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Biochemical parameters of patients presenting for elective and urgent caesarean sections at Chris Hani Baragwanath Hospital

A Pilot Study

Gladness Dakalo Nethathe

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Anaesthesia.

Johannesburg, 2011

Declaration

I, Dakalo Gladness Nethathe declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesia in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

Signature of candidate

_____ day of _____, 2011

Presentations and publications arising from this study

- South African Society of Anaesthesiologists National Congress, Bloemfontein, March 2010, Presentation.
- South African Society of Anaesthesiologists National Congress Journal, March 2010, Abstract Publication.

Abstract

Introduction

Maternal volume depletion at the time of caesarean section plays a role in maternal and fetal outcome. Measuring fluid volume status currently requires invasive monitors. It would be useful to determine biochemical measurements which would accurately determine fluid volume status in these patients. We investigated the difference in biochemical parameters of participants presenting for elective and urgent caesarean section at Chris Hani Baragwanath Hospital and made inferences about their fluid volume status. We also sought to determine whether this difference in biochemical parameters if present could be linked to a potential difference in the intra-operative haemodynamic course as well as fetal outcome between the two groups.

Method

This was a prospective open-label observational cross-sectional pilot study. The sample was 54 participants, 27 elective and 27 urgent cases.

Blood and urine samples were taken at the red line. Parameters from the blood samples were haematocrit, haemoglobin, sodium, urea, creatinine and plasma osmolality. Parameters from the urine samples were sodium, creatinine, osmolality and specific gravity.

Intra-operatively, all participants received a standard spinal anaesthetic. Variables measured intra-operatively were systolic, diastolic and mean arterial blood pressure, heart rate, highest level of block achieved as well as 1 and 5 minute Apgar scores of the newborn.

The primary outcome variable was hypotension (mean arterial drop of more than 15% from the baseline).

The secondary outcome variable were the Apgar scores of the infants.

Results

Urine specific gravity showed a trend towards statistical significance (mean, median, standard deviation for elective, urgent): 1.01, 1.010, 0.01 and 1.02, 1.015, 0.01 $p = 0.06$. The other biochemical parameteres displayed higher p-values.

The average relative blood pressure change was -11,7% (median, standard deviation) (-12.4, 11.1) for the elective group and -15.1% (-14.9, 15.1) for the urgent group $p = 0.36$. The relative blood pressure change to end point of study was -9.6% (-9, 12.7) for the elective group and -15.4% (-17, 17.6) for the urgent group $p = 0.17$. When comparing baseline blood pressure and heart rate measurements to the 10 minute end point measurements; 15 participants experienced hypotension in the urgent group compared to 9 in the elective group $p = 0.17$. When comparing baseline blood pressure measurements to the average at 2, 4, 6, 8, and 10 minute intervals; 13 participants from the urgent group experienced hypotension compared to 9 participants in the elective group $p = 0.40$.

The average Apgar scores at 1 min were 8.89 (9,0.32) for the elective group and 8.37 (9,0.93) for the urgent group $p = 0.01$.

Conclusion

This was a pilot study and as such statistical significance between variables was not expected. However possible trends were identified to guide future investigations. The higher incidence rate of hypotension in the urgent group showed such a trend towards significance as well as the higher urine specific gravity in the urgent group. We also noted that Apgar scores differed significantly between elective and urgent cases.

To Uli for your belief in me and my mother, and siblings for always supporting me in my endeavors

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Contents

1 Introduction **17**

1.1 Background 17

1.2 Problem statement and hypothesis 21

1.3 Aims 21

1.4 Objectives 22

1.5 Definitions 22

1.6 Study design 23

1.7 Ethical considerations 23

1.8 Summary of Methodology 24

1.8.1 Study site 24

1.8.2 Study population 24

1.8.3 Sample size 24

1.8.4 Study period 24

1.8.5 Methodology 25

1.8.6 The data collection and analysis 26

1.8.7 The significance of the study 27
1.8.8 Inclusion criteria 27
1.8.9 Exclusion criteria 28
1.8.10 Limitations of the study 28
1.9 Outline of report 29

2 Literature Review **31**

2.1 Physiology of fluid and electrolyte balance 31
2.1.1 Normal water distribution 31
2.1.2 Control of water balance 33
2.1.3 Electrolyte distribution 35
2.2 Physiological changes in fluid and electrolyte homeostasis during pregnancy 35
2.2.1 Regulation of plasma osmolality 37
2.2.2 Renal effects 37
2.2.3 Cardiovascular changes 38
2.2.4 Haematological effects 38
2.2.5 Conclusion 39
2.3 Disorders of water homeostasis 39
2.3.1 Types of fluid loss 39
2.3.2 Hypotonic fluid loss 39
2.3.3 Isotonic fluid loss 40
2.4 Methods of assessing hydration status 41

