A Reevaluation of the Role of Crystalloid Preload in the Prevention of Hypotension Associated with Spinal Anesthesia for Elective Cesarean Section


Background: Hypotension after spinal anesthesia for cesarean section remains a common and serious complication despite the use of uterine displacement and volume preloading. The current study reevaluated the role of crystalloid volume preloading in this context.

Methods: In a two-stage open sequential design, patients presenting for elective repeat cesarean section were allocated to receive either no preload or 20 ml/kg crystalloid administered over 15–20 min before spinal anesthesia. Hypotension was defined as a decrease in systolic pressure to less than 100 mmHg and to less than 80% of baseline value, and the study was designed to detect a 20% difference in the incidence of hypotension between the groups, with statistical significance at the 10% (α = 0.1) level, one-tailed.

Results: One hundred forty patients were studied. Hypotension occurred in 43 (55%, 95% CI 43.4–66.4) preloaded and 44 (71%, 95% CI 58–81.8) unpreloaded subjects, a difference in incidence of 16% (95% CI 0.04–31.6), which was statistically significant. There were no significant differences in the severity, timing, or duration of hypotension; the dose requirement for ephedrine; or the clinical and biochemical status of neonates between the groups. The only difference seen was a lower mean base excess (−3.4, SD 2.81 mmol/l) in the neonates of hypotensive mothers compared to neonates of nonhypotensive mothers (−2.4, SD 1.99 mmol/l).

Conclusions: The study confirms that hypotension associated with spinal anesthesia for cesarean section cannot be eliminated by volume preloading in the supine wedged patient. The relatively small reduction in incidence of hypotension challenges our perception of the value of crystalloid preload. Though volume preload in the elective cesarean section is advocated, the requirement for a mandatory administration of a fixed volume before spinal anesthesia for urgent cases has been abandoned. (Key words: Anesthesia, obstetric; Anesthetic techniques, spinal; Complications, hypotension; Intravenous fluids, crystalloid.

THE most common serious problem associated with spinal anesthesia for cesarean section remains the rapid onset of profound hypotension. Anesthetic texts continue to emphasize both uterine displacement and intravenous volume loading as prophylactic measures to reduce the incidence of hypotension.1–3 Recent invasive studies have confirmed the decrease in cardiac output associated with the supine position and, hence, the mandatory use of lateral tilt.4 However, only two studies have demonstrated complete prevention of hypotension by volume loading.5,6 One of these was performed before the introduction of uterine displacement, and the conclusions drawn may not apply to current practice.5 Subsequent studies indicate an incidence of hypotension varying between 4.1% and 83%.7–24 Volume loading may not be completely effective because of fluid redistribution outside the vascular compartment during the time taken for administration. Giving the intravenous fluid more rapidly (20 mg/kg over 10 min compared with 20 min) has been shown by us not to reduce the incidence of hypotension,25 with the onset of spinal block being associated with a precipitous decrease in central venous pressure, suggesting that the fluid given was unlikely to have made much impact. Because of this and the persistence of a high incidence of spinal hypotension, we began to question the value of intravenous preloading. In this study, we have reevaluated volume loading in the prevention of spinal hypotension associated with elective cesarean section.

Methods

With institutional ethical approval and informed consent, patients were allocated to receive either intravenous crystalloid preload or no preload before spi-
nal anesthesia for elective repeat cesarean section. All patients were American Society of Anesthesiologists physical status 1 at term with an uncomplicated singleton pregnancy and not in labor. Patients weighing more than 90 kg were excluded to minimize technical difficulty as a variable. Patients were transferred to the operating room while in the left lateral decubitus, and intravenous access was gained using a 16-G cannula in the left forearm. The cuff of an automated noninvasive study-dedicated monitor (Critikon Dinamap, Tampa, FL) was attached to the right arm, and blood pressure and heart rate were measured with the patient in the left supine wedged position (15° obstetric wedge under the right buttock). Baseline values were taken as the mean of three successive readings at 2-min intervals when the systolic pressure did not vary by greater than 10%. Volume loading was then commenced in patients allocated to receive fluid using 20 ml/kg crystalloid (Plasma-Lyte L, Baxter, Deerfield, IL) warmed to 38°C and administered over 15–20 min. Patients not receiving preload had the intravenous infusion running only to keep the vein open.

