Intensive Care Treatment of Uncontrolled Status Epilepticus in Children: Systematic Literature Search of Midazolam and Anesthetic Therapies

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**Objective:** A systematic literature search and review of the best evidence for intensive care treatment of refractory status epilepticus in children using continuous infusion of midazolam or anesthetic agents.

**Design:** MEDLINE and EMBASE search before December 2013 using key words and/or Medical Subject Headings identified English-language citations that were screened for eligibility and used if 1) the study was about high-dose benzodiazepine or anesthetic agent for children; 2) the treatment protocol was described and used for refractory status epilepticus; 3) the outcomes included seizure control; and 4) the series included at least five children.

**Main Results:** Sixteen studies (645 patients) were identified, including midazolam (nine studies), barbiturate (four studies), and other anesthetic approaches (three studies). When midazolam was used as the initial agent for refractory status epilepticus, the rate of clinical seizure control was 76%, which was achieved on average 41 minutes after starting the infusion. When midazolam was used in conjunction with continuous electroencephalography, the time to seizure control was much longer and the mean dose required for seizure control was 10.7 μg/kg/min compared with a lower dose (2.8 μg/kg/min) in the studies not using this form of monitoring, suggesting that continuous electroencephalography provided additional targets for treatment. Barbiturates were usually used after midazolam failed and treatment was started, on average, 66 hours after refractory status epilepticus onset with the goal of electroencephalography burst suppression, which was achieved, on average, 22.6 hours later. Among patients failing midazolam, barbiturate infusion was effective in 65%. Inhaled anesthetics, ketamine, and hypothermia were generally used after prior therapy with midazolam and barbiturates had failed, usually several days after seizure onset.

**Conclusions:** The data on intensive care treatment of pediatric refractory status epilepticus are of poor quality, yet they show a hierarchy in strategies: early midazolam, then barbiturates, and then trial of other anesthetic strategies. In addition, using a solely clinical endpoint for seizure control may be missing significant seizure burden in pediatric refractory status epilepticus. (Pediatr Crit Care Med 2014; XX:00–00)

**Key Words:** anesthesia; barbiturates; midazolam; refractory status epilepticus; status epilepticus; super-refractory status epilepticus

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The initial treatment of status epilepticus (SE) usually consists of one or two doses of a benzodiazepine, which is frequently referred to as “first-tier therapy,” followed by some combination of fosphenytoin or phenobarbital, which is frequently referred to as “second-tier therapy.” Refractory status epilepticus (RSE) is most commonly defined as continued seizure activity despite administration of two adequately dosed anticonvulsants. RSE accounts for 1.6–4% of all admissions to the PICU and develops in 10–25% of pediatric patients presenting with uncontrolled seizures (1–5).

After failure of first- and second-tier therapies for SE, most treatment protocols recommend high-dose benzodiazepine, pentobarbital infusions, and anesthesia (6–9). Despite these recommendations, little is known about the relative efficacy between agents and the options available when anesthesia fails and so-called super-RSE is present (10). Nor is there high-quality evidence from randomized controlled trials (RCTs) for an appropriate therapeutic goal. That is, whether the primary goal is clinical seizure control or whether neuroprotection by an induced state of reduced cerebral metabolic demand should be targeted. The aim of this systematic literature search and review of the best available clinical evidence was to evaluate, summarize, and quantify the use of these two strategies in pediatric RSE and super-RSE.

**METHODS**

**Search Strategy**

The literature search was conducted prior to December 31, 2013, in MEDLINE and EMBASE databases. The key words...
and/or Medical Subject Heading (MeSH) terms were used in searching status epilepticus, refractory status epilepticus, super-refractory status epilepticus, and prolonged seizures and cross-referenced in series with the following treatment options: benzodiazepines, midazolam, barbiturates, thiopental, pentobarbital, ketamine, inhaled anesthetics, isoflurane and desflurane, and hypothermia. Since propofol is not recommended for PICU practice, this drug was not included in the search (11). We limited the search to English-language articles.

