Application of the Continual Reassessment Method to Dose-finding Studies in Regional Anesthesia

An Estimate of the ED\textsubscript{95} Dose for 0.5% Bupivacaine for Ultrasound-guided Supraclavicular Block

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ABSTRACT

Background: Previously reported estimates of the ED\textsubscript{95} doses for local anesthetics used in brachial plexus blocks vary. The authors used the continual reassessment method, already established in oncology trials, to determine the ED\textsubscript{95} dose for 0.5% bupivacaine for the ultrasound-guided supraclavicular block.

Methods: A double-blind, prospective trial was scheduled for 40 patients of American Society of Anesthesiologists class I–III presenting for upper limb surgery and supraclavicular block. The study dose to be administered was arbitrarily divided into six dose levels (12, 15, 18, 21, 24, and 27 ml) with a priori probabilities of success of 0.5, 0.75, 0.90, 0.95, 0.98, and 0.99 respectively. A continual reassessment method statistical program created a dose–response curve, which would shift direction depending on the success or failure of the block. Our starting dose was 21 ml and the next allocated dose was reestimated by the program to be the closest to 0.95.

Results: After recruitment of eight patients, our initial dose levels and associated probabilities were deemed too low to determine the ED\textsubscript{95}. Updated a priori probabilities were calculated from the statistical program, and the study recommenced with a new starting dose of 30 ml. On completion, the ED\textsubscript{95} dose was estimated to be 27 ml (95% CI, 24–28 ml).

Conclusions: The continual reassessment method trial design provided a credible estimate for the ED\textsubscript{95} dose for 0.5% bupivacaine for our technique of supraclavicular block and may be of value as a statistically robust method for dose-finding studies in anesthesia.

What We Already Know about This Topic

- The up-down study design method, such as used to define minimum alveolar concentration, is commonly used to determine a dose or concentration to produce an effect in half the subjects
- This approach is not efficient to estimate the more clinically important dose or concentration producing an effect in 95% of the subjects (ED\textsubscript{95})

What This Article Tells Us That Is New

- Applying a different design, the continual reassessment method, to determine the ED\textsubscript{95} for local anesthetic dose needed for supraclavicular block, resulted in a tight estimate (95% CIs of <10%) after the study of only 48 patients
- This study design might be widely applied for ED\textsubscript{95} estimates in the specialty

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VER the past 10 yr, up-and-down trial designs have become increasingly popular for dose-finding studies in regional anesthesia, especially neuraxial blocks.\textsuperscript{1,2} The methodology used in these trials has the advantage that fewer patients are required than random dose allocation in order to determine the ED\textsubscript{50} dose. However, in terms of determining clinically relevant doses, the ED\textsubscript{50} dose is of limited value,
and it would be much more useful to assess the ED$_{95}$ dose. Unfortunately, extrapolation toward the upper and lower centiles of the dose–response relationship using data from classical up-and-down designs is inappropriate because the estimates lack precision.$^{3,4}$ In this study, we set out to demonstrate the utility of the continual reassessment method (CRM), which was originally designed for phase I oncology trials. With the CRM it is possible to estimate any percentile of the dose–response relationship, including the ED$_{95}$.

As a case in point, we have conducted a trial using a CRM design to estimate the ED$_{95}$ dose of 0.5% bupivacaine for ultrasound-guided supraclavicular brachial plexus block. The supraclavicular approach to the brachial plexus is popular for distal upper limb surgery, particularly because ultrasound has been hypothesized to reduce the risks of inadvertent pleural and arterial puncture.$^5$ Yet, despite the advantage of continuous needle visualization via ultrasound, local anesthetic toxicity remains a major concern. With regards to brachial plexus blocks, there have been several recently published case reports of toxicity from commonly used local anesthetics, such as ropivacaine and bupivacaine, even in their recommended “safe” clinical doses.$^6,7$ Bupivacaine, despite its well established cardiotoxic risks, remains a popular local anesthetic for peripheral nerve blocks because it provides excellent medium to long-term postoperative analgesia. Increasing plasma levels of bupivacaine can produce symptoms ranging from facial paresthesia, visual hallucinations, seizures, coma, cardiac arrest, and finally, if not recognized or promptly treated, death. By using the lowest effective total dose we can reduce the risk of toxicity either from rapid absorption from extravascular tissues, or in the case of more profound toxicity, from direct intravascular injection of even a part of the total dose.