Spinal anesthesia was instituted with patients in the sitting position with 1.5 ml plain 0.5% bupivacaine administered through a 26-G needle via the L3–L4 or L4–L5 interspace. Patients promptly were repositioned in the left supine wedged position, and blood pressure and heart rate were recorded at 1-min intervals for 20 min and at 5-min intervals thereafter for 20 min or until the end of surgery.

Hypotension was defined as a decrease in systolic pressure to less than 100 mmHg and less than 80% of the baseline value. No prophylactic ephedrine was administered. Hypotension was treated immediately by increasing the rate of intravenous fluid administration and by 5-mg bolus increments of intravenous ephedrine every minute until the systolic pressure increased to greater than 80% of baseline or to above 100 mmHg. The total dose requirement of ephedrine was recorded.

During surgery, the times of uterine incision and cross-clamping of the umbilical cord were recorded. After delivery, oxytocin was administered to all patients as a 5-unit bolus, followed by an intravenous infusion of 15 units in the first hour. Papaveretum (10–20 mg; equivalent to 7.5–15 mg morphine) was administered intravenously to provide early postoperative analgesia. Maternal radial arterial blood was withdrawn at the time of uterine incision. At delivery, umbilical venous and arterial blood was sampled from a double-clamped segment of umbilical cord. All blood samples were analyzed within 10 min for blood gas and acid–base status. The clinical condition of the neonate was assessed using a modified Apgar score (minus color) at 2 and 5 min after delivery.

Study Design and Data Analysis

The study was designed to expose the minimum number of patients to a potentially detrimental management, i.e., no volume loading. A sequential analysis design was used with the first 40 patients as prerandomized pairs and "play the winner" thereafter. For the prerandomized pairs, the first patient of each pair was allocated on the basis of a prerandomized sequence in sealed envelopes. The second case was then allocated to the alternate group. With "play the winner," patients are allocated to a group on the basis of the success or failure of the treatment used in the previous case. Randomization occurred only in the first 40 cases, and the study was not blinded. The data were analyzed after the first 40 patients and then after each subsequent 50 patients to determine whether the study could be terminated. The statistical model (the triangular test) incorporated both systems of patient allocation. The rationale for the use of a two-stage sequential analysis and the triangular test are outlined in the Appendix. The study was designed to detect a 20% difference in the incidence of hypotension between the groups, assuming an approximate incidence of 50% in the preload group, with statistical significance at the 10% (α = 0.1) level, one-tailed and 90% power.

All other statistical analysis was performed at the 5% (P = 0.05) level, two-tailed. Hemodynamic differences between the groups were compared using one-way analysis of variance for repeated measures. Correction for individual variation in baseline values was made by using the baseline value as a covariate. Changes within the groups were analyzed using analysis of variance for repeated measures and paired Student's t tests with Bonferroni correction. Demographic data and blood gas and acid–base values were compared using the appropriate analysis of variance technique. Univariate and multiple logistic regressions with backward elimination were used with hypotension as the output variable to identify factors associated with postspinal hypotension. Covariate analysis was performed on umbilical arterial pH (UA pH) results using patient variables as covariates to identify factors associated with low pH values. Pearson correlation coefficients were calculated where appropriate.
Results

The study was terminated after the third statistical analysis when 140 patients had been studied. The two groups were comparable for demographic and operative data (table 1). Two patients (one in each group) had a block height of T10 and T11 at 5 min. In these patients, surgery was delayed until 10 min after spinal, when the block heights were T6 and T5, respectively. Another patient, despite a block to T4 at 5 min and delivery under spinal anesthesia, required conversion to general anesthesia because of prolonged surgical time.

At termination of the study, 78 patients had received volume loading and 62 patients had not. Hypotension occurred in 43 volume-loaded patients (incidence 55%, 95% CI 43.4–66.4) and 44 unpreloaded patients (incidence 71.0%, 95% CI 58.0–81.8), resulting in a difference in incidence of 16% (95% CI 0.04–31.6) between the groups, which was statistically significant \((P = 0.073)\). Duration of hypotension was similar between preloaded (median 3, range 1–8 min) and unpreloaded patients (median 3, range 1–7 min).