2.4.1 Invasive methods 42
2.4.2 Clinical parameters in the assessment of hydration status 42
2.4.3 Isotope dilution 43
2.4.4 Multifrequency bioelectrical impedance analysis 43
2.4.5 Haematological indices 44
2.4.6 Urine parameters 44
2.4.7 Conclusion 45
2.5 Application to the obstetric patient 46
2.5.1 Methods of assessing hydration status during pregnancy . 46
2.5.2 Effect of dehydration on the obstetric patient 46
2.5.3 Effect of dehydration on anaesthesia for caesarean section 48
2.5.4 Importance of accurate assessment 48
2.6 Conclusion 49

3 Materials and methods **50**

3.1 Problem statement 50
3.2 Ethical considerations 51
3.3 Research methodology 51
3.3.1 Study design 51
3.3.2 Study population 52
3.3.3 Study sample 53
3.3.4 Study period 53
3.3.5 Detailed methodology 53

3.3.6 Inclusion criteria 58
3.3.7 Exclusion criteria 58
3.3.8 The data collection and analysis 59
3.4 Reliability 60
3.5 Conclusion 60

4 Results **61**

4.1 Participants' groups characteristics 62
4.2 Laboratory parameters 68
4.2.1 Haematological laboratory parameters 68
4.2.2 Biochemical parameters 68
4.2.3 Urine laboratory parameters 76
4.3 Blood pressure and heart rate measurements in theatre 81
4.4 Intraoperative events 86
4.4.1 Level of block 86
4.4.2 Apgar scores 86
4.4.3 Amount and type of fluid given 88
4.4.4 Amount and type of vasopressor given 88
4.4.5 Estimated blood loss during the study period 88
4.5 Conclusion 89

5 Discussion **91**

5.1 Discussion of results 91
5.1.1 Demographic data and group characteristics 91

5.1.2 Laboratory parameters 93

5.1.3 Blood pressure and heart rate measurements in theater . 94

5.1.4 Intraoperative events 95

5.2 Limitations of the study 97

5.3 Recommendations 98

6 Conclusion **100**

Appendices **110**

A Ethics clearance certificate **111**

B Postgraduate Committee Approval **113**

C Patient information **115**

D Consent form **117**

E Data capture sheet **119**

F Description of Violin Plot Components **122**

List of Figures

2.1 Water distribution in the different body compartments. 32

2.2 Water homeostasis. 36

3.1 Illustration of the group divisions. 53

4.1 Violin-plot illustrating the differences in age distribution between the elective group and the urgent group. 64

4.2 Violin-plot illustrating the differences in the BMI between the elective group and the urgent group. 65

4.3 Violin-plot illustrating the differences in the duration of starvation between the two groups. 66

4.4 Histogram illustrating the ASA score distribution in the elective and the urgent group. 67

4.5 Violin-plot illustrating the differences in Hct between the elective and the urgent group. 69

4.6 Violin-plot illustrating the differences in Hb between the urgent and the elective group. 70

4.7 Violin-plot illustrating the differences in plasma sodium concentration between the elective and the urgent group. 71

4.8 Violin-plot illustrating the differences in urea concentration between the elective and the urgent group. 72

4.9 Violin-plot illustrating the differences in plasma creatinine between the urgent and elective group. 73

4.10 Violin-plot illustrating the differences in plasma osmolality between the elective and the urgent group. 74

4.11 Violin-plot illustrating the differences in urine creatinine between the elective and the urgent group. 77

4.12 Violin-plot illustrating the differences in urine sodium concentration between the elective and the urgent group. 78

4.13 Violin-plot illustrating the differences in urine osmolality between the urgent and the elective group. 79

4.14 Violin-plot illustrating the differences in urine specific gravity between the elective and the urgent group. 80

4.15 Heart-rate and (mean-arterial) blood pressure against time. -2 initial supine, 0 supine after administration of the spinal anaesthetic. 82

