An estimate of the ED_{95} dose for 0.5% bupivacaine for the ultrasound guided supraclavicular block: a dose finding study using the Continual Reassessment Method.

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The supraclavicular approach to the brachial plexus is popular for distal upper limb surgery particularly since ultrasound has been shown to reduce the risks of inadvertent pleural and arterial puncture. Yet despite the advantage of continuous needle visualisation via ultrasound, local anaesthetic toxicity remains a major concern for anaesthetists. With regards to brachial plexus blocks, there have been several recently published case reports of toxicity from commonly used local anaesthetics such as ropivacaine and bupivacaine even in their recommended "safe" clinical doses.[1-8] Bupivacaine, despite its well established cardiotoxic risks, remains a very popular local anaesthetic for peripheral nerve blocks as it provides excellent medium to long-term postoperative analgesia. Increasing plasma levels of bupivacaine can produce symptoms ranging from facial paraesthesia, visual hallucinations, seizures, coma, cardiac arrest and finally, if not recognised or promptly treated, death.

Avoidance of toxicity demands the use of the minimum effective dose of local anaesthetic for any technique. Finding the balance between providing high enough doses as to be effective yet safe form toxicity is difficult. One problem with dose finding studies for brachial plexus blocks is that, until the advent of ultrasound guided techniques, it was not possible to distinguish an inadequate dose of local anaesthetic from misplacement of drug as the cause of block failure. Another problem is clinical trial design. Many researchers have tried to either vary the concentration and volume of local anaesthetic or keep a fixed

dose and evaluate endpoints thereon.[9-11] A particular problem with fixed dose studies is that dangerously high doses can be given to patients who are underweight. A large report of 2020 supraclavicular blocks used 'fixed doses' of 35-40mls of 1.5% mepivacaine in patients weighing as little as 44kg.[11] This would constitute approximately 12mg/kg (recommended dose 7mg/kg).

Over the past 10 years, up-and-down trial design has become increasingly popular for dose finding studies in regional anaesthesia, especially neuraxial blocks.[12,13] The methodology used in these trials has the advantage that fewer patients are required than random dose allocation in order to determine the ED_{50} dose. Indeed we have determined the ED_{50} for 0.5% bupivacaine using up-and-down methodology in a study of 21 patients.[14] However, in terms of determining clinically relevant doses, the ED50 dose is of limited value and it would be much more useful to know the ED_{95} dose. Unfortunately, extrapolation towards 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.[15,16] Our study used the Continual Reassessment Methodology (CRM), which was originally designed for Phase I and II oncology drug trials, in order to estimate a reliable ED_{95} dose.

Methods

Recruitment

After approval form our local ethics committee and the Medicines and Healthcare Regulatory Authority UK, a double blind dose finding study (EudraCT 2009-011829-13) commenced in 2009. The initial design of the study aimed to recruit 40 ASA 1-3 adult patients 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 BMI greater than 35 were not included in the study.

Block protocol

A single investigator (the operator) with over eight years of experience with ultrasound guided supraclavicular brachial plexus blocks carried out the procedures. After infiltrating the overlying skin with 1% lidocaine, a 22-gauge nerve block needle was passed under ultrasound guidance so that its tip was adjacent to the brachial plexus. After negative aspiration on the needle the study dose of 0.5% bupivacaine was injected at various locations around the plexus. This was done under ultrasound visualization throughout to ensure correct location of the needle was maintained. After the initial and each subsequent needle position, its location was further confirmed by injecting a small (≤ 0.25 ml) bolus of saline, whilst observing tissue displacement under ultrasound visualisation.