**Eligibility Criteria**

Studies were included if 1) the study of interest was the administration of high-dose benzodiazepine or anesthetic agent for pediatric participants; 2) the treatment was administered for RSE; 3) the outcomes of interest including seizure control were described; and 4) the report of case series had at least five children. All identified studies were reviewed independently for eligibility by two authors. Reference lists from the identified studies were examined for additional relevant studies.

**Evidence Quality**

The studies varied in quality, and because our primary goal was to obtain the best evidence available for each agent, we included publications of prospective and retrospective case series and selected the best data for each strategy. The evidence for midazolam was the more robust with a number of pediatric prospective and retrospective case series (12–21). The evidence for barbiturate anesthesia was limited (22–25) and for the other anesthetics extremely limited (26–28). In some of these articles, we attempted to contact the authors by using the address and e-mail for correspondence provided in the article. We received two responses, but no additional information was available.

The quality of the articles identified by our search (12–28) was classified using recently developed definitions for level of evidence (29). In the 16 studies, there was only one level II study (14), classified as “moderate- or poor-quality RCT with violations of one or more of the criteria for a good-quality RCT.” The other 15 studies were level III, that is, “case series, databases, or registries with either prospectively collected data that are purely observational or retrospectively collected data.” Therefore, we have also used a scoring system for assessment of methodological quality of studies of SE (30). This system assigns a value to each of nine domains (design, score 3–12; type of study, score 0–6; time of follow-up, score 0–6; methodological definition, score 0–4; causal factor, score 0–4; standardization, score 0–4; ascertainment adjustment, score 0–4; therapeutic algorithm, score 0–4; and definition and quality of outcome variables, score 1–6), which are added and used as a score that summarizes the quality of the article (range 4 to maximum of 50).

**Data Extraction**

Data were extracted independently by the authors and cross-checked to reach a consensus. The following variables were recorded: the first author’s last name, publication year, study period, participant age group, sample size, anticonvulsant treatment, and mortality.

**Statistical Analysis**

Descriptive and summary statistics are presented and, where appropriate, comparative tests of rates and proportions have been applied with statistical significance set at p value less than 0.05.

**RESULTS**

Figure 1 shows the flowchart details of how we identified and selected studies for the review (last reassessment of search on January 31, 2014). The search using “status epilepticus” produced 9,003 articles, from which we identified 176 referring to the terms “midazolam,” “thiopentone,” “pentobarbital,” “desflurane,” “isoflurane,” “ketamine,” and “hypothermia.” Each of these articles was then hand searched: there were 27 duplicates, and only 16 studies with 645 pediatric patients met our criteria for assessment. Fifteen studies were assessed as level III evidence, and one study (14) met the criteria for level II evidence. The quality scores ranged from 8 to 20 (mean ± SD, 14.3 ± 3.4), which reflect an overall low quality of evidence. There was no significant difference in the scoring between the studies for midazolam (14.3 ± 2.8), barbiturates (16.8 ± 3.8), and other anesthetic strategies (11.7 ± 3.2).
Midazolam and Seizure Control

There are nine studies with pediatric data where midazolam infusions were used to treat RSE (12–21). Four of these studies were prospective and five were retrospective for a combined total of 521 patients. In general, the midazolam studies for RSE target control of clinical seizures as the primary aim. The definition of what constituted RSE—based on number of failed doses of anticonvulsant drug—differed in the nine PICU studies of midazolam infusion (Tables 1 and 2). Failure to gain seizure control after two, three, or more anticonvulsant drugs was used in two (13, 17), three (12, 15, 16, 21), and three (14, 18, 19) studies, respectively (Table 1). In the remaining study (20), a time of 10 minutes without receiving midazolam was used to define the population that should receive midazolam infusion.

**Efficacy.** The majority of the studies used clinical seizure control as the initial treatment endpoint. Saz et al (21) gave no definition for seizure control. Hayashi et al (20) defined seizure control as the complete cessation of clinically observed seizures for at least 24 hours after stopping the midazolam infusion. In the other seven studies, seizure control was defined in relation to the period of time since treatment was started, ranging between 30 minutes and 48 hours, where no clinical seizure was evident. Only two studies used continuous electroencephalography (cEEG) to monitor for subclinical seizures and treat clinical and cEEG-identified endpoints (13, 19).

In nine studies, seizure control occurred in 396 of 521 patients (76%). The four prospective studies (12, 14, 18, 19) showed a higher proportion of cases with seizure control compared with the findings in the five retrospective studies (combined seizure control of 83 of 89 [93%] vs 313 of 432 [72%], chi-square 17.5, p < 0.001). In the six studies where average times are provided, the weighted mean time from beginning the midazolam protocol to seizure control in responders was 271 minutes (12–16, 18, 19). However, when the two studies

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Prospective or Retrospective</th>
<th>Failed Antiepileptic Drugs</th>
<th>Cases</th>
<th>Evidence Level/Quality Score</th>
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</thead>
<tbody>
<tr>
<td>Rivera et al (12)</td>
<td>Prospective</td>
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<td>III/13</td>
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<tr>
<td>Igartua et al (13)</td>
<td>Retrospective</td>
<td>Phenytoin; phenobarbital</td>
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<td>III/14</td>
</tr>
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<td>Singhi et al (14)</td>
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<td>Diazepam 0.3 mg/kg × 2; phenytoin 20 mg/kg</td>
<td>21</td>
<td>II/18</td>
</tr>
<tr>
<td>Koul et al (15, 16)</td>
<td>Retrospective</td>
<td>Diazepam; phenytoin 20 mg/kg; phenobarbital</td>
<td>51</td>
<td>III/11</td>
</tr>
<tr>
<td>Brevoord et al (17)</td>
<td>Retrospective</td>
<td>Midazolam 0.1 mg/kg × 2; phenytoin 20 mg/kg; phenobarbital 20 mg/kg</td>
<td>45</td>
<td>III/16</td>
</tr>
<tr>
<td>Ozdemir et al (18)</td>
<td>Prospective</td>
<td>Diazepam 0.3 mg/kg × 3; phenytoin 20 mg/kg; phenobarbital 20 mg/kg</td>
<td>27</td>
<td>III/19</td>
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<td>Morrison et al (19)</td>
<td>Prospective</td>
<td>Diazepam/orazepam; phenytoin; phenobarbital; multiple others</td>
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<td>III/14</td>
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<td>Hayashi et al (20)</td>
<td>Retrospective</td>
<td>Drugs not given</td>
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<td>III/11</td>
</tr>
<tr>
<td>Saz et al (21)</td>
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<td>Diazepam 0.5 mg/kg rectal × 2</td>
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<table>
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<th>Initial Rate (μg/kg/min)</th>
<th>Mean Rate (μg/kg/min)</th>
<th>Maximum Rate (μg/kg/min)</th>
<th>Time to Control</th>
<th>Cases (%)</th>
</tr>
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<tr>
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<td>0.15</td>
<td>1</td>
<td>2.3</td>
<td>18</td>
<td>Mean 47 min</td>
<td>24/24 (100)</td>
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<td>1–2</td>
<td>14</td>
<td>24</td>
<td>Mean 78 hr</td>
<td>7/8 (88)</td>
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<tr>
<td>Singhi et al (14)</td>
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<td>2</td>
<td>5.3</td>
<td>10</td>
<td>Mean 16 min</td>
<td>18/21 (86)</td>
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<tr>
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<td>1</td>
<td>2</td>
<td>7</td>
<td>Mean 35 min</td>
<td>50/51 (98)</td>
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<td>4</td>
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<td>Not given</td>
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</tr>
<tr>
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<td>3</td>
<td>5</td>
<td>Mean 65 min</td>
<td>26/27 (96)</td>
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<tr>
<td>Morrison et al (19)</td>
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<td>2</td>
<td>9</td>
<td>24</td>
<td>Mean 34 min</td>
<td>15/17 (88)</td>
</tr>
<tr>
<td>Hayashi et al (20)</td>
<td>Not given</td>
<td>Not given</td>
<td>4.3</td>
<td>20</td>
<td>Not given</td>
<td>203/306 (66)</td>
</tr>
<tr>
<td>Saz et al (21)</td>
<td>0.15</td>
<td>Not given</td>
<td>Not given</td>
<td>1.2</td>
<td>Not given</td>
<td>21/22 (96)</td>
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</table>
using cEEG monitoring (13, 19) are excluded, the weighted mean (including 118 of 123 patients with seizures controlled) is 41 minutes. Taken together, this finding suggests that in these studies using clinical monitoring alone, dating from 1993 to 2005, there may have been a failure to identify a significant treatment target since cEEG monitoring results in an almost seven-fold increase in time to seizure control. Alternatively, dosing and dose escalation of midazolam may have accounted for the difference.

**Dosing.** The range in bolus dose of midazolam used at the start of treatment was 0.15–0.5 mg/kg (Table 2). The initial rate of infusion of 1–2 μg/kg/min is described in seven studies (12–19). Subsequent dose escalation is described in six studies (12, 13, 15–19). In general, dosing is escalated by 1–2 μg/kg/min every 10–15 minutes after clinical assessment of seizure control. In one study, the dosing escalation was higher and more frequent; Morrison et al (19) increased dosing by 2–4 μg/kg/min every 5 minutes with the aid of cEEG to assess seizure control. In all studies, the combined, mean dose required for seizure control, weighted according to patient number, was 3.2 μg/kg/min. The study by Igartua et al (13)—the other study using cEEG monitoring—used the highest mean dose of midazolam (14 μg/kg/min). In this study, seizure control was defined as a seizure-free period of 48 hours, and cEEG monitoring was used in all eight patients. The study by Morrison et al (19) used the highest maximum dose of midazolam (24 μg/kg/min). Two studies reported on the duration of midazolam infusions. Igartua et al (13) reported a mean duration of 192 ± 120 hours, whereas Hayashi et al (20) reported a mean of 108.6 ± 175.5 hours. Taken together with the inspection of Table 2, it is evident that the two studies using cEEG (13, 19) used higher mean and higher maximum rates of midazolam infusion when compared with the studies not using a cEEG endpoint (mean rate for control 10.7 μg/kg/min vs 1.5 μg/kg/min; weighted-mean maximum rate for control 24 μg/kg/min vs 15 μg/kg/min). Hence, the longer duration to seizure control in those undergoing cEEG monitoring noted in the previous section cannot be attributed to lower midazolam dosing and dose escalation. If anything, the opposite is the case; cEEG monitoring was associated with higher midazolam administration rates.

**Electroencephalography Use.** cEEG use was reported in only two studies. Neither study describes the technique. Igartua et al (13) used cEEG in all eight patients, and Morrison et al (19) used cEEG monitoring in 13 of 17 patients. In both of these studies, midazolam was titrated to cessation of both clinical and electroencephalographic (EEG) seizure activity. The combined weighted mean dose used to achieve seizure control in these two studies was 10.7 μg/kg/min. Four studies reported on the use of intermittent EEG in order to confirm seizure control and the mean dose used to achieve seizure control (12, 14–16, 18); the weighted mean dose for control was 2.8 μg/kg/min, which appears to be much less than the mean doses used when applying cEEG during treatment (13, 19).

**Breakthrough Seizure and Recurrences.** Breakthrough seizures and recurrent seizures are variably defined and inconsistently reported in the nine studies. In general, breakthrough seizures refer to seizures that occur after initial seizure control has been achieved. Recurrent seizures describe seizures that occur during or after the infusion dose is tapered. Koul et al (15, 16) described five of 51 patients with “recurrent status epilepticus, mostly related to drug default.” Morrison et al (19) reported five of 15 initial responders with breakthrough seizures and one of 15 initial responders with recurrent seizures. In the report by Singh et al (14), 12 of 18 initial responders had breakthrough seizures, and four responders had recurrent seizures after stopping the infusion. Taken together, the combined total for breakthrough seizures and recurrent seizures was 52% (17 of 33 patients) and 12% (10 of 84 patients), respectively.