4.16 Probability density function for the incidence rate of hypotension for elective and urgent cases 83

4.17 Violin-plot illustrating the distributions of the relative blood pressure after 10 minutes. 84

4.18 Violin-plot illustrating the distributions of the average relative blood pressure. 85

4.19 Violin-plot of Apgar scores illustrating the difference between the elective and the urgent group. 87

4.20 Violin-plot of estimated blood loss between the elective and the urgent group. 90

A.1 Ethics approval document 112

B.1 Approval document. 114

E.1 First page of the data capture sheet. 120

E.2 Second page of the data capture sheet. 121

F.1 An example of a violin-plot. 124

List of Tables

2.1 Total body water distribution at different ages and between different genders 32

2.2 Normal water intake and output of an average adult 33

2.3 Electrolyte composition of the different body fluids 36

2.4 Comparison of hypotonic fluid loss to isotonic fluid loss 41

2.5 Table showing the differences between pre-renal azotaemia and acute tubular necrosis 45

4.1 Participant demographics and group characteristics 62

4.2 Indication for the Ceasarean Sections 63

4.3 Haematological parameters of participants in the elective and urgent groups 75

4.4 Biochemical parameters of participants in the elective and urgent groups 75

4.5 Results for the urine parameters in the elective and urgent groups 76

4.6 Average heart rate and average of the mean arterial pressure over time. 81

4.7 Number of occurences of hypotension between elective and urgent groups 83

4.8 Number of participants for each level of block. 86

4.9 Apgar scores of infants delivered in the two groups. 86

4.10 Average amount of fluid given. 88

4.11 Average intra-operative vasopressor use and blood loss. 89

Chapter 1

Introduction

This chapter will provide an overview on the significance of adequate fluid volume status for maternal and fetal well being. Problems that may arise as a result of inadequate fluid resuscitation pre-operatively will be highlighted. The different methods of assessing fluid volume status will be addressed and applications of these to our setting at Chris Hani Baragwanath Hospital (CHBH) will be mentioned. The problem statement, aims, objectives, hypothesis and significance of the study have been included. The methodology, limitations of the study and ethical considerations are also discussed. To summarise an outline of the report is presented.

1.1 Background

Pregnancy is a state associated with a number of haemodynamic changes, for example decreased systemic vascular resistance, increased plasma volume, increased total blood volume and increased cardiac output. These maternal changes play a significant role in fetal outcome and prepare the parturient for potential blood loss during delivery [1].

Maternal volume depletion and hypotension can lead to placental hypoperfusion, adversely affecting the fetus [1–4]. Intravascular volume expansion has been identified as one of the interventions to decrease maternal hypotension [5, 6].

Any patient undergoing a surgical procedure is likely to have fluid volume changes. Reasons for these include the condition that necessitated the surgical procedure, blood loss, peri-operative fluid administration as well as effects of the anaesthetic technique employed [7]. The current favoured trend of selecting neuraxial anaesthesia for caesarean sections, with its associated risk of hypotension [1], requires meticulous peri-operative fluid management to prevent any complications arising.

The pregnant patient presenting for a caesarean section is at particular risk for fluid volume shifts. Often the decision to do the caesarean section occurs after many hours of labour. The parturient is also often kept starved in case she requires operative delivery. Secondly labour pains and the stress of labour may increase insensible fluid losses and also result in inadequate fluid intake. In addition, the indication for the caesarean section may itself be associated with fluid volume changes, for example pre-eclampsia [8, 9].

Assessment of hydration status is usually made based on clinical examination and evidence of haemodilution or haemoconcentration on laboratory tests [10]. Severe disturbances can occur before they are detectable by clinical and laboratory findings [10], and these can have a negative impact on cardiovascular functioning. An accurate assessment of the deficit is thus of paramount importance for safe maternal and fetal outcome. The concern on which this study is based is that patients presenting for caesarean sections after labouring at CHBH are inadequately assessed with regards to their fluid volume status. They are thus at risk of presenting in a state of covert dehydration.

There is currently no gold standard for assessing hydration status [11]. However

a number of methods have been used to determine hydration levels in humans:

Invasive methods have been mainly used to assess intravascular volume status. These have included pulmonary artery catheter placement,central venous pressure monitoring as well as arterial waveform pulse pressure variation during mechanical ventilation. These methods have specific indications and the use of each of these methods is associated with known morbidity [12–15]. As a result of this, the focus in this study was on less invasive methods, namely biochemical parameters from which deductions about hydration status can be made.

Numerous other non invasive methods of assessing fluid volume status have been described. These have included the following:

Clinical data such as changes in body weight [11, 16, 17], skin fold thickness [18], blood pressure and heart rate, changes in heart rate variability [19, 20], orthostatic vital sign changes [21] and bioelectrical impedance [22].

