

**COMPARISON OF THE EFFECT OF CO- ADMINISTRATION OF
CRYSTALLOID VERSUS COLLOID, WITH PHENYLEPHRINE INFUSION
FOR THE PREVENTION OF HYPOTENSION FROM SPINAL ANAES-
THESIA DURING ELECTIVE CAESARIAN SECTION**

(A PROSPECTIVE COMPARATIVE STUDY)

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POTENSION FROM SPINAL ANAESTHESIA DURING ELECTIVE
CAESARIAN SECTION**

BY

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RESEARCH DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of

MASTER OF MEDICINE (MMED):ANAESTHESIOLOGY

in the

FACULTY OF HEALTH SCIENCES (SCHOOL OF MEDICINE)

at the

UNIVERSITY OF LIMPOPO

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DECLARATION

I declare that this dissertation submitted to the University of Limpopo for the degree of MASTER OF MEDICINE(Anaesthesiology),has been designed, performed and written by me and has not submitted by me at another institution.

DR L.J. FRANS

Student number 19103123

01 DECEMBER 2010

(i)

DEDICATION

This work is dedicated to all colleagues who have contributed positively towards my understanding of anaesthesiology and the acquisition of skills. Moreover, I dedicate it to the thousands of patients who over the years have provided a source of learning that is better than any textbook ever written.

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Graph 2: Blood pressure changes in Group B at 5 minute intervals.

LIST OF ABBREVIATIONS

1. *ug* = microgram
2. *mg* = milligram
3. *ug/ml* = micrograms per milliliter
4. *C/S* = Caesarian section
5. *N* = Number

ABSTRACT

Aims and objectives of study

Aim: To determine whether there is any difference when phenylephrine infusion is combined with either a crystalloid or a colloid in the prevention of symptomatic hypotension during spinal anaesthesia for caesarian section.

Objectives:

1. To determine whether there is any difference in the total dose of phenylephrine needed to maintain normal blood pressure when crystalloid or a colloid is used.

2. To determine the number of women who develop symptoms (viz. dizziness, restlessness, nausea and vomiting) when phenylephrine infusion is combined with either a crystalloid or a colloid.

3. To determine the severity of symptoms in the phenylephrine plus crystalloid group versus the phenylephrine plus colloid group.

Sampling methods ,study designs and procedures

Study design: A prospective, randomised, comparative study of women who had caesarian section under spinal anaesthesia was conducted. The aim was to determine whether giving a phenylephrine infusion plus_a crystalloid versus a phenylephrine infusion plus a colloid made a difference in the prevention of symptomatic hypotension.

Sample criteria: Pregnant women undergoing caesarian section under spinal anaesthesia were selected and divided randomly into two groups; one to receive a phenylephrine infusion plus a crystalloid (group A), the other to receive a phenylephrine infusion plus a colloid (group B). Patients were excluded for the following reasons:

1. Absolute contra indications to spinal anaesthesia.
2. Emergency Caesarian section
3. Diabetes mellitus
4. Renal disease

Sample size: The necessary sample was determined to be 122 patients, each group having 61 patients.

Procedures: Each patient received bupivacaine with dextrose (12.5 mg) plus sufentanyl $2.5\mu\text{g}$ intrathecally at L3-L4 intervertebral space. Patients in group A received 350ml of Ringer's Lactate over 15 minutes, started immediately after administration of anaesthesia, and 3ml of the same fluid for each 1ml of blood lost. Patients in group B received 150ml of Voluven (Hydroxyethyl starch 130/40) over 15 minutes, started immediately after administration of anaesthesia, and 1ml of the same fluid for each 1ml of blood lost. Each patient also received an infusion of phenylephrine ($50\mu\text{g}/\text{min}$), started within a minute of giving anaesthesia and stopped if the mean blood pressure exceeded the baseline by 20%. A 50ug bolus was given any time the mean blood pressure was 20% below the original. Non-invasive blood pressure measurements were taken every 2.5 minutes for 45 minutes.

At the end of the procedure patients were questioned for the following symptoms: dizziness, nausea, vomiting and restlessness (as observed by researcher). They were then classified as follows: asymptomatic, mildly symptomatic (symptoms discovered only on questioning), moderately symptomatic (patient complained about symptoms but not restless), or severely symptomatic (patient complained about symptoms and was restless).

Statistical analysis

The analysis was based on descriptive statistics with variables expressed as Mean \pm Standard deviation. Differences between the two groups were determined using the student *t*-test and conversion of the value of (*t*) to p-value. Differences were considered significant when the p-value was ≤ 0.05 . Relational statistics were calculated using the Chi-Square analysis to reflect the association of the use of a crystalloid or colloid plus phenylephrine infusion, with prevention of hypotension during spinal anaesthesia for elective Caesarian section.

Results

Blood pressure readings at the beginning and the end of measurement period were statistically similar between the two groups, suggesting equal effectiveness in maintaining blood pressure. The medians for the infused amounts and total amounts of phenylephrine were the same for both groups (2200 μ g). There was no statistically significant difference in the number of patients requiring rescue boluses of phenylephrine ($p=0.52$), nor was there a significant difference in the total amount of drug used as bolus ($p=0.7$). The majority of patients in both groups were asymptomatic (57% in group B and 69% in group A), with a p-value of 0.2. Most of these patients experienced mild symptoms (63% in group A versus 64% in group B, $p=0.8$).

Conclusion

The results of this study suggest there is no added advantage in using a colloid co-administration with a phenylephrine infusion to prevent hypotension during spinal anaesthesia for elective caesarian section. A crystalloid co-administration is equally effective.

1. INTRODUCTION

Hypotension resulting from intrathecal injection of a local anaesthetic is the commonest complication of spinal anaesthesia. It is caused by sympathetic blockade in the segments affected by the block, causing vasodilation, reduced venous return to the heart and a reduced cardiac output.

Pregnancy exacerbates the problem and it is associated with symptoms such as dizziness, nausea and vomiting and can cause restlessness.