Blinding

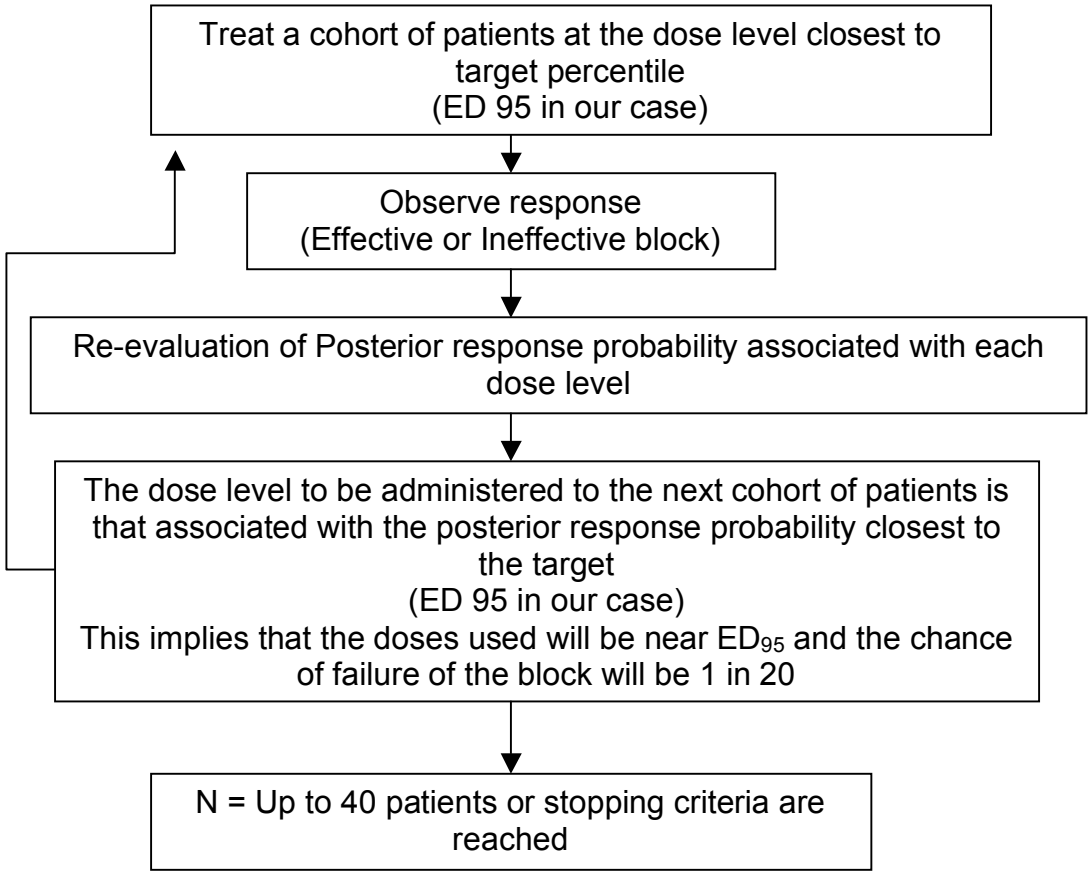
The study dose was divided equally into three 10 ml syringes ready for injection. The operator remained blind to the study dose. To do this, another investigator prepared the injections in the absence of the operator and then covered the entire length and circumference of the syringes with non-transparent 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, 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 anaesthetic used. The efficacy of the block was assessed at 15-minute intervals for up to 45 minutes at the sensory dermatomes of the median, ulnar, radial and musculocutaneous nerves in the upper limb to cold using an alcohol swab. Failure to achieve complete loss of cold sensation at any of these four dermatomes after 45 minutes constituted an ineffective block. For patients having an ineffective block supplementary local anaesthesia 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 anaesthetic was to be administered.

CRM incorporation

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 2 patients per cohort to be blocked. The starting dose of bupivacaine was predetermined using *a prioris* incorporated within the statistical program. Subsequent doses were based on the continual reassessment method and the operator remained blind to these doses. The results for each cohort was in turn conveyed to one of the researchers (SZ) who used the CRM program to advise the appropriate investigator of the dose level to be used in the next cohort of patients. The following is a schematic representation of subsequent steps in the CRM design:



The design of this study was such that the trial could halt well before the 40th

patient had been recruited if the statistical program delineated that the original dose levels along with their assigned prior probabilities would not allow an estimate of the ED_{95} to be obtained. In this eventuality the study would enter a second phase with new dose levels and prior probabilities to be used to recruit up to another 40 patients.