**Hemodynamic Instability.** Seven studies gave information about hemodynamic instability. Three studies reported that there was no hemodynamic instability attributable to midazolam infusion (12, 15, 16, 18). In the patients reported by Hayashi et al (20), 37 had “circulatory distress”; however, in none of these cases was the midazolam considered to be a contributory factor. In the study by Igartua et al (13), which used the highest mean dose of midazolam out of all nine studies, no inotrope was needed for their patients despite a 5 mm Hg decrease in mean arterial pressure between pretreatment and peak midazolam dosing. Saz et al (21) reported three of 22 patients requiring fluid boluses. Singh et al (14) reported five of 21 patients with hypotension that required inotropes. When combining these eight studies, the number of patients reported to have hypotension or require inotropes is five of 215 (2.3%).

**Barbiturates and Seizure Control**

We identified four retrospective studies using barbiturate coma alone for RSE in pediatric patients, for a combined total of 95 patients (22–25) (Tables 3 and 4). In contrast to the studies of midazolam for RSE, the four studies of barbiturate coma lacked explicit definitions for RSE, seizure control, breakthrough seizures, and seizure recurrence during treatment. In three studies (22–24), continuous infusion of midazolam had been used and failed in 49 of 65 cases (75%). In the other study, 37% had received benzodiazepines before barbiturate anesthesia (25). In the 49 midazolam failure cases, 32 (65%) responded to barbiturate anesthesia (22–24). Two studies reported the duration of SE before barbiturate anesthesia was used; the median time was 24 and 35 hours (22, 25).

Overall, there was some degree of treatment success, either induction of EEG burst suppression (BS) or seizure control was obtained in 66 of 95 patients (69%) in the four studies (22–25). Two studies commented on the achievement of BS. Barberio et al (25) found that 30 of 30 patients (100%), at least transiently, reached this goal, whereas Sakuma et al (24) found that 17 of 22 patients (77%) obtained BS. The study by Kim et al (22) reported the period before pentobarbital was used as 24 (2.5–48) hours (median [interquartile range]). Barberio et al (25) also reported the time a patient remained in RSE before starting pentobarbital, which varied widely with a mean time of 49.6 ± 47.4 hours (median, 35; range, 4–192 hr). This study also reported a mean time of 22.6 ± 17.5 hours from beginning...
pentobarbital therapy until seizure control and/or BS (25). Two studies provided information on the pentobarbital infusion rate required to obtain seizure control and/or BS. The mean maximum dose was similar in the studies reported by Sakuma et al (24) and Barberio et al (25), 4.98 and 4.8 mg/kg/hr, respectively. A maximum hourly infusion rate of pentobarbital was reported in one study and was 10 mg/kg/hr (25). Barberio et al (25) reported the occurrence of breakthrough seizures in 20 of 30 patients (67%), even after achieving BS. Kim et al (22) found that seizures recurred in five of 23 patients (22%) after stopping pentobarbital. The weighted mean duration of barbiturate treatment in all four studies was 17.5 days (22–25).

Last, in regard to the hemodynamic tolerance of prolonged barbiturate therapy, two studies reported on the use of vasoactive support. Barberio et al (25) found that 28 of 30 patients (93%) required vasoactive support (with 16 of 30 needing two agents). van Gestel et al (23) found that all 20 of 20 of their patients (100%) needed vasoactive support. None of the studies reported that hypotension limited the dose of barbiturate anesthesia. The isoflurane administration ranged from end-tidal concentrations of 0.5% to 2.25%. The median duration of RSE prior to treatment with inhaled anesthetic was 7 days.

One study reported the use of IV ketamine in nine children with RSE who had all failed to respond to midazolam, and five had also failed to respond to barbiturate anesthesia (27). Rosati et al (27) used a ketamine infusion of 36.5 μg/kg/min (range, 10–60 μg/kg/min) after a median of 6 days (range, 2–26 d) of RSE along with midazolam (to prevent emergence reactions) and found that six of nine patients had their seizures controlled.