Nausea and vomiting are associated with dissatisfaction with spinal anaesthesia. These may lead to women refusing spinal anaesthesia in subsequent caesarian sections (1).

Many solutions have been attempted to alleviate the problem. These include limb elevation, elastic stockings, preloading with large volumes of crystalloids, and boluses of vasopressors. The most appealing preventive treatment was published by a group from Hong Kong. They had good results using an infusion of phenylephrine (100ug/minute) plus co-administration of a crystalloid (up to 2 litres of Ringers Lactate) (2).

This study uses the same treatment, though reduced phenylephrine doses ($50\mu\text{g}/\text{minute}$) and lesser fluid volumes. The main thrust of the study is to determine whether using a crystalloid or a colloid makes a difference in the effectiveness of this form of treatment.

LITERATURE REVIEW

Administration of a local anaesthetic intrathecally at the lower lumbar levels causes enough sensory and motor block to allow surgery to the lower half of the body. This form of anaesthesia is currently the backbone of obstetric anaesthesia as it is associated with less mortality than general anaesthesia and allows earlier mother and child bonding (3). Unfortunately, the sympathetic nervous system is not spared by the block. The sympathetic block causes loss of vasomotor tone, leading to vasodilation; reduced venous return to the heart; reduced stroke volume and cardiac output, thus causing hypotension. Pregnancy compounds the situation in the following ways:

First, the pregnant uterus compresses the inferior vena cava when the patient lies supine, causing further reduction in venous return. Second, engorgement of epidural venous plexuses (a result of caval compression) narrows the spinal canal, resulting in higher migration of the local anaesthetic. This tends to cause a higher sympathetic block.

Various, ineffective methods to counter the problem have been attempted. Examples are lower limb elevation and use of elastic stockings. Preloading with crystalloids had been the gold standard for a long time. This practice involved administration of a predetermined volume of a crystalloid before giving a spinal anaesthetic. Initially volumes were as high as 4 liters, but they have been reduced over time to as low as 350-500 ml in local practice.

Many researchers have successfully demonstrated that preloading does not necessarily reduce the incidence or severity of hypotension during spinal anaesthesia for Caesarian section (4, 5, 6). Practice has shifted to rapid administration of a pre-determined volume of crystalloid, commenced during or immediately after administration of anaesthesia (co-loading, co-hydration or co-administration)(1).

Colloids have been a subject of interest in this regard. In support of their superiority, Ueyama and Tinigami cited their much better intravascular retention and improved vascular volume (7). Opponents to this line of practice have presented evidence that in practice, there is no improved blood pressure control when colloids are used (8). Just as in the case of crystalloids, it has been demonstrated that colloid pre-loading is not superior to colloid co-loading. This aspect of prevention of hypotension still remains a minefield of debate among obstetric anaesthesiologists.

The undisputed and definite method of treatment of this hypotension is administration of vasoconstrictors. They are commonly used as boluses to treat hypotensive episodes (e.g. ephedrine 5-10 mg or phenylephrine 25-100 μ g). Ephedrine has been used and researched extensively for rescue therapy, prophylaxis and side effects (9; 10). However, phenylephrine has a short duration of action and elimination half-life. Infusions of this drug have better preventive and therapeutic effects than boluses. This has been demonstrated in studies involving pregnant women, and outside the sphere of obstetric anaesthesia.

The most commonly used and researched regimen is based on infusion of 100 μ g/min of phenylephrine to maintain blood pressure within 20% of the baseline(11,12).Ronald George et.al demonstrated better stability(i.e. absence of excessive rebound hypertension) using an infusion of only 50ug/ml(13). Ngan Kee, et, al demonstrated great success using a combination of phenylephrine infusion(100 μ g/minute) plus Ringer's lactate co-administration(up to 2 liters).This is probably the first truly successful method of prevention, with a success rate as high as 96%.Despite the success they have demonstrated, the method is not widely practiced. Therefore, there are no large review studies that evaluate the success of the practice on a large scale.

3. AIMS AND OBJECTIVES

Aim: The aim of this study was to determine whether there is any difference when a phenylephrine infusion is combined with a crystalloid versus a colloid, in the prevention of hypotension following spinal anaesthesia in women undergoing elective Caesarian section.

Objectives: The objectives were set out as follows.

1. To determine whether there is any difference in the total dose of phenylephrine needed to maintain a normal blood pressure when a crystalloid or a colloid is used.

2. To determine the number of women who develop symptoms (i.e. dizziness, restlessness, nausea and vomiting) when a phenylephrine infusion is combined with either a crystalloid or a colloid.

3. To determine the difference in the severity of symptoms between the phenylephrine plus crystalloid group, and the phenylephrine plus colloid group.

4. **METHODS AND STUDY DESIGNS**

Study design: A prospective, randomized, comparative study of women who received spinal anaesthesia for elective Caesarian section, was performed.

The study was aimed at determining whether giving phenylephrine infusion plus a crystalloid versus a phenylephrine infusion plus a colloid, makes any difference in the prevention of symptomatic hypotension in these women.

Setting: The study was performed at Dr. George Mukhari Hospital, a tertiary hospital serving as a teaching hospital for the University of Limpopo (Medunsa campus).

Sample size: The sample size of the study was calculated to conform to 95% certainty that no more than 10% discrepancy exists between the use of a crystalloid and a colloid with phenylephrine infusion. The effectiveness of a phenylephrine infusion together with a crystalloid is reported to be at least 95%(1), and the anticipated effectiveness of using a colloid is expected to be at least 85%. Once these factors were considered, and at a level of power of 80%, each arm of the study was set at 61 patients, i.e. a total of 122 patients, randomized into two groups.

Sample criteria: Women undergoing elective Caesarian section under spinal anaesthesia were randomized into either a group to receive phenylephrine infusion plus a crystalloid, or a group to receive phenylephrine infusion plus a colloid. Randomization was conducted based on a double blind procedure in which both the researcher and the patient were blinded to the choice for either of the groups. This was done using 122 envelopes, of which 61 were labeled (A), and another 61 labeled (B).