Statistical considerations & power analysis

Personal and surgical details were collected and the data are presented as median (interquartile and range) or percentage as appropriate. The ED_{95} was estimated using CRM. We deemed a sample size of 40 patients to be sufficient to provide an estimate of the ED_{95}. The CRM (O'Quigley et al 1990)[17] using a modification in order to control outliers (Resche-Rigon et al. 2008)[18] was used in order to determine the minimal effective dose (MED) of 0.5% bupivacaine for supraclavicular brachial plexus block of 95% of patients. The CRM is a sequential Bayesian method based on a one-parameter model, which aims at estimating the percentile of desired responses for a number of distinct dose levels di (i=1,...,5). The initial step required the investigators to identify a series of dose levels, within the range of which the desired percentile response (95^{th} centile in our case) is likely to be produced. Based on our previous experience, including previous dose-finding studies, we anticipated that the ED_{95} of 0.5% bupivacaine for supraclavicular brachial plexus block to be between 15 and 27 ml. Next, we have arbitrarily divided this range into six dose levels (12, 15, 18, 21, 24 and 27 ml) to be available within the study and assigned *a priori* probabilities of successful block of 0.5, 0.75, 0.90, 0.95, 0.98 and 0.99 respectively to the six dose levels. Then, a one-parameter power model was used to fit the dose-response curve, with an exponential prior distribution (with mean = 1) for the model parameter. The posterior response probability of each dose level was re-estimated by SZ using the CRM program after inclusion of each cohort of patients. The allocated dose to the next cohort of patients was the dose level with the updated posterior response probability closest to 0.95.

Any decision to end the study was based on stopping criteria that detected whether all doses levels were likely to be ineffective or a suitable estimation of the ED_{95} has been reached (Zohar and Chevret 2001).[19]

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 3 cohorts at different dose levels (table 3). After the 4th cohort had been recruited we discovered that a stopping criterion had been met. With 2 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. These initial results allowed updated dose levels with associated *a prioris* (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 safe dose (35 ml) as stated by the summary of the drug characteristics, was not exceeded,

Phase II:

As the CRM program had readjusted the estimated dose-response curve, a further 40 patients were deemed necessary to provide the ED_{95} dose. A new starting dose of 30 ml was used with the trial recommencing as per the CRM (table 5). Since, 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 37/40 successful blocks. The 3 failed blocks were at dose levels 21,

24 and 27 ml. The dose level changed a total of 6 times throughout this phase. Our study statisticians, using the CRM estimate the ED_{95} to be 27 ml (95 % CI: 24 – 28 ml).

Table 1 – Patient characteristics

Median Age	66.5 (40-90)
Gender – M / F	13 / 35
Median Height [m] (range)	1.64 (1.49-1.9)
Median Weight [kg] (range)	66.5 (50-95)
BMI [kg/m^2] (range)	24 (18-34)
ASA – I / II / III	7 / 29 / 12
Surgery – hand / wrist / elbow	28 / 18 / 2

Table 2 – *a prioris* for original dose range

Dose level (ml)	*priori* Probability
12	0.50
15	0.75
18	0.90
21	0.95
24	0.98
27	0.99

Table 3 – Posterior estimated dose-response curve for the first dose range

			Bupivacaine dose (ml)					
			12	15	18	21	24	27
Cohort	Administered Dose (ml)	Clinical response	Working *priori* model					
			0.50	0.75	0.90	0.95	0.98	0.99
			Updated estimated probability of success					
1	21	S, S	0.62	0.85	0.96	**0.98**	1.00	1.00
2	18	S, F	0.37	0.60	0.79	0.87	0.93	**0.95**
3	27	F, S	0.24	0.42	0.60	0.69	0.79	**0.84**
4	27	S, F	0.19	0.35	0.51	0.60	0.70	**0.76**

In bold is the estimated ED95 after the inclusion of each cohort, S = success, F = fail

Table 4 – updated *prioris* for the second dose range

Dose level (ml)	Updated *prioris*
21	0.60
24	0.70
27	0.76
30	0.86
33	0.91
35	0.94