Materials and Methods

Recruitment

After approval from our local ethics committee and the United Kingdom Medicines and Healthcare Regulatory Authority, a double-blind dose-finding study (EudraCT 2009-011829-13) commenced in 2009. The initial design of the study aimed to recruit 40 adult patients (American Society of Anesthesiologists class I–III) presenting for elective upper-limb surgery. Patients who were pregnant, allergic to bupivacaine, unable to give informed consent, with existing sensory deficit in the arm, or with a body mass index greater than 35 kg/m$^2$ were not included in the study.

Block Protocol

A single investigator (the operator) with more than 8 yr of experience with ultrasound-guided supraclavicular brachial plexus blocks carried out the procedures. The brachial plexus was visualized with an ultrasound probe positioned in the supraclavicular fossa parallel to the clavicle, to visualize the subclavian artery in cross-section as it passes over the first rib. After infiltrating the overlying skin with 1% lidocaine, a 22-gauge nerve-block needle was inserted in-plane with the array of the ultrasound probe in a lateral to medial and caudal direction so as to keep it visualized throughout. The local anesthetic was deposited at three locations; in the “corner pocket” (between the artery and the first rib), adjacent to the middle of the neural plexus, and adjacent to the superficial aspect of the plexus. The proportion of the study dose deposited in each of these areas was at the discretion of the expert operator according to the visualized spread of local anesthetic. Before injection at each location, the needle tip position was confirmed by injecting a small (≤0.25 ml) bolus of saline, while observing tissue displacement under ultrasound visualization.

Blinding

The study dose was divided equally into three 10-ml syringes, ready for injection. The operator remained blind to the study dose. To do this, another investigator prepared the injections in the absence of the operator and then, covered the entire length and circumference of the syringes with nontransparent stickers. This investigator attached each syringe in turn to the injection port of the nerve-block needle, after the operator had positioned the needle in the correct place, and then injected the drug as instructed by the operator. In preliminary studies we have demonstrated that this blinding is effective.

Block Assessment

A third investigator, who was not present during the conduct of the block and hence, was completely blind to the dose used, then assessed each block. The subjects were also not aware of the dose of local anesthetic used. The efficacy of the block was assessed at 15-min intervals for up to 45 min, at the sensory dermatomes of the median, ulnar, radial, and musculocutaneous nerves in the upper limb, using an alcohol swab to determine ability to detect cold sensation. Cold sensation has been shown to have similar accuracy to pinprick sensation in predicting inadequate surgical anesthesia.$^8$ Failure to achieve complete loss of cold sensation at any of these four dermatomes after 45 min constituted an ineffective block. For patients having an ineffective block, supplementary local anesthesia was administered according to the distribution of the block and site of surgery. If the patient experienced any pain during their surgery, this was also deemed a failed block, and supplementary analgesia, sedation, or general anesthesia was administered as required.

Dose Allocation

We set out to recruit up to 40 patients in order to obtain a reliable estimate of the ED$_{95}$ for 0.5% bupivacaine. For any given dose, we recruited two patients per cohort to be blocked. The starting dose of bupivacaine was predetermined using a priori estimates based on our previous experience.$^9$ Subsequent doses were allocated on the basis of the CRM (fig. 1), and the operator remained blind to these doses. The
results for each cohort was in turn conveyed to one of the researchers (Dr. Zohar), who used the CRM program to advise the appropriate investigator of the dose level to be used in the next cohort of patients.