Last, Guilliams et al (28) reported the use of therapeutic hypothermia in five children with RSE managed in two centers between 2009 and 2012. The authors also included a review of a further seven similarly managed children that had been reported in the literature. Nine of these 12 children had failed to respond to midazolam, four had also failed to respond to barbiturate anesthesia (27). Rosati et al (27) used a ketamine infusion of 36.5 μg/kg/min (range, 10–60 μg/kg/min) after a median of 6 days (range, 2–26 d) of RSE along with midazolam (to prevent emergence reactions) and found that six of nine patients had their seizures controlled.

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### DISCUSSION

In this systematic search of the literature, we sought to evaluate the best available clinical evidence for intensive care treatment of uncontrolled SE in children by summarizing quantitatively the strategy of using midazolam for clinical seizure control.
and the strategy of inducing anesthesia and BS. Our principal finding is that the literature discloses a hierarchy in the interventions used: midazolam is the primary agent for RSE; barbiturate anesthesia is used when midazolam fails; and iso-
flurane, ketamine, or hypothermia is used when other thera-
pies have failed. Along with this progression from midazolam to the more potent anesthetic strategies is a change in the end-
point of therapy. In general, the midazolam studies (published 1993–2005) used cessation of clinical seizures as the goal while the anesthetic studies titrated therapy to BS. Additionally, the time course from beginning the infusion until seizure control is markedly different between the studies using midazolam (i.e., minutes to hours) and those using the anesthetic agents (i.e., 24 hr to days).

All nine studies involving midazolam used this agent as the first line of therapy for RSE (12–21), and overall rate of control was 76%. The time from beginning treatment until clinical seizure cessation in responders was, on average, 41 minutes. Additionally, the need for vasoactive agents occurred in only 2% of patients. This combination of high efficacy, ability to be rapidly titrated to clinical seizure control, and relatively benign hemodynamic profile supports its use as the initial agent for RSE. However, we identified an apparent discrep-
ancy that will warrant further study. When cEEG monitoring is used to identify seizures needing treatment, considerably higher doses of midazolam were used (2.8 μg/kg/min vs 10.7 μg/kg/min) and time to seizure control was longer. These two observations raise the concern that nonconvulsive seizures and SE may be undertreated when cEEG monitoring is not used during therapy (31). This finding could be a largely histori-
cal phenomenon since some PICU centers would now con-
sider that cEEG monitoring is standard management for RSE treated with midazolam (32). However, the data do question the expectation that seizure control should be achieved within 1 hour, since the two cEEG monitoring studies gained seizure control at ~4.5 hours.

In the four studies describing the use of barbiturate anesthe-
sia for RSE, the majority of the patients had failed to respond to midazolam therapy (22–25). In this situation, barbiturate infusion was successful at achieving BS and seizure control in 65% of the patients. The median interval between seizure onset and starting the barbiturate infusion in the two studies reporting this information was 24 hours (22) and 35 hours (25). There were two reports from the multicenter study of seizure control in “febrile infection-related epilepsy syndrome” that we were not able to incorporate in our analyses (33, 34). In this study, 46 of 77 children with RSE were treated with midazolam or barbi-
turate BS coma. The investigators did not have any information on the drug dosing (personal communication) but did come to the conclusion that more prolonged BS coma was associated with worse cognitive outcome. Whether this effect is related to cumulative dose of barbiturate or a complication of barbiturate administration is unknown. However, it is noteworthy that 96% of patients treated with barbiturate infusion had hemodynamic instability requiring at least one vasoactive agent (22–25), which may have important consequences on matching cerebral blood flow to metabolism and activity. In this context, it is also note-
worthy that recent literature in adults with RSE is beginning to question whether IV anesthesia is doing more harm than good (35, 36). There is now class III evidence that adults with RSE receiving either IV infusion of midazolam alone, or midazolam followed by propofol, or barbiturates after midazolam had a 2.9-fold relative risk for death (95% CI, 1.45–5.73) when com-
pared with SE patients not receiving these therapies (35).