Table 5 – Posterior estimated dose-response curve for the second dose range

			Bupivacaine dose (ml)					
			21	24	27	30	33	35
			Working *priori* model					
			0.60	0.70	0.76	0.86	0.91	0.94
Cohort	Administered Dose (ml)	Clinical response	Updated estimated probability of response					
1	30	S, S	0.76	0.84	0.89	**0.95**	0.98	0.99
2	30	S, S	0.81	0.89	0.92	**0.97**	0.99	0.99
3	30	S, S	0.84	0.91	**0.94**	0.98	0.99	1.00
4	27	S, S	0.86	0.93	**0.96**	0.99	0.99	1.00
5	27	S, S	0.88	**0.94**	0.96	0.99	1.00	1.00
6	24	S, S	0.90	**0.95**	0.97	0.99	1.00	1.00
7	24	S, S	0.91	**0.96**	0.98	0.99	1.00	1.00
8	24	S, S	0.92	**0.97**	0.98	1.00	1.00	1.00
9	24	S, S	**0.93**	0.97	0.98	1.00	1.00	1.00
10	21	F, S	0.87	0.93	**0.96**	0.99	1.00	1.00
11	27	S, S	0.88	**0.94**	0.96	0.99	1.00	1.00
12	24	S, S	0.89	**0.94**	0.97	0.99	1.00	1.00
13	24	S, S	0.90	**0.95**	0.97	0.99	1.00	1.00
14	24	S, S	0.90	**0.95**	0.97	0.99	1.00	1.00
15	24	S, F	0.85	0.92	**0.95**	0.98	0.99	1.00
16	27	S, S	0.86	0.92	**0.95**	0.98	0.99	1.00
17	27	S, S	0.86	0.93	**0.96**	0.99	0.99	1.00

18	27	S, S	0.87	0.93	**0.96**	0.99	1.00	1.00
19	27	F, S	0.83	0.90	**0.93**	0.98	0.99	1.00
20	27	S, S	0.83	0.90	**0.94**	0.98	0.99	1.00

In bold the estimated ED95 after the inclusion of each cohort, S = success, F = fail

Discussion

The present study estimates an ED_{95} dose for 0.5% bupivacaine to be 27 ml for the supraclavicular block when performed using ultrasound. This is the first clinical trial that has directly sought to determine this dose rather than extrapolating data from a study designed to find the ED_{50}. Dosing studies, particularly for this block and local anaesthetic combination, are scarce. There have been many trials of the supraclavicular block using a variety of techniques, local anaesthetics, or adjuvant drugs yet most have evaluated alternative endpoints rather than the effective dose. Extrapolating from published data it appears our estimate of the ED_{95} is lower.

An early study of 20 patients suggested that 30 ml of 0.5% bupivacaine led to a 95% success rate. [20] The authors used absence of pin-prick sensation as their method of detecting the ulnar, median, radial and musculocutaneous nerves were blocked, however their data suggested that surgical anaesthesia was the primary determinant of successful block. Another study comparing 30 ml 0.5 % bupivacaine with 0.5% levo-bupivacaine showed a success rate ranging from 87-91% when pin-prick sensation was assessed at individual dermatomes of C5-8 but we cannot predict the success of all dermatomes being blocked. [21] Both studies involved fewer patients being blocked as compared to our study. Another study using nerve stimulation instead of ultrasound demonstrated a much lower success of 74% when using 0.4 ml/kg of 0.5% bupivacaine.[22] Extrapolating from their data the volumes used could have ranged from 22-33 ml (mean 27 ml).

Because of the scarcity of literature for 0.5% bupivacaine for this block we could further extrapolate by using equivalent dosing of alternative local anaesthetics. Studies involving 2% lidocaine alone or in combination with 0.5% bupivacaine are relatively more common. Bupivacaine has 4 times the potency of lidocaine therefore 1 ml of 0.5% bupivacaine is equivalent to 1 ml of 2% lidocaine.[23,24] With this in mind, a recent study found a 95.7% success rate (CI: 85-99%) when 35 ml of 1.5% lidocaine (equivalent to 26.25 ml 0.5% bupivacaine) was used for the ultrasound guided supraclavicular block.[25] This is comparable to our estimate of 27 ml and our credibility interval of 83-98%. In contrast when 30 ml of 2% lidocaine was used in a study of 30 patients only 57% of them had complete loss of sensation of the four nerves.[26] When mixing 0.5% bupivacaine with 2% lidocaine plus adrenaline in a 1:3 ratio there was a 71% success rate.[27] This study used 0.5 ml/kg of the local anaesthetic mixture for each patient. The mean weight was 75 kg (SD 15 kg), which would correspond to 32.5 ml, however taking into account 1.96 SD could have ranged from 23 ml – 52 ml. The most common mixture of local anaesthetic investigated was a 1:1 ratio of 0.5% bupivacaine with 2% lidocaine with adrenaline. Using 40 ml of this mixture led to a 95% success rate in achieving motor and sensory block in a study of 40 patients.[28] This result was comparable to a later smaller study which, although found a 50% success at 23 ml, using logistic regression, predicted a 95% success at 42 ml in 20 patients.[29] This method of extrapolation however has been proven to be inaccurate.[15,16] A recent large retrospective study of 460 patients however suggested the ED_{95} dose to be lower, around 33 ml, however there wasn't any

standardisation on how the block was performed and a successful block was deemed one that didn't require supplementation presumably during surgery.[30] None of the mentioned studies intended to seek out the ED_{95} dose and the methodology employed in the trials varied greatly.

The continual reassessment method, first proposed in 1990, was used in this study in order to determine the ED_{95} dose.[17] A good tutorial on its applications in clinical trials is available.[31] This method has most frequently been applied in oncology phase I trials where the primary objective is to estimate the maximum tolerated dose whilst mimimizing the number of patients treated above that dose.[32-34] Some non-cancer trials have also used this method. Studies involving midazolam in neonates, the opioid antagonist nalmefene in patients with epidural fentanyl, and stimulating current threshold for regional anaesthesia in pigs have more direct relevance to anaesthetists.[35-37] The method is based on Bayesian inference hence it relies on prior probabilities to be incorporated in the design. The *a prioris* for the present study were determined from previously published data as well our own clinical experience in order to create a dose-repsonse curve which could continuously alter after each cohort had been recruited. When it was first introduced, the continual reassessment method was criticized for allocating too 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.[38] After just 4 cohorts, our study reached one of the stopping rules described where all dose levels were deemed ineffective.[39] 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.

The authors would like to reflect that by changing our injection methodology from 3 syringes to 6 not only allowed greater flexibility as to where to deposit the local anaesthetic within the brachial plexus but also provided more visual discrimination as to where it had spread. It is possible the high failure rate in the first recruitment phase may be attributable to this. There is however, no credible evidence that altering the number of injection points above the three commonly used (between the subclavian artery and rib, in the middle of the plexus and its more superficial part) significantly alters the block success rate. We investigated racemic bupivacaine rather than its isomeric formulation levo-bupivacaine. There is evidence of similar profile with regards to onset, duration, ECG morphology, biochemical, haematological and urine analysis between the two.[22] We excluded pregnant women from the study as it has been reported that this block can cause respiratory compromise in such patients.[40] Our study is also limited to patients with a BMI < 35 and ASA < IV. Deviating away from these patient groups leads to a higher failure rate of blocks.[41] Thirty-four out of 48 patients (83%) investigated were female as most of our patients presenting for upper limb surgery had some form of rheumatic disease which is more prevalent in this gender. Hence, one could assume that our sample does not reflect the true population. We would argue that to our knowledge gender does not have any direct pharmacological impact on any of the commonly used anaesthetic agents. Females tend to be of smaller frame and weight as compared to males however BMI doesn't significantly affect the dose for the supraclavicular block.[14] Our method of

block assessment is comparable with other trials, yet we also decided not to assess the medial brachial or antebrachial nerves which can contribute to tourniquet pain.

This trial has deviated away from the standard random dose allocation methods already published, to an inherently safer calculated probability of dose success. Based on our findings and the described technique, we estimate the minimum effective dose for 0.5% bupivacaine in 95% patients receiving a supraclavicular block, to be 27ml.

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