**Statistical Analysis**

Personal and surgical details were collected and the data were presented as median (interquartile and range) or percentage, as appropriate.

The ED$_{95}$ of 0.5% bupivacaine for supraclavicular brachial plexus block was estimated using a modified CRM.$^{10–12}$ The CRM is an iterative adaptive method designed to estimate any targeted percentile of response among several dose levels. The ED$_{95}$ dose is first defined as the 5th percentile of the dose–failure relationship, which is modeled throughout a power model as follows:

$$P \left( Y = 1/x_i \right) = p_i^{*}$$

where $\theta$ is the model parameter to be estimated, considered as a random variable with exponential unit prior, and $p_i$ ($i = 1, \ldots, k$) is the initial guess of failure probabilities at the $i$th dose level. We chose $k = 6$ dose levels, namely 12, 15, 18, 21, 24, and 27 ml, and corresponding (decreasing) failure probabilities were given by clinicians as 0.5, 0.25, 0.10, 0.05, 0.02, and 0.01. The range of dose levels was based on our previous experience, including previous dose-finding studies, from which we anticipated that the ED$_{95}$ of 0.5% bupivacaine for supraclavicular brachial plexus block to be between 15 and 27 ml. The first cohort is administered the initial candidate of the ED$_{95}$, that is the dose level 21 ml. Then, once the response is observed for both patients in the cohort, Bayes theorem is applied, to provide the actualized posterior distribution of the model parameter, from which the posterior mean estimate is computed, $E \left( \theta / y \right)$. This estimate is used in the above formula, to give an updated probability of failure at each dose level. Then, that dose level, with an updated failure probability closest to the 0.05 target, is chosen as the current ED$_{95}$, and given to the next cohort.

The CRM continued until one of the following discontinuation criteria was met: (1) when the planned number of 40 subjects was reached; (2) when the estimated probability of response was either too low or too high for all dose levels; (3) when a suitable estimation of the ED$_{95}$ was obtained, based on the predictive gains (mean and maximum) of further patients’ inclusions on the response probability, and on the width of its credibility interval lower than 5%.$^{13}$

The dose-finding allocation was performed using R software version 2.10# (R CRAN, Vienna, Austria).

**Results**

Our study consisted of two recruitment phases, with a total of 48 patients recruited. The patient characteristics for both phases are shown in table 1.

**Phase I**

Eight patients were involved in the first phase. The initial dose levels with their subsequent prior probabilities (table 2) suggested a starting dose of 21 ml. This starting dose produced a successful block in both patients in the first cohort, yet, there was a block failure in each of the next three cohorts at different dose levels (table 3 and fig. 2). After the fourth cohort had been recruited, we discovered

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**Table 1.** Patient Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yr (SD)</td>
<td>66.5 (12.6)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>13/35</td>
</tr>
<tr>
<td>Median height, m (SD)</td>
<td>1.64 (0.11)</td>
</tr>
<tr>
<td>Median weight, kg (SD)</td>
<td>66.5 (10.9)</td>
</tr>
<tr>
<td>BMI, kg/m$^2$ (SD)</td>
<td>24 (2.8)</td>
</tr>
<tr>
<td>ASA—I/II/III</td>
<td>7/29/12</td>
</tr>
<tr>
<td>Surgery—hand/wrist/elbow</td>
<td>28/18/2</td>
</tr>
</tbody>
</table>

ASA—I/II/III = American Society of Anesthesiologists classification of physical fitness (I = normal healthy individual, II = mild systemic disease, and III = severe systemic disease); BMI = body mass index.

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**Table 2.** Initial Guesses of Response Probability for Original Dose Range

<table>
<thead>
<tr>
<th>Dose Level, ml</th>
<th>Response Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>0.50</td>
</tr>
<tr>
<td>15</td>
<td>0.75</td>
</tr>
<tr>
<td>18</td>
<td>0.90</td>
</tr>
<tr>
<td>21</td>
<td>0.95</td>
</tr>
<tr>
<td>24</td>
<td>0.98</td>
</tr>
<tr>
<td>27</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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*Available at: http://cran.r-project.org. Accessed August 1, 2012.*
that a stopping criterion had been met. With two block failures at the top dose level (27 ml), it became evident that our initial dose levels with their probabilities of success were too low. The ED$_{95}$ was estimated to be the dose 27 volume unity with associated response probability of 76% (95% CI, 41.1–94.5%).