A nursing assistant was responsible for randomizing the patients for either (A) or (B), and the researcher knew of the allocation only immediately prior to administration of anaesthesia.

Exclusion criteria: Patients with any of the following conditions were excluded from the study:

1. All known contra-indications to spinal anaesthesia , 2. Emergency Caesarian section, 3. Cardiovascular disease(hypertension, heart disease, peripheral vascular disease), 4. Diabetes mellitus, 5. Renal disease.

Patient allocation: Patients were allocated as indicated above, randomly into two groups

Group A- These patients received a phenylephrine infusion plus a crystalloid.

Group B-These patients received a phenylephrine infusion plus a colloid.

Procedures: All patients received bupivacaine with dextose(12.5 mg) plus sufentanyl(2.5 μ g) intrathecally at L3-L4 intervertebral space, using a 25-gauge spinal needle. A baseline, non-invasive blood pressure measurement was taken before giving anaesthesia. Subsequent readings were taken every 2.5 minutes, commencing within a minute of giving anaesthesia. A 50 μ g/ml phenylephrine solution was prepared and infused within a minute after giving anaesthesia. The infusion device was set to run at 60ml/hr. Rescue boluses of phenylephrine (50 μ g) were given when the mean blood pressure dropped by more than 20% below the baseline.

The crystalloid used was Ringer's lactate, starting with a bolus of 350ml given over 15 minutes (commenced within a minute of giving anaesthesia), and the rest given to replace volume loss. The colloid used was Voluven (Hydroxyethyl starch 130/04)given as a bolus 150ml over 15 minutes(commenced within a minute of giving anaesthesia), and the rest given to replace volume losses. These volumes were chosen because equal volumes of a colloid and a crystalloid are not equivalent. The former has high molecular weight compounds that promote longer intravascular retention, whereas, two thirds of the former migrates to the interstitium within an hour of administration. The following volume replacement equivalents for the two fluids were adhered to:

1. Three millilitres of Ringer's lactate for each volume of blood lost.
- 2 .One millilitre of Voluven for each volume unit of blood lost.

Ethical considerations: Proposal to perform the study was submitted to the hospital management and the Medunsa Campus Research Committee, and approval from both bodies was obtained. Patients participating in the study had the procedure explained before coming to theatre. They had to give written consent when they were satisfied.

5. DATA COLLECTION AND ANALYSIS

Data collection: Data was collected using forms that reflected the following variables:

1. Patient number and indication for operation.
2. Time of administration of anaesthesia.
3. Blood pressure readings with time intervals.
4. Time of commencement and stoppage of phenylephrine infusions plus all boluses given.

5. Grading of symptoms:

Grade 0= asymptomatic.

Grade I=1 symptoms graded as mild.

Grade II= 2 symptoms or 1 symptom graded moderate to severe

Grade III= more than 2 symptoms.

Data analysis: This was based on descriptive statistics with variables expressed as a Mean \pm Standard deviation. Differences between the two groups were determined using the Student *t* - test and the transformation of (*t*) to p-value. Differences between the two groups were considered significant if the p-value was ≤ 0.05 . Relational statistics were calculated using the Chi-Square analysis to reflect the association of the use of a crystalloid or a colloid co-administration with phenylephrine in preventing hypotension during elective Caesarian section.

6. RESULTS

One hundred and twenty-two (122) patients were prospectively randomized for this study in a ratio of 1:1 for patients who received co-infusion of phenylephrine and crystalloid fluid (Group A) and those who received phenylephrine infusion with colloidal fluid (Group B). Two patients who received co-infusion of phenylephrine and colloidal fluid (Group B) were excluded from data analysis because they were eventually transferred to general anaesthesia following failure to achieve spinal block. Therefore, the results presented for this study is a comparison between 61 patients (Group A) and 59 patients (Group B).

Table 1 shows the list of indications for the elective caesarean section (C/S) in the two groups. The most prominent indication for C/S in the two groups of pregnant women was previous C/S, followed by foetal breech presentation. Other notable indications include foetal macrosomia, oblique lie, previous caesarean complicated by foetal macrosomia and cephalopelvic disproportion. None of these indications showed any significant statistical difference between the two groups.

Table 1: Indications for elective C/S Group A [N=55] vs. Group B [N=53]