The use of heart rate variability analysis, a non - invasive method that reflects activity of the autonomic nervous system, has also proved to be useful as a method of predicting hypotension after subarachnoid block [14, 16]. However, it requires specialised monitoring.

Multifrequency bioelectrical impedance analysis has been used in total body water analysis. Its usefulness is limited however, as the sensitivity and specifity are not known [23, 24]. It also requires specialised equipment.

Haematological and urinary indices have also been used [11, 16, 17]. Haemoglobin concentration and the haematocrit may increase with dehydration. Depletion of water results in a rise in the concentrations of large molecules such as proteins and blood cells, resulting in an increase in blood haemoglobin concentration and haematocrit [10]. Although these parameters need a baseline measurement in order to be reliable, they can be useful in estimating the percentage change in plasma volume. This is shown in the equation derived by Dill

and Costill [25] for the relative change in plasma volume

$$\frac{\mathrm{Hb}_{\mathrm{control}}}{\mathrm{Hb}_{\mathrm{incidental}}}\frac{\mathrm{Hct}_{\mathrm{incidental}}}{\mathrm{Hct}_{\mathrm{control}}} - 1.$$

Plasma osmolality and urine osmolality appear to be the most widely used markers of hydration [11, 16, 17]. They may be more useful in diagnosing hydration status than changes in parameters like serum protein and blood urea nitrogen, which are influenced by other factors [26].

Urine specific gravity is a measure of the weight of dissolved particles in urine, and urine osmolality reflects the number of such particles [27]. They are both useful in the differential diagnosis of oliguria, polyuria or in the syndrome of inappropriate antidiuretic hormone secretion (SIADH). These parameters are easily obtainable measures of concentrating ability but are unreliable in the presence of glycosuria or other osmotically active substances in urine [27] such as may occur in pregnancy. The use of diuretics can also affect the values obtained as a result such patients were excluded in this study [28].

Serum sodium level increases with water depletion, and changes in serum sodium level most often reflect a change in water balance rather than sodium balance [26]. Hypernatraemia suggests a water deficit, except in the face of an increased sodium intake. Similarly, hyponatraemia suggests over hydration [26]. Urine and plasma sodium level have also been used to calculate the fractional excretion of sodium in the diagnosis of pre-renal vs. intra-renal pathology as follows [27]

$$\frac{[\mathrm{Na}]_{\mathrm{urine}}}{[\mathrm{Na}]_{\mathrm{plasma}}}\frac{[\mathrm{Creat}]_{\mathrm{plasma}}}{[\mathrm{Creat}]_{\mathrm{urine}}}$$

The above is a ratio of creatinine clearance to sodium clearance. For a patient with determined renal disease, values less than one percent indicate pre-renal pathology and values of more than one percent indicate intra renal pathology [27].

In the setting at CHBH, laboratory parameters are readily attainable. Use of these parameters may thus be a practical means of predicting preoperative hydration levels [9–11]. The result of these study may indicate the usefulness of this method of assessment.

1.2 Problem statement and hypothesis

Maternal dehydration during labour and during caesarean delivery can have a negative impact on both the mother and the fetus. The hypothesis is that patients presenting for urgent caesarean sections after having been in labour will have a higher incidence of covert dehydration as indicated by biochemical parameters, in comparison to the patients presenting for elective procedures.

1.3 Aims

The aims of this pilot study are the following:

1. To investigate the difference in biochemical parameters of patients presenting for elective caesarean section and patients presenting for urgent caesarean section at CHBH and to make inferences about their fluid volume status using these parameters.

2. To investigate whether there is a difference in the intra operative course as well as fetal outcome between the two groups.

3. To highlight potential shortfalls in the preoperative management of patients presenting for urgent caesarean sections. This information will be useful in finding ways to improve optimisation of patients for surgery.

1.4 Objectives

The aims of this study will be supported by the following objectives:

1. To investigate the incidence of covert dehydration in patients presenting for elective caesarean sections, compared with patients presenting for urgent caesarean sections at CHBH, based on selected biochemical parameters

2. To investigate the incidence of intra operative hypotension occurring in patients presenting for emergency caesarean sections compared to patients presenting for elective caesarean sections.

3. To investigate if there is a difference in Apgar scores between babies born of mothers having urgent caesarean sections and those born of mothers who had elective caesarean sections.

1.5 Definitions

The following definