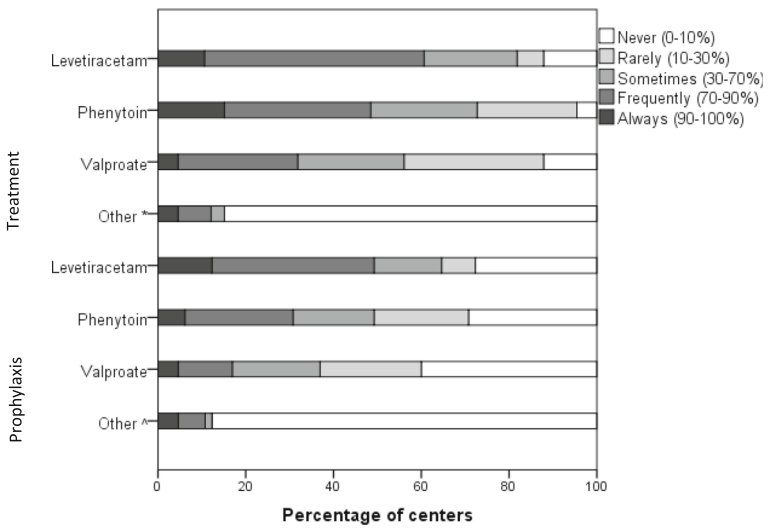

Fig. 3 Agents for seizure prophylaxis and treatment with corresponding percentage of centers that indicated that they never (in 0–10% of cases), rarely (in 10–30% of cases), sometimes (in 30–70% of cases), frequently (in 70–90% of cases), or always (in 90–100% of cases) use the agent. *Carbamazepine/phenobarbital, phenobarbital, benzodiazepines, no prophylaxis used in our hospital, carbamazepine ($n = 3$). ^Phenobarbital, benzodiazepines, carbamazepine ($n = 4$), midazolam/diazepam, lorazepam

targets, the timing of tracheostomy in unconscious patients, nutritional targets, and seizure prophylaxis and treatment.

Large between-center variation was found in topics that are not addressed in the recommendations of the BTF guidelines (Additional file 4), suggesting the role of guidelines in reducing variances in clinical practice. International guidelines (BTF guidelines and guidelines of the American College of Surgeons) do recommend the use of normalized thresholds (e.g., normoglycemia, normocapnia, and normothermia) in patients with TBI, although this is not based on high-level evidence [16, 17]. Indeed, randomized controlled trials (RCTs) on these topics are too limited in number to lead to high-level evidence [10]. Considering CPP targets, the BTF guidelines are unclear whether to use an optimum threshold of > 60 or > 70 mmHg (and a range of 50–70 mmHg in the previous BTF guidelines [24]). Despite this ambiguity, a majority of respondents (60%) preferred a target CPP of > 60 mmHg. In addition, the current BTF guidelines added that the CPP target might depend on the individual cerebral autoregulatory status, reflected by 38% of respondents who indicated to use an individualized target CPP. The uniformity in reported CPP targets between income groups also suggests that these concepts are widespread. It may be that the willingness to individualize CPP in patients with TBI reflects the growing trend for use of precision medicine [25], where therapies and therapy targets are individualized to patient need, rather than used on a "one size fits all" basis.

Marked variation was also found on topics where consensus was expected based on high-level evidence from RCTs or the recommendations in the BTF guidelines. The use of steroids for the primary management of TBI was reported by 13% of the respondents (one respondent reported frequent use), but is against the advice of the BTF guidelines and contradicts the prevailing evidence from the CRASH study [26, 27]. However, use in the majority of centers was for vasopressor dependence and/or sepsis, a use in keeping with current guidelines for the management of sepsis [28]. The use of albumin was reported by 23% of the respondents, while the SAFE study showed that albumin was associated with higher mortality rates in patients with TBI [29]. It is difficult to interpret the continued use of albumin for volume expansion as a lack of knowledge of the evidence, since worse outcomes in the albumin-treated arm in SAFE-TBI may have been the consequence of a hypotonic carrier causing elevated ICP [30], and well-informed clinicians may have used albumin that was isotonic or corrected any accompanying hyponatremia. Finally, the use of tight glycemic control was reported by 28% of respondents, while the NICE-SUGAR and CGAO-REA studies recommend using moderate instead of tight glucose control in patients with TBI [31, 32].

On the other hand, we found consensus where variation was expected; a high number of centers indicated they use antipyretic agents for the treatment of fever when there is no consensus on the optimal choice of agent and when their potentially deleterious side-effect of CPP lowering is well known [33]. This suggests a strong aversion amongst treating clinicians to allow pyrexia in patients with TBI. The choice of NSAIDs, despite their well-known potentially harmful systemic side-effect profile, as antipyretics in many centers probably also reflects this, although a continuous intravenous infusion instead of intermittent NSAID dosing might improve fever control (with relatively higher CPP) in neurocritical care [34]. In addition, respondents indicated employing below-normal $PaCO_2$ goals (30–35 mmHg) in the presence of raised ICP in mechanically ventilated TBI patients. This was unexpected given the BTF recommendation to avoid prolonged hyperventilation. Furthermore, even patients in whom intracranial hypertension was not a concern were ventilated to normal carbon dioxide tensions showing a reluctance to use permissive ventilatory strategies that have been shown to be effective in reducing mortality in acute respiratory distress syndrome (ARDS) patients [35].

Our results further suggest that respondents use TBI-specific strategies instead of general strategies (as used in the general critically ill patients) in the ICU. For example, respondents indicated they frequently or always treat fever since hyperthermia is associated with worse outcomes in TBI [14, 33], whereas fever is often considered beneficial to some extent in critically ill patients with infections [36].

We found some differences between relatively lower versus higher income countries. It was striking that levetiracetam was significantly more frequently reported by higher income countries as an agent of choice for seizure prophylaxis and treatment, while valproate and phenytoin were reported more frequently by lower income countries, although high-level evidence in the literature on the agent of choice is lacking [37]. However, there were no clear structural differences in management overall, and this could not therefore be considered an explanation for the treatment variation. Indeed, some high-cost interventions, such as intravascular cooling and parenteral nutrition, were more commonly used in the lower income countries, suggesting that choices of treatment options are not solely based on cost considerations, but also reflect local clinical culture in different institutions.

Our study has several strengths. To our knowledge, this is the first survey that provides an overview of multiple components of general supportive or preventive ICU management in patients with TBI. The survey was developed in several stages with involvement of clinical

experts of various disciplines and the response rate of the survey was high (97%). However, this study also has limitations, as the centers participating in the CENTER-TBI study may still be a biased selection of European centers with a specialist interest in the topic, or a large engagement in research, or more expertise overall. In a small number of centers, the questionnaire was completed by administrative staff (with no clinical expertise). However, presumably this was in close collaboration with a clinician considering the high number of clinicians that completed the survey, and clinical involvement was encouraged throughout the survey. Other limitations are inherent to surveys in that the results are self-reported and are not confirmed by independent observations in daily practice and, therefore, represent what the respondents 'believe' is clinical practice and this may not, in fact, reflect reality. Another limitation is that the survey questions represent generalizations and do not include patient factors (such as demographics, laboratory results, or imaging), or very specific circumstances, while in clinical practice these details influence clinicians' judgement. In line with this, we did not specify time frames (for ventilation goals) and laboratory values (for tight glucose control). Also, we asked about general patients with TBI in the survey and did not specify adult or pediatric TBI.

Overall, the practice variation (and consensus) in general ICU management we found might be explained by a lack of evidence (or incomplete implementation of evidence), by the use of individualized approaches, or by a tension between general and TBI-specific strategies. We presume that increased and more evidence-based uniformity in good practices in general ICU management might improve outcome in TBI. In fact, general ICU management is part of daily routine (e.g., temperature measurements, laboratory results, and mechanical ventilation) and deviations are generally easily detected and corrected. It is noteworthy that non-neurological complications are frequent; in one report on TBI patients these were more frequent (around 22%) than neurological complications (around 3%) [29]. Our survey showed that future research on individualized management is needed; a high number of respondents reported individualized practices which implies a trend towards precision medicine. In addition, the existence of practice variation in general ICU management provides direction to comparative effectiveness research (CER) analyses or RCTs. As RCTs in the field of TBI have been disappointing [10], CER might be a promising approach to enhance future knowledge on the effectiveness of general ICU management, and understanding what process variances occur, as we have attempted to do, is a critical starting point. Hence, in the CENTER-TBI study we will evaluate the effect of different ICU management practices on TBI outcome (after case-mix correction); for example, the difference in patient outcome between the 13 centers that plan tracheostomy within 1 week, the 36 centers that time tracheostomy between 1 and 2 weeks, and the 16 centers that delay tracheostomy longer than 2 weeks.

Conclusions

This study shows that general supportive and preventive ICU management policies in TBI vary between European neurotrauma centers. These findings stress the need for continued knowledge transfer of existing evidence, further research on optimized individualized management (precision medicine) and, as we propose, comparative effectiveness research.

Additional files

Additional file 1: Survey questions: survey questions of the 'Provider Profiling Questionnaire' used in the study (treatment in the intensive care unit). (DOCX 23 kb)

Additional file 2: Overview of all results: circulatory and respiratory management (**Table S1**), fever control (**Table S2**), use of corticosteroids (**Table S3**), glucose and nutrition management (**Table S4**), seizure prophylaxis and treatment (**Table S5**). (DOCX 26 kb)

Additional file 3: Variation between higher and lower income countries: variation in thresholds used for circulatory and respiratory management (**Table S6**) and general treatments in the ICU (**Table S7**). (DOCX 22 kb)

Additional file 4: Comparison with the Brain Trauma foundation recommendations: items of the questionnaire with corresponding recommendations in the Brain Trauma Foundation guidelines for the Management of Severe Traumatic Brain Injury (4th edition). (DOCX 17 kb)

Additional file 5: CENTER-TBI investigators and participants participating in the CENTER-TBI study and their corresponding affiliations. (DOCX 33 kb)

Abbreviations

BTF: Brain trauma foundation; CENTER-TBI: Collaborative european neurotrauma effectiveness research in traumatic brain injury; CER: Comparative effectiveness research; CPP: Cerebral perfusion pressure; ICP: Intracranial pressure; ICU: Intensive care unit; NSAID: Nonsteroidal anti-inflammatory drug; $PaCO_2$: Partial pressure of carbon dioxide in arterial blood; PaO_2: Partial pressure of oxygen in arterial blood; RCT: Randomized controlled trial; TBI: Traumatic brain injury

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Availability of data and materials

There are legal constraints that prohibit us from making the data publicly available. Since there are only a limited number of centers per country included in this study (for two countries only one center), data will be identifiable. Readers may contact Dr. Hester F. Lingsma (h.lingsma@erasmusmc.nl) for reasonable requests for the data.

Authors' contributions
JAH analyzed the data and drafted the manuscript, the supplementary tables and the figures. VV and MvdJ gave feedback on the manuscript and MvdJ supervised the project. All coauthors were involved in the design of the survey and the distribution of the survey. All coauthors gave feedback on (and approved) the final version of the manuscript.

Ethics approval and consent to participate
Not applicable since no patients participated, and the centers have given consent by completing the questionnaire.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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