Mean heart rate and systolic pressure changes in the two groups are shown in figure 1. Data obtained after the administration of ephedrine have been excluded. Mean systolic pressure was significantly lower \((P < 0.0025)\) than baseline values from 2 to 6 min from spinal injection in volume-loaded patients and from 2 to 4 min in unpreloaded patients. The largest decrease in the volume-loaded patients was from a baseline mean of 121 (SD 13.42 mmHg) to 106 mmHg (SD 16.91 mmHg) and in unpreloaded patients from 120 (SD 13.98 mmHg) to 103 mmHg (SD 18.69 mmHg), both nadirs occurring at 3 min from spinal injection. Heart rate was significantly greater \((P < 0.0025)\) than baseline from 1 to 3 min in preloaded patients and from 1 to 4 min in unpreloaded patients after spinal injection. There were no significant differences in heart rate or systolic pressure between the groups at any time. The maximum increase in heart rate occurred at 1 min, volume-loaded patients increasing from a baseline mean of 84 (SD 11.44 beats/min) to 101 beats/min (SD 15.80 beats/min) and unpreloaded patients increasing from 84 (SD 13.54 beats/min) to 98 beats/min (SD 15.92 beats/min; fig. 1).

Mean systolic pressure and heart rate in patients who became hypotensive and therefore required ephedrine

<table>
<thead>
<tr>
<th>Table 1. Group Comparability</th>
<th>Preload</th>
<th>Un preload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>28.1 (6.10)</td>
<td>27.6 (5.24)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.0 (9.86)</td>
<td>73.9 (9.35)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>153.3 (6.68)</td>
<td>155.2 (5.31)</td>
</tr>
<tr>
<td>Preload, ml</td>
<td>1413 (254)</td>
<td>—</td>
</tr>
<tr>
<td>Parity*</td>
<td>2 (1–6)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Gravidity*</td>
<td>3 (2–7)</td>
<td>3 (2–6)</td>
</tr>
<tr>
<td>Total fluid, ml</td>
<td>2005 (391)</td>
<td>695 (434)</td>
</tr>
<tr>
<td>Block height at 5 min*</td>
<td>T4 (C4–T11)</td>
<td>T4 (C6–T10)</td>
</tr>
<tr>
<td>ID time, min</td>
<td>18.1 (4.71)</td>
<td>17.5 (4.34)</td>
</tr>
<tr>
<td>UD time, s</td>
<td>101 (71.5)</td>
<td>99 (50.6)</td>
</tr>
<tr>
<td>Baseline recordings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>121.1 (13.42)</td>
<td>120.4 (13.98)</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>66.5 (11.38)</td>
<td>68.33 (12.73)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>83.7 (11.44)</td>
<td>84.0 (13.54)</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD) except where indicated.

Total fluid = preload and intrathecal fluid.

ID = spinal injection to delivery; UD = uterine incision to delivery.

* Median (range).

† \(P < 0.05\).

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Fig. 1. Systolic pressure and heart rate (mean, SEM) after spinal injection. Data obtained after ephedrine administration have been excluded from analysis, resulting in decreasing measurements used at successive times. At no time were there fewer than 19 patients (unpreloaded) or 38 patients (preloaded) available for analysis. —○— = preloaded patients; —— = unpreloaded patients.
are depicted in figure 2. The systolic pressure and heart rate at the onset of hypotension and after ephedrine are compared to baseline values. Mean systolic pressure at the onset of hypotension was 85 mmHg (SD 10.02 mmHg) in preloaded patients (baseline 122 mmHg, SD 13.21 mmHg, \( P < 0.0025 \)) and 83 mmHg (SD 13.26 mmHg) in unpreloaded patients (baseline 120 mmHg, SD 12.85 mmHg, \( P < 0.0025 \)). Systolic pressure was significantly less than baseline values for a further 4 min after the onset of hypotension in preloaded patients and for 2 min in unpreloaded patients. There were no significant differences between the groups. Heart rate was significantly greater \( (P < 0.0025) \) than baseline at the onset of hypotension in both groups and at 1, 2, and 4–17 min thereafter in preloaded patients and 5–8, 10, 11, 14, and 15 min in unpreloaded patients. There was no significant change in heart rate in preloaded patients after ephedrine administration. In unpreloaded patients, the heart rate decreased 1 min after the onset of hypotension and was significantly lower than in preloaded patients between 1 and 3 min after the onset of hypotension. The dose requirement for ephedrine was similar in each group. Preloaded patients received a mean of 18.1 mg (SD 13.8 mg, range 5–70 mg), and unpreloaded patients received a mean of 16.8 mg (SD 8.6 mg, range 5–40 mg; fig. 2).