These initial results allowed updated dose levels, with initial guesses of response probability (table 4) to be calculated and incorporated into a second recruitment phase of the trial. Our new dose levels for the next phase ensured that the maximum recommended dose (35 ml), as stated in the summary of drug characteristics approved by the regulatory body, was not exceeded.

Phase II
As the CRM had readjusted the estimated dose–response curve, a further 40 patients were deemed necessary to estimate the ED$_{95}$ dose. A new starting dose of 30 ml was used, with the trial recommencing as per the CRM (table 5). Because the maximum dose of 35 ml exceeds the capacity of three 10-ml syringes, we decided for this phase of recruitment to draw up the study dose equally into six 10-ml syringes instead. This second phase of recruitment yielded 37 of 40 successful blocks. The three failed blocks were at dose levels 21, 24, and 27 ml. The dose level changed a total of six times throughout this phase (fig. 3).

In total, over the two recruitment phases, we encountered six failed blocks. Three of these failures required further local anesthetic supplementation of 10 ml of either 0.5% bupivacaine, or 2% lidocaine with adrenaline. None required further analgesia during surgery. Anesthesia was inadequate in the dermatomes of ulnar, median, musculocutaneous, and radial nerves in three, three, three, and one patient, respectively. Finally, the ED$_{95}$ was estimated to be 27 ml (95% CI, 24–28 ml).

Discussion
The CRM, first proposed in 1990,\textsuperscript{10} was used in this study in order to determine the ED$_{95}$ dose of 0.5% bupivacaine for ultrasound-guided supraclavicular block. A good tutorial on the application of CRM in clinical trials is available.\textsuperscript{14} The method has most frequently been applied in oncology phase I trials, where the primary objective is to

Table 3. Posterior Estimated Dose–Response Curve for the First Dose Range

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Administered Dose, ml</th>
<th>Clinical Response</th>
<th>Updated Estimated Probability of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>S, S</td>
<td>0.62</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>S, F</td>
<td>0.37</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F, S</td>
<td>0.24</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>S, F</td>
<td>0.19</td>
</tr>
</tbody>
</table>

In bold is the estimated ED$_{95}$ after the inclusion of each cohort. F = failure; S = success.

Table 4. Updated Guesses of Response Probability for the Second Dose Range

<table>
<thead>
<tr>
<th>Dose Level, ml</th>
<th>Updated Guesses of Response Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>0.60</td>
</tr>
<tr>
<td>24</td>
<td>0.70</td>
</tr>
<tr>
<td>27</td>
<td>0.76</td>
</tr>
<tr>
<td>30</td>
<td>0.86</td>
</tr>
<tr>
<td>33</td>
<td>0.91</td>
</tr>
<tr>
<td>35</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Fig. 2. Dose–response during phase I recruitment. ○ Indicates block success. ● Indicates block failure.
estimate the maximum tolerated dose, while minimizing the number of patients treated above that dose.\textsuperscript{15–17} Some noncancer trials have also used this method. Studies involving midazolam in neonates and the opioid antagonist nalmefene in patients with epidural fentanyl have more direct relevance for anesthesiologists.\textsuperscript{18,19} The method is based on Bayesian inference, hence, it relies on prior probabilities to be incorporated in the design, determined from previously published data as well as from clinical experience to create a dose–response curve, which can alter after each cohort has been recruited.