### Table 5: Isoflurane, Ketamine and Hypothermia for Refractory Status Epilepticus in Children

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Additional Approach</th>
<th>Cases</th>
<th>Failed AEDs</th>
<th>Anesthetic Failures</th>
<th>Evidence Level/Quality Score</th>
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<tr>
<td>Kofke et al (26)</td>
<td>Isoflurane</td>
<td>5</td>
<td>Diazepam, phenytoin, phenobarbital, pentobarbital</td>
<td>Pentobarbital 4/5</td>
<td>III/8</td>
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<td>Rosati et al (27)</td>
<td>Ketamine</td>
<td>9</td>
<td>Multiple, midazolam, thiopental</td>
<td>Midazolam 9/9, thiopental 4/9</td>
<td>III/13</td>
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<td>Guilliams et al (28)</td>
<td>Hypothermia</td>
<td>12</td>
<td>Multiple, midazolam, pentobarbital</td>
<td>Midazolam 9, pentobarbital 4, ketamine 1</td>
<td>III/14</td>
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### Table 6: Isoflurane, Ketamine, and Hypothermia and Seizure Control

<table>
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<tr>
<th>Study (Reference)</th>
<th>Agent</th>
<th>Therapeutics</th>
<th>Seizure Control</th>
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<tbody>
<tr>
<td>Kofke et al (26)</td>
<td>Isoflurane</td>
<td>Titrated to end-tidal concentration 0.5–2.2%</td>
<td>Range 1–55 hr</td>
</tr>
<tr>
<td>Rosati et al (27)</td>
<td>Ketamine</td>
<td>Mean 36.5 (range, 10–60) μg/kg/min</td>
<td>Range 1–17 d</td>
</tr>
<tr>
<td>Guilliams et al (28)</td>
<td>Hypothermia</td>
<td>30–35.3°C</td>
<td>Range 1–5 d</td>
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</table>
finding was independent of possible confounders (i.e., duration and severity of SE, nonanesthetic third-line anticonvulsant drugs, and critical medical conditions) and without significant effect modification by different grades of SE severity and etiologies, such as infection.

The literature on inhaled anesthetics, ketamine, and therapeutic hypothermia is very limited. The study by Kofke et al (26) reported that four pediatric patients responded to isoflurane even after failure to respond to barbiturate anesthesia. Rosati et al (27) found that ketamine could bring about seizure control when midazolam and pentobarbital had failed. Guilliams et al (28) found that therapeutic hypothermia could bring about seizure control when midazolam, pentobarbital, and ketamine had failed. These relatively small case series suggest that anesthetic strategies and therapeutic hypothermia may have a place in the treatment of RSE, but by this stage in view of its refractoriness, these episodes are better defined as “super-RSE” (10).

This analysis of the RSE literature has three main limitations. First, despite the importance of the problem, we cannot get away from the fact that the data on RSE in children are of poor quality in regard to the standards of evidence-based literature (37, 38)—albeit extremely important for practitioners. None of the studies compared the different strategies for RSE. Rather, the literature presents the hierarchy or escalation in therapy, and there is likely a reporting bias of successes rather than failure. Consequently, conclusions made comparing efficacy must be made with caution, but we consider this work as a starting point for future investigations (10). Second, inconsistencies in defining terms such as RSE, seizure control, breakthrough seizures, and seizure recurrence make it difficult to compare outcomes even between studies using the same therapy. A similar problem arises from the inconsistency in reporting variables such as the duration of RSE prior to therapy and the time until seizure control is achieved. In the future, this problem may be solved by consensus on “Common Data Elements” for reporting of case series and studies in RSE. Last, in this analysis, we were unable to analyze mortality or long-term cognitive outcome in relation to treatment since the numbers were small. Despite these limitations, this analysis does provide a semiquantitative description of how midazolam and the anesthetic strategies are used in current clinical pediatric practice and how successful they are at controlling RSE. Additionally, this study provides insights as to how data might be collected in the future to facilitate research (38).

In conclusion, the findings of this analysis highlight the need for a multicenter registry/database to accumulate data on the treatment and timings of RSE in the PICU. We believe that such an approach has the potential to both help the clinician at the bedside and pave the way for future prospective studies.

REFERENCES