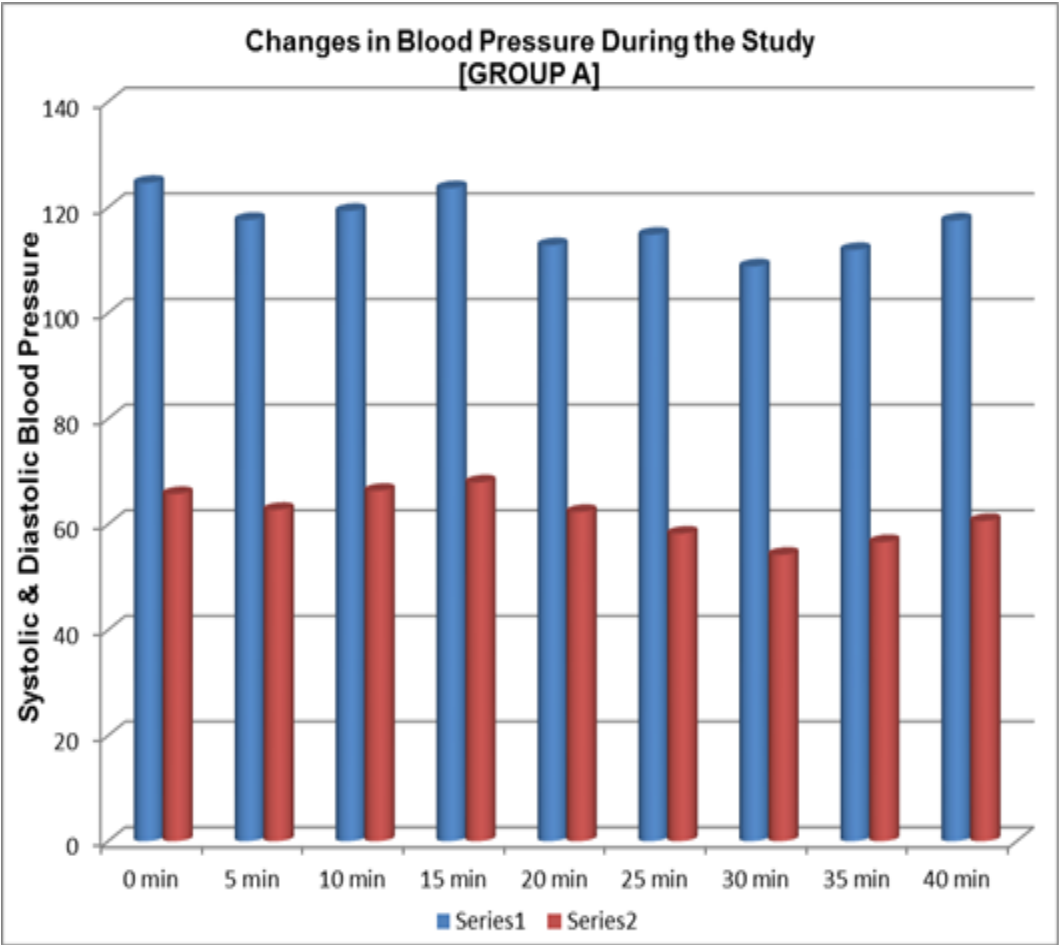
Table1: Indications for elective C/S Group A [N = 55] vs. Group B [N = 53]	Group A	Group B	p-value
Previous Caesarean Section	16 (29.1%)	18 (34.0%)	0.6298
Foetal Breech Presentation	12 (21.8%)	7 (13.2%)	0.2698
Foetal Macrosomia	8 (14.5%)	7 (13.2%)	0.9339
Previous Caesarean Section x 2	7 (12.7%)	6 (11.3%)	0.9235
Foetal Oblique Lie	4 (7.3%)	7 (13.2%)	0.9044
Cephalopelvic Disproportion	3 (5.5%)	6 (11.3%)	0.8978
Previous Caesarean Section + Big Baby	3 (5.5%)	2 (3.8%)	0.8792
Foetal Horizontal Lie	2 (3.6%)	Nil	-

Key: N= Number of patients (percentage); p-value (level of significant difference)

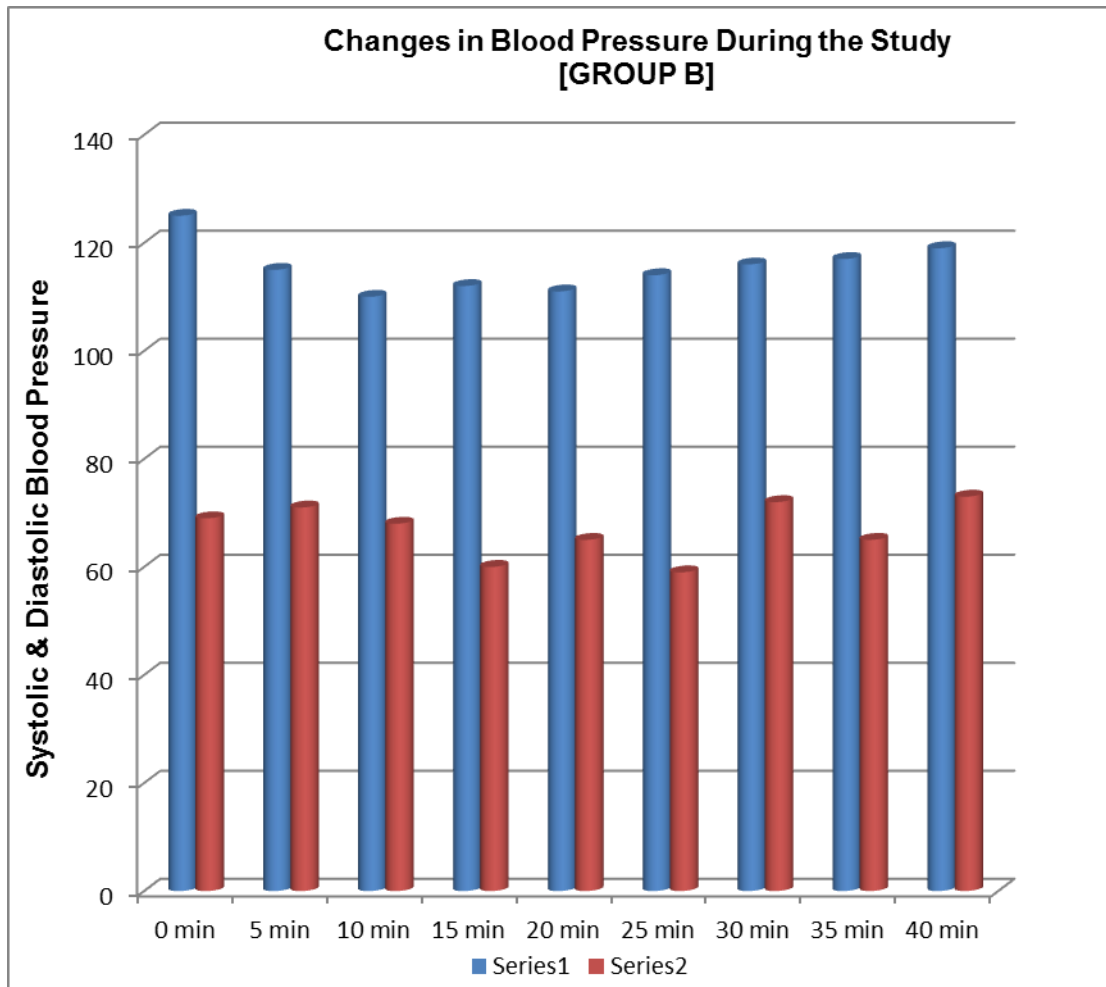
Table 2: Prevention of hypotension after spinal anaesthesia using infusion of phenylephrine plus crystalloid co-hydration (Group A) or infusion of phenylephrine plus a colloid co-hydration (Group B)