The CRM has advantages over other dose-finding designs because it uses a one-parameter model (a power model), rather than a logistic model, to create the dose–response relationship so that it requires less information to fit the data and achieves more accurate estimates. Furthermore, it uses all information on the drug, both outside and in the trial, thus, allowing the administration of the best candidate dose to each patient enrolled in the trial. Therefore, the program is constantly trying to compute the lowest possible dose to administer to the next cohort of participants to be tested.

When it was first introduced, the CRM was criticized for allocating toxic doses to be given in trials. Modifications have since been made looking at the posterior density function of an occurrence at each dose level.\textsuperscript{20} After just four cohorts, phase I of our study reached one of the stopping rules described where all dose levels were deemed ineffective.\textsuperscript{13}

### Table 5. Posterior Estimated Dose–Response Curve for the Second Dose Range

<table>
<thead>
<tr>
<th>Bupivacaine Dose, ml</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Priori Model</td>
<td>0.60</td>
<td>0.70</td>
<td>0.76</td>
<td>0.86</td>
<td>0.91</td>
<td>0.94</td>
</tr>
</tbody>
</table>

In bold the estimated ED\textsubscript{95} after the inclusion of each cohort.

F = failure; S = success.

### Fig. 3. Dose–response during phase II recruitment.

- ○ Indicates block success.
- ● Indicates block failure.
This early detection had the advantage of preventing further patients from being recruited with an increased probability of receiving a failed block. However, the study continued with updated dose levels and probabilities, to improve the likelihood of finding the ED$_{95}$ dose.

In using the CRM, ours is the first trial designed to provide a direct estimate of the ED$_{95}$ dose of local anesthetic for supraclavicular block, thus, providing a useful comparison to extrapolated values from studies designed to find the ED$_{50}$ or from purely observational data. Dosing studies for this block and local anesthetic combination are scarce, but the limited credible data for 0.5% bupivacaine$^{21,22}$ and other local anesthetics$^{23,24}$ for supraclavicular block provide evidence of face validity for our estimate of 27 ml.

It is important to note that our ED$_{95}$ estimate is based on a multiple injection technique. Although there is no evidence that altering the number of injection points from single to multiple significantly alters supraclavicular block success rate, we can reflect that by changing our injection methodology from three syringes to six, not only allowed greater flexibility as to where to deposit the local anesthetic around the brachial plexus, but also provided more visual discrimination as to where it spread. Although a multiple injection technique theoretically increases the chance of inadvertent intravascular deposition of local anesthetic, it also reduces the maximum dose of intravascular local anesthetic likely to be administered to a level that is not life-threatening, especially if the lowest total effective dose is used.

It is probable that the failure rate of blocks will be higher using our ED$_{95}$ estimate in less experienced hands if not all the local anesthetic is deposited evenly around the target nerve plexus. This estimate was dependent on the timing of block assessment. We opted for 45 min as our previous ED$_{50}$ study using the same drug, and block protocol showed that some patients required 45 min to be fully blocked.$^9$ Indeed in the current study, only 28 of 42 successful blocks were successful within the 30-min assessment period. Our results are also only representative of our study population, although we have previously demonstrated that body mass index does not significantly affect the ED$_{50}$ dose of 0.5% bupivacaine for ultrasound-guided supraclavicular block.$^9$

Although it would be unwise to strictly generalize our findings to other operators and techniques, our estimate of the ED$_{95}$ dose of 0.5% bupivacaine for supraclavicular block provides a useful guide. We would, however, caution against extrapolation of our results to other local anesthetic agents or concentrations of bupivacaine, as the relative potency of different agents and the relationship between concentration and volume on dose requirements have not been established in this setting.

In this trial we have demonstrated the application of the CRM to derive directly a clinically relevant dose level for a single concentration of bupivacaine in a defined regional anesthesia setting. We feel this trial design has specific benefits. By continuously recalculating probabilities of success at a given dose range, it allows researchers to obtain their target dose estimate, while also minimizing the number of subjects exposed to larger doses. We suggest that the CRM might usefully be applied further for dose-finding studies in regional anesthesia and acute pain.

References