The mean time to onset of hypotension was 3.3 min (median 3 min, range 1–17 min) in the unpreloaded patients and 4.1 min (median 3 min, range 1–12 min) in preloaded patients (NS). Univariate analysis of demographic and baseline variables with hypotension as the outcome demonstrated age as the only significant patient variable associated with hypotension. Mean age was 28.7 yr (SD 5.38 yr) in hypotensive patients and 26.7 yr (SD 4.51 yr) in nonhypotensive patients \( (P = 0.0026) \). Group was not identified as associated with a hypotensive outcome \( (P = 0.055, \text{chi-squared} = 3.68) \). Stepwise logistic regression confirmed the association with age \( (P = 0.03) \) and also did not identify group as a significant factor \( (P = 0.09) \).

All infants had full Apgar (minus color) scores 5 min after delivery. Two minutes after delivery, one infant had an Apgar minus color score of 6 and another of 7 in the unpreloaded group, and one of 5, one of 6, and two of 7 in the preloaded group. There were no significant differences between the groups in maternal, umbilical venous, or umbilical arterial blood gas analysis (table 2). Two-way analysis of variance examining both group and hypotension demonstrated that umbilical arterial standard base excess was significantly lower in hypotensive patients \( (\text{mean} -3.4 \text{ mm}, \text{SD} 2.81 \text{ mm}) \) than in patients who did not become hypotensive \( (\text{mean} -2.4 \text{ mm}, \text{SD} 1.99 \text{ mm}, P = 0.04) \). Covariate analysis of UA pH demonstrated that a longer spinal injection to delivery time \( (P = 0.007) \) and a longer uterine incision to delivery time \( (P = 0.004) \) were associated with lower UA pH. Subsequent Pearson correlation analysis for UA pH confirmed the association with spinal injection to delivery time \( (P = 0.0005, r = -0.31) \) and uterine incision to delivery time \( (P = 0.0001, r = -0.35) \) and also demonstrated a correlation with baseline systolic pressure \( (P = 0.01, r = -0.22) \). Preloading was not significantly associated with UA pH \( (P = 0.27) \), nor was hypotension \( (P = 0.72) \).

Discussion

Acute hydration for the prevention of hypotension of spinal anesthesia in human parturients was first studied in 1968 by Wollman, who administered 11.5% dextrose in Ringer’s lactate solution over 14–20 min before spinal anesthesia.\(^5\) Both the study group (14 patients) and the control group (10 patients) were small, and 6 patients in the study group and 5 in the control group were in active labor, a group in which we now know the incidence of hypotension is less than in nonlaboring parturients.\(^{10}\) In addition, patients were kept supine and, notably, no patient in the fluid-loaded group became hypotensive.

A second study from the same center using a similar volume of fluid with left uterine displacement confirmed the findings of the first study in that, again, no patient became hypotensive.\(^6\) Subsequent to these two studies, there have been numerous publications on spinal anesthesia; despite the use of lateral tilt and crystalloid volume loading equal to or greater than 1 l, there has been a failure to completely eliminate the incidence of hypotension.\(^{7–24}\)

In 1976, Clark et al. viewed spinal hypotension to be a persistent problem and investigated the interaction of fluid loading and uterine displacement.\(^{10}\) This was the first study to challenge the findings of Marx et al.\(^6\) since Clark et al. showed that the combination of fluid and uterine displacement did not eliminate hypotension. One major flaw in the Clark et al. study was the failure to include a group that had uterine displacement alone. When Clark et al.'s results are reanalyzed on the basis of requirement for ephedrine once the patients had been turned on their side (and hence aortocaval compression eliminated), the incidences of significant
hypotension are 48% (no preload, no uterine displacement), 42% (preload alone), and 43% (preload and uterine displacement), respectively (no significant difference). This suggests that, in the absence of aortic compression, fluid preload would make little difference.

An alternative to crystalloid preloading would be to use colloid or a colloid substitute. Only one study has examined the effect of colloid administration on the incidence of spinal hypotension in parturients. Mathru et al. demonstrated that 5% albumin in a crystalloid solution (15 mg/kg) eliminated hypotension compared to a 21% incidence in those who received a similar volume of crystalloid alone. This study has not been repeated, however, and it is accepted that colloid solutions are unlikely to achieve widespread use because of the increased expense and potential for anaphylactoid reactions. If Mathru et al.’s results are accepted, then it is likely that about 3–4 times the volume of crystalloid would be needed to achieve the same results. This equates to 45–60 mg/kg, which not only would take a long time to be infused but could result in acute hemodilution.

The results of the present study challenge our perceptions of the volume of loading as hypotension was not eliminated by fluid preloading, occurring in 55% of cases. Because fluid preloading may have influenced the hemodynamic response not only to the spinal anesthetic but also to the administration of ephedrine, the two factors were analyzed separately. In this way, one can assess how the groups responded after spinal anesthesia, uncomplicated by ephedrine, and also how the groups responded to ephedrine once hypotension had been detected. Apart from subtle differences in the heart rate response after hypotension and administration of ephedrine, the hemodynamic behavior was remarkably similar between the two groups. The different.
ence in the heart rate response (fig. 2) may have been due to differences in right atrial filling between the groups. The association between age and hypotension was unexpected, and we do not consider this to be of clinical significance. The reason that group was not significantly associated with hypotension on univariate analysis (chi-squared = 3.68, \( P = .055 \)) was the 10% significance level accepted on the sequential design.

The clinical and biochemical status of neonates did not differ between the groups and other than a small but statistically significant difference in umbilical arterial base excess, there were no biochemical differences in the neonates of hypotensive versus nonhypotensive patients. This confirms the value of frequent measurement of blood pressure and immediate treatment of hypotension when it occurs. There was a weak but statistically significant negative correlation between UA pH and baseline systolic pressure, spinal injection to delivery, and uterine incision to delivery times. These times depend mainly on surgical factors, such as the technical difficulty of the procedure and experience of the operator. Thus, it would appear that operative factors are more important in influencing UA pH provided that hypotension is promptly recognized and treated. It is possible that some patients had a higher systolic pressure than others reflecting a higher level of anxiety and catecholamine release. This might influence the biochemical status of the fetus by reducing uterine blood flow, an effect that would be compounded by delayed delivery.

The clinical relevance of a difference in incidence of hypotension between the groups of 16% is debatable. Whereas the design of the study would not have influenced the incidence of hypotension in either group or the resulting 16% difference, the statistical significance of this difference would be greater if a more conventional study design with groups of equal sizes had been used. Using the sequential analysis design, the \( P \) value equalled 0.073; whereas if patients had been randomized to two groups with 70 per group, the \( P \) value would have been 0.05. Clearly increasing group sizes would further increase the level of statistical significance but should not alter the conclusion regarding the clinical significance of the 16% difference, which remains. Some investigators have not regarded a difference of 35% as clinically important enough to justify the use of inflatable splints to prevent hypotension. Any reduction in the incidence of hypotension by preloading must be viewed in the appropriate clinical setting. For the elective case, in which the delay caused by preloading is of little consequence, any reduction in the incidence of hypotension might be considered worthwhile. However, in the urgent case, there may be insufficient time to complete preloading, and we believe that the risk associated with a 16% increase in hypotension is not as great as the risk associated with choosing general anesthesia as an alternative.

One possible criticism of our study is that the dose of bupivacaine used (7.5 mg) is smaller than that used in other centers, thus limiting the applicability of our conclusions. The dose of bupivacaine we used has been tailored to our population, which is of short stature compared to the norm. The mean heights of our two groups were 153 and 155 cm, respectively, whereas normal mean body height for 18-year-old women is 162.5 cm.28 Because the reduced dosage leads to rapid regression of the block, we routinely administer an intravenous dose of opioid after delivery of the baby. We do not believe that our results are inapplicable to other centers because our incidence of hypotension is similar to reported incidences in other spinal studies, and the level of sensory blockade (and thus sympathetic blockade) would be similar between our patients and those where a higher dose was used. A second criticism is that our study was not blinded and that open knowledge of the group assignment might allow for selection bias. However, the patients were as clinically homogeneous as possible, the groups were comparable and all hemodynamic data were recorded by a study-dedicated monitor. Therefore, we do not consider study bias to be a significant factor. Third, we studied elective cesarean section patients, which provides only indirect evidence regarding the value of preload in the urgent case. We chose elective ASA physical status 1 patients because they were uncomplicated. Our results, therefore, are not complicated by considerations regarding maternal health, and neonatal assessments are unaffected by preexisting fetal compromise. In addition, we believed it would have been unethical to embark on the study in urgent cases.