Blood Pressure (mmHg)	Group A (N = 61)	Group B (N = 59)	p-value
Blood Pressure at Start			
Systolic: Range	103 – 143	107 – 142	0.1131
Mean	121	123	
Std. Dev.	6.54	6.90	
Diastolic: Range	51 – 92	57 – 90	0.1732
Mean	71.4	73.4	
Std. Dev.	8.23	7.80	
Blood Pressure at the End			
Systolic: Range	98 - 134	107 – 142	0.2050
Mean	120	123	
Std. Dev.	6.85	7.60	
Diastolic: Range	41 – 86	45 – 92	0.3690
Mean	69.8	73.2	
Std. Dev.	9.4	8.2	

Key: Std. Dev. =Standard deviation, p-value=significance of variation



GRAPH 1: BLOOD PRESSURE CHANGES IN GROUP A AT 5 MINUTE INTERVALS



GRAPH 2: BLOOD PRESSURE CHANGES IN GROUP B AT 5 MINUTE INTERVALS

Table 2 in page 20 compares the blood pressure at the start of C/S procedure just before spinal anaesthesia was given, with blood pressure achieved at the end of the procedure, with continuous infusion of phenylephrine to prevent hypotension. Neither the blood pressure readings prior to spinal anaesthesia nor the readings immediately following the cessation of infusion of phenylephrine showed any significant statistical differences between the two groups of women.

Graphs 1 and 2 show comparable maintenance of blood pressures between the groups over similar time intervals.

The mean time for infusion of phenylephrine co-infusion with either a crystalloid or colloid was 44 minutes for both groups of women who underwent C/S under spinal anaesthesia. The amount of phenylephrine co-infusion with crystalloid or colloidal fluid as well as the amount of rescue phenylephrine used to prevent hypotension is shown in Table 3 below. Again, the median amount of phenylephrine used, as well as the amount needed as rescue medication to avoid hypotension, were not statistically different between the two groups.

Table 3: The amount of phenylephrine infusion and the need for rescue medication in GROUP A versus GROUP B.

Phenylephrine Infusion(μg)	Group A	Group B	p-value
Amount of Infusion:			
Range	250 – 2250	400 – 2300	-
Median	2200	2200	
Number of patients requiring rescue bolus	22 (36.1%)	26 (44.1%)	0.5208
Amount of drug used for rescue:			
Range	50 – 150	50 – 250	0.7961
Mean	86.4	88.5	
Std. Dev.	38.4	49.6	
Total amount of phenylephrine:			
Range	250 – 2350	400 – 2450	
Median	2200	2200	

Table 4 shows the range of symptoms experienced by the women following the use of either phenylephrine co-infusion with a crystalloid (Group A) or phenylephrine co-infusion with a colloid (Group B). It also shows the grading of the severity of the symptoms experienced. The majority of the women did not experience any symptoms and this was observed in both groups of women with no statistical difference between the two groups. Dizziness was the most common symptom and it occurred in more than 50% of the women in both groups. This was followed by nausea (23.5%, crystalloid group; 19.5%, colloid group). Restlessness was experienced by 17.6% (crystalloid group) and by 22% in the colloid group. Very few patients had symptom of vomiting (5.9% in the crystalloid group; 2.4% in the colloid group), and these symptoms were statistically similar for both groups. Among women who had experienced symptoms, more than 60% of them in both groups had mild symptoms and very few of the patients experienced severe symptoms. Irrespective of which fluid (crystalloid or colloid) was used as co-infusion with phenylephrine, the range and grading of the symptoms were statistically similar for both groups of patients.

Table 4: Symptoms experienced by women who received infusion of phenylephrine with crystalloid co-hydration (Group A) or phenylephrine infusion with colloid co-hydration (Group B): Number of patients (percentage).

Symptoms	Group A [N = 61]	Group B [N = 59]	p-value
Asymptomatic	42 (69.0%)	34 (57.6%)	0.2057
Nausea	8 (23.5%)	8 (19.5%)	0.5188
Vomiting	2 (5.9%)	1 (2.4%)	0.5209
Dizziness	18 (52.9%)	23 (56.1%)	0.8842
Restlessness	6 (17.6%)	9 (22.0%)	0.5603
Grades of symptoms			
1. Mild	12 (63.2%)	16 (64.0%)	0.8045
2. Moderate	4 (21.0%)	7 (28.0%)	0.4555
3. Severe	3 (15.8%)	2 (8.0%)	0.9605

Correlation coefficient [R], which is a measure of the closeness of a relationship between different variables, was determined to establish any correlation between the range of blood pressure before, during and after use of co-infusion of phenylephrine with either a crystalloid or a colloid.

The correlation coefficient equals zero if the variables are not associated and the closer the value of [R] is to zero the higher the probability of no association between the variables. This statistical phenomenon was calculated to demonstrate any correlation between the range of blood pressure observed during the use of spinal anaesthesia, in association with co-infusion of phenylephrine with a crystalloid or a colloid. This is illustrated in Table 5 below, in which the blood pressure readings at the time of spinal anaesthesia and at regular intervals throughout C/S surgery, were used in a correlation analysis between those who received co-infusion of phenylephrine with a crystalloid (Group A) and those who had co-infusion with a colloid (Group B).

Table 5: Correlation Coefficient for blood pressure measurements between patients in Group A versus patients in Group B.

Blood Pressure	Correlation Coefficient	p-value
Systolic Blood Pressure	0.0456	0.6180
Diastolic Blood Pressure	0.0606	0.5073

The result of this exercise further demonstrates the similarity in outcomes for the patients who underwent caesarean section after spinal anaesthesia and in whom the occurrence of hypotension was avoided by the use of continuous co-infusion of phenylephrine and a crystalloid or co-infusion with a colloid. This means that the use of either a crystalloid or colloid co-administration with phenylephrine does not lead to differences in blood pressure readings during the performance of C/S for patients under spinal anaesthesia.

7 DISCUSSION

The two groups of patients analyzed in this study were similar in all respects. They were women of reproductive age undergoing elective Caesarian section, without co-morbidities or contraindications to spinal anaesthesia. Indications for operation were statistically similar between the two groups. A decision was taken to exclude age as a variable as it would add no value to the study.

Time over which data was collected was capped at 45 minutes based on the observation that this was the average time that patients spent in the operating room despite the wide variation in operating times.

Analysis of pre-operative versus end-operative blood pressures showed statistically equivalent success in maintaining blood pressure between the two groups (table 2, graphs 1&2). Two thirds of patients in group A, and nearly sixty percent in group B were asymptomatic (table 4). Calculation of the p-value for these variables showed no significant statistical difference between the two groups. Notably, the success of prevention in this study was not as marvelous as that reported by Ngan Kee, as one-third of patients in each group did experience symptoms associated with hypotension. This is attributable to the restrictive administration of fluid and phenylephrine employed in this study. However, a claim of success is reasonable, because, among those with symptomatic hypotension, an overwhelming majority had mild symptoms (see table 4).

A comparison of the doses of phenylephrine (infusions and boluses) required to prevent symptomatic hypotension showed no statistically significant difference between the two groups (see table 4).

This falls in line with the other variables in highlighting a lack of difference in outcomes between patients receiving phenylephrine infusion plus crystalloid co-loading and those receiving phenylephrine infusion plus colloid co-loading.

Studies looking at this aspect have yielded varying results. Ngan Kee found no difference in maternal and foetal outcomes between patients receiving colloids and those receiving crystalloids (8). Dahlgren used equal volumes of crystalloids and colloids, and concluded that colloids showed better blood pressure control, but no difference in foetal outcomes (14). Both studies used were based on pre-loading.

All variables analyzed in this study suggest there is no added advantage in routinely giving colloids to patients undergoing caesarian section under spinal anaesthesia. A study of this nature is important in the promotion of cost-effective health care.

Colloids are known to be far more expensive than crystalloids. Moreover they have been associated with fatal anaphylactic reactions and haemato-genic derangements.

The advantage of colloids as volume expanders seems not to be of any significance in patients undergoing elective Caesarian section under spinal anaesthesia. The most logical explanation is that these patients do not have identifiable causes for a clinically significant pre-operative fluid deficit(except insensible losses).Based on these results, it seems the logical question a clinician should ask himself / herself is this: If crystalloids are effective, affordable and safe, should we not use them instead of colloids, alongside an infusion of phenylephrine to prevent symptomatic hypotension associated with spinal anaesthesia during Caesarian section?

This study did not compare intravascular volumes between the two groups, but it rather looked at easily measurable variables that would interest a simple clinician. It therefore, does not refute the value of colloids as plasma expanders in situations of severe haemorrhage during caesarian section.

There are other interests it opens up for further research and debate, viz. What is the effective, yet safe rate of phenylephrine infusion and what is the correct volume of a crystalloid or colloid to be used as co-administration? There is quite a wide variety of practices in this regard, but it would be advantageous to work towards standardization.

8. STUDY LIMITATIONS

1. A potential weakness in the study is the inequality in volumes used for co-loading between the two groups. A question arises as to whether one would not see a different picture if equal volumes were used.
2. There were variables that showed appreciable numerical differences between the two groups, but the differences were not statistically significant. Would the differences had been more pronounced, or, the similarities clearer if a bigger sample had been chosen?

9. CONCLUSION

This study shows that there is no added value in using colloids to prevent symptomatic hypotension from spinal anaesthesia during elective Caesarian section. Co-administration of equivalent volumes of crystalloids plus infusion of phenylephrine worked equally well. This is an important consideration in the interest of cost-effective health care.

APPENDIX

1. Research proposal (35-48)
2. Approval letter from the Medunsa Research and Ethics Committee (49)
3. Consent form in English (50)
4. Consent form in Setswana (51)
5. Data form A (52)
6. Data form B (53)

RESEARCH PROPOSAL

Research Topic : Comparison of the effect of co-administration of crystalloid versus colloid with phenylephrine infusion for the prevention of hypotension from spinal anaesthesia during elective caesarian section .

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1. Study Problem

Hypotension following spinal anaesthesia is a known complication that can be explained by blockade of sympathetic output to the segments affected by the block, causing vasodilation, reduced venous return to the heart and a reduced cardiac output. This problem is more marked in pregnancy and often accompanied by symptoms such as dizziness, nausea and vomiting.

Many solutions have been attempted, but the most appealing was published in 2004 by a group from Hong Kong(2). They had good results using a phenylephrine infusion(100 μ g/minute) plus co-administration of a crystalloid(Ringer's Lactate up to 2 litres).

The present study is planned to use the same method, but reduced doses of phenylephrine (50 μ g/minute) and lesser fluid volume. The main thrust of this study is to determine whether using crystalloid or a colloid for a fluid, makes any difference in the effectiveness of this form of therapy.

2. Literature review

Administration of a local anaesthetic intrathecally causes motor and sensory block to allow surgery to the lower end of the body. Sympathetic output to the affected areas is also not spared, leading to loss of vasomotor tone and vasodilation, reduced venous return to the heart, reduced stroke volume and cardiac output, thus causing hypotension. This hypotension can be profound in pregnancy, compounded by the haemodynamic changes related to pregnancy and delivery of the foetus. Pregnant women usually experience unpleasant symptoms such as dizziness, nausea and vomiting and they can be restless.

Historically, methods such as limb elevation and elastic stockings were used without any encouraging results. Pre-loading patients with 10-20 ml/kg of a crystalloid has been used for a long time. It has recently been challenged and dismissed as ineffective by some researchers (4, 5, 6). Fluid therapy that is now being advocated is administration of 350-500 ml of a crystalloid and the rest is given to replace losses.

The use of colloids has been attempted, with some researchers concluding that it yields no better results while others claim that there is better intra-vascular retention and blood pressure control (7, 8).

The undisputed and definite method of treating this is hypotension is the administration of vasopressors. These drugs have also been administered in various ways, viz.

- i. Pre- administration of ephedrine intramuscularly before the anaesthetic.
- ii. Boluses of either ephedrine (5-10 mg) or phenylephrine (25-50 μ g) when mean blood pressure drops by more than 20% of the original reading.

Recently a group from Hong Kong reported good results in prevention of symptomatic hypotension from spinal anaesthesia during caesarian section following a combination of phenylephrine infusion (100ug/minute) and co-administration of up to 2 litres of Ringer Lactate. This has been heralded as the first successful method preventing this problem. Concerns are:

- (a) The high doses of phenylephrine can compromise placental perfusion

(b) The high volumes of fluid used, if one considers that pregnant women already have an increased plasma volume. This becomes even more worrying if one considers the possibility of undetected cardiac and renal dysfunction.

3. Aim and Objectives

Aim: To determine whether there is any difference when phenylephrine infusion is combined with crystalloid or a colloid in the prevention of symptomatic hypotension following spinal anaesthesia in women undergoing elective caesarean section.

Objectives:

- i. To determine whether there is any difference in the total dose of phenylephrine needed to maintain normal blood pressure when a crystalloid or a colloid is used.

- ii. To determine the number of women who develop symptom (vis. Dizziness, restlessness, nausea and vomiting) when phenylephrine infusion is combined with either a crystalloid or a colloid.
- iii. To determine the severity of symptoms in the phenylephrine plus crystalloid group compared with the phenylephrine plus colloid group.

4. Methods and Study Design

Study Design: A prospective, randomized, comparative study of pregnant women, who will receive spinal anesthesia for elective caesarean section, will be conducted. This will be for the purpose of determining whether giving a phenylephrine infusion plus a crystalloid co-administration versus a phenylephrine infusion plus colloid co-administration makes a difference in the prevention of symptomatic hypotension.

Sample Size : The sample size for this study has been calculated to conform to 95% certainty that not more than 10% discrepancy exists between the use of a crystalloid and a colloid in a co-administration with phenylephrine infusion . The effectiveness of the conventional infusion (phenylephrine plus a crystalloid) is reported to be 95% and anticipated effectiveness using a colloid is expected to be at least 85%. Once these factors have been taken into considering and at a level of power of the study of 80%, each arm of the study should have 61 patients i.e. total of 22 patients, randomised into two groups will be needed.

Sampling method:

Sample criteria – Women undergoing elective caesarean section with spinal anesthesia will be randomised into either a group to receive phenylephrine plus a crystalloid or a group that will receive phenylephrine plus a colloid. Randomisation will be conducted based on a double blind procedure in which both the researcher as well as the patient will be blinded to choice for either group. This will be done using 122 sealed envelopes, of which 61 envelopes will be labeled (A) and another 61 labeled as (B).

A nursing assistant in the theatre will be responsible for randomising the patients for either (A) or (B) , the composition of which will only be revealed to the researcher after the envelop has been opened and immediately prior to administration of an aesthesia.

Exclusion criteria:-

- i. All condition for which spinal anaesthesia is contra-indicated.
- ii. Emergency caesarean section.
- iii. Cardiovascular disease (hypertension , heart disease , peripheral vascular disease)
- iv. Diabetes mellitus.
- v. Renal disease.

Patients Allocation

Patients will be allocated as indicated above, randomly into two groups:

Group A– to receive phenylephrine infusion plus crystalloid co-administration.

Group B – to receive phenylephrine infusion plus colloid co-administration.

Procedures

i. Drugs:

Anaesthesia – Bupivacaine with dextrose, known as heavy machine (12,5 mg) plus sufentanyl (2,5 μ g) will be given intrathecally at L3 - L4 inter- vertebral space , space, using a 25 – gauge spinal needle.

ii. Phenylephrine – a 50 μ g/ml solution will be prepared and administered within a minute after spinal anaesthesia is given. The infusion will be run using a syringe pump set to run of 1ml/minutes or 60ml/hour, depending on design. Rescue boluses of 50 μ g each will be given if mean blood pressure drops by more than 20% from baseline.

iii. Fluid: - The crystalloid to be used is ringer's Lactate, starting with a bolus of 350ml given over fifteen minutes (commenced within a minute after the anesthesia is given) and the rest given per need.

The colloid to be used is Voluven (hydroxyethyl starch 130/04) given a bolus of 150ml over 15 minutes (commenced within a minute after the anaesthesia is given) and the rest given per need.

Volume replacement equivalents for the two fluids are the following:-

1. Three volume units of crystalloids for each volume unit of blood lost.
2. One volume unit of colloid for each volume unit blood lost.

These will be adhered to for fluid administration.

Blood pressure measurements: A non-invasive automated blood pressure monitor will be used. A baseline blood pressure reading will be taken before administration of the anaesthetic and subsequent readings taken at two minute intervals.

5. Data Collection and Data Analysis

A **data collection form** reflecting the following variables, relevant to the study, will be developed and used for each patient:-

- i. Patient number and age
- ii. Time of administration of anaesthesia
- iii. Blood pressure readings with time intervals
- iv. Dose of phenylephrine received i.e. total infused dose plus rescue boluses
- v. Grading of symptoms: Grade I – 1 symptom graded as mild

Grade II- 2 symptoms or 1 symptom graded

moderate to severe

Grade III – more than 2 symptoms

Data analysis: This will be based on descriptive statistics with variables expressed as a Mean \pm Standard deviation. Differences between the two groups will be determined using the Students *t-test* and the transformation of (*t*) to p-value. Differences between the two groups will be recorded as being statistically significant if the p-value is ≤ 0.05 . Relational statistics will be calculated using the Chi-Square analysis to reflect the association of the use of a crystalloid or colloid as co-administration with phenylephrine in preventing hypotension during elective caesarian section.

Ethical considerations

- i. Permission to conduct this study will be obtained from the Clinical Superintendent of Dr. George Mukhari Hospital.
- ii. Institutional approval to conduct the study will also be obtained from the Medunsa Campus Research and Ethics Committee (MCREC).
- iii. Patients will be visited pre-operatively and informed consent to participate in the study will be obtained.

6. Reliability and Validity of the study

The design of the study has been carefully planned so as to ensure the acceptability of results that will emanate from the study. A prospective, randomised, controlled trial is the hallmark of the study which minimises an inherent bias. The statistical determination of the minimum number of patients needed to establish the validity of the original hypothesis, will also contribute to the reliability of the study.

Bias- To reduce any inherent bias in the study, an anaesthetic assistant or nursing staff not taking part in the study will be requested to conduct the randomisation process. The researcher will be responsible for administration of infusions, monitoring of patients and data collection. A statistician who had not been involved in the study will be responsible for all statistical analyses. All these will contribute in ensuring the elimination of any form of bias.

7. Budget

i. Stationery	R 150.00
ii. Literature search (Internet access)	R 100.00
iii. Statistician	R1300.00
iv. Typist	R500.00
v. Binding	R1200.00
Total =	R3250.00

UNIVERSITY OF LIMPOPO

Medunsa Campus



MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

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MEETING: 06/2008

PROJECT NUMBER: MREC/M/125/2008: PG.

PROJECT :

Title: Comparison of the effect of co-administration of crystalloids versus colloids with Phenylephrine infusion for the prevention of hypotension from spinal Anaesthesia during elective caesarian section

Researcher: Dr L.J. Frans
Supervisor: Dr D.R. Bhagwandas
Co-supervisor: Dr J.L.Y. Bumba
Hospital Superintendent: Dr B.A. Benganga (Dr George Mukhari Hospital)
Department: Anaesthesiology
School: Medicine
Degree: M Med (Anaesthesiology)

DECISION OF THE COMMITTEE:

MREC approved the project.

DATE: 6 August 2008


PROF GA OGUNBANJO
CHAIRPERSON MREC



Note:

- i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.
- ii) The budget for the research will be considered separately from the protocol. PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

UNIVERSITY OF LIMPOPO(Medunsa Campus)CONSENT FORM

Statement concerning participation in a clinical Trial / Research Project
Comparing of the effect of co-administration of crystalloids versus colloid with phenylephrine infusion for the prevention of hypotension from spinal anesthesia during elective caesarian section.

I have read the information on/ heard the aims and objectives of the proposed study and was provided the opportunity to ask questions and given adequate time to rethink the issue. The aim and objectives of the study are sufficiently clear to me. I have not been pressurized to participate in any way.

I understand that participation in this Clinical Trial/ study/project is completely voluntary and that I may withdraw from it at any time and without supplying reasons. This will have no influence on the regular treatment that holds for my condition neither will it influence the care that I receive from my regular doctor.

I know that this trial /study /project has been approved by the Research . Ethics and Publications committee of the faculty of medicine , University of Limpopo (Medunsa Campus) / Dr George Mukhari hospital. I am fully aware that the results of this trial/study/project will be used for scientific purposes and may e published. I agree to this provided my privacy is guaranteed.

I hereby give consent to participate in this Trial / Study /Project.

.....
Name of Patient/volunteer

.....
Signature of patient or guardian

.....
Place

.....
Date

.....
Witness

Statement by the Research

I provided verbal and/ or written information regarding this Trial/ Study /Project. I agree to answer any future question concerning the trial /Study /Project as best as I am able. I will adhere to the approved protocol.

.....
Name of Researcher

.....
Signature

.....
Date

.....
Place

UNIVERSITY OF LIMPOPO (MEDUNSA CAMPUS) CONSENT FORM

Bopaki ka ga go tsaya karolo mo ditekong

Leina la diteko

Papiso magareng ga tiriso ya metsi a "crystalloid" le a colloid; a a tlhakantsweng le setlhare sa phenylephrine, go thibela go wa ga kgatelelo ya madi (blood pressure) morago ga go thabiwa ka loma mo mokokotlong (spinal), ka nako ya karo ya go belega.

Ke badile dintlha k/ke utlwile maikaelelo le moona wa diteko. Ke ne ka fiwa tetla ya bo botsa dipotso, le nako ee lekaneng ya go i kakanyo. Ke tllhaloganya maikaelelo le moonoo wa diteko sentle ga ke a patelediwa go tsaya karolo.

Ke tllhaloganya gore go tswa mo go nna go tsaya karolo le gore nka ikogelo morayo nako nngwe kwntle ga gofa mabaka. Se seka se tllhagise diphetogo mo kalafing e ke eboning ya bolwetse ba me, le go fetolwa ga tlhokomele e ke e boning go ngaka ya me ya metlha.

Kei se gore diteko tse di dumetswe ke karolo ya direko manareo le diphatlalatso yo karolo ya bongaka ya university

Ke tllhalogany gore motswedi waditeko o tllha phatlaladiwa le go dirisetswa mabka a bonetetsi.

Ke dumlan le se, fa fela boleng jwa m bo ka sireletswa.

Ke dumcla go tsaya karolo mo ditekong.

.....
Leina la molwetse/motsaya karolo

.....
leina la motsetse/motlhakomeli

.....
Lejelo

.....
Letsatsi

.....
Bopaki

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