The results of our study have changed our clinical practice for urgent cesarean section, for which the use of spinal anesthesia is increasing. Because of the emphasis on the importance of fluid preloading, the practice in our unit was to insist on administration of 20 ml/kg crystalloid preload before spinal injection. In many instances, patients were denied spinal anesthesia and general anesthesia was administered. The implication of our results, albeit conducted in elective patients, is that, though fluid preloading will reduce the
incidence of postspinal hypotension, the reduction is not sufficient to justify delay in commencing spinal anesthesia when this is the most appropriate method of anesthesia for the patient. Accordingly, our current practice is to commence preloading via a fully open administration set and to proceed with spinal anesthesia without delay despite the possibility of "insufficient" preload before onset of sympathetic block.

Appendix

Rationale for Study Design

Anesthetic literature mandates fluid preload in the prevention of spinal hypotension at cesarean section, and our routine clinical management has followed this standard of practice. The implication is that withholding preload would result in an increased incidence of hypotension with adverse maternal and neonatal effects. Therefore, conducting a randomized controlled study in which 50% of the patients would receive an inferior treatment was deemed unethical. To commence the study, two criteria had to be met. First, the study had to be stopped as soon as possible after a significant difference in outcome of the two treatments was detected. Second, the number of patients receiving a potentially inferior treatment had to be minimized. A sequential analysis design met the first criterion and the "play the winner" rule met the second. Therefore, the rationale of both the sequential design of this study and the use of the "play the winner" rule was ethical. Because sequential analysis is based on repeated statistical analysis of accumulating data, there is a loss of statistical efficiency and potentially more patients are required. However, in the event of a large difference in treatment effect between the groups, the study would be terminated early, thus using fewer patients than in a conventional randomized controlled design. Early termination of the study was encouraged by the choice of a high nominal significance level (α = 0.1) and a one-tailed test, which we felt was justified by the overwhelming view of the literature in support of preloading. In the event of a "no difference" result, we wished to decrease the risk of a type II error and chose a β level of 0.1 (fig. 3).

The "play the winner" rule creates the problem that, in the event of a large difference between the groups, it is possible for a statistically significant difference in the parameter of main interest to be detected with insufficient patients in one group to allow statistical comparison of other parameters (e.g., group comparability). In this event, insufficient data would be obtained to validate the difference seen in the parameter of main interest. A two-stage design with the first 40 patients studied as prere-randomized pairs was adopted because the outcomes of each phase of the study were statistically independent, the two phases can be combined under one statistical treatment. The triangular test was chosen because a one-tailed test was appropriate, the boundaries are calculated easily, and it is based on the odds ratio, which takes into account any change in the incidence of failure in the reference (preloaded) group. The triangular test compares the success rate between the two groups by use of Z, the efficient score, which is given by Z = (N_1 - N_2) / (N_1 * N_2)^1/2. I.e., a weighted estimate of the difference between the two success proportions, and V, Fisher's information, which is approximately

\[ Z = 0.25 \left( \bar{p} - \bar{p}_0 \right) \]

where \( \bar{p} \) is the average proportion of success of both groups from the study results, \( \bar{p}_0 \) is the total sample size, \( n_1 \) and \( n_2 \) are the numbers of subjects in each group, and \( p_1 \) and \( p_2 \) are the observed proportions of success in each group. \( V \) increases as the total number of subjects increases. \( Z \) and \( V \) are calculated at each point of analysis and plotted against the position of the predetermined boundaries (fig. 3). The choice of interval between analyses (every 50 cases) represents an arbitrary compromise between frequent analysis (decreasing statistical efficiency) and infrequent analysis (resulting in an excessive number of patients studied unnecessarily after a significant result). The calculated maximum requirement for subjects using our study design (represented by the point at which the two boundaries in fig. 3 would meet) was 230 subjects. We achieved a significant result after 140 subjects had been studied, with 62 patients being offered the potentially "inferior treatment."

Conventional randomized comparison between the two groups, with equal numbers in each group, \( \alpha = 0.1 \) and \( \beta = 0.1 \) would have required 158 subjects to detect a 20% difference, with 79 being allocated the "inferior treatment."

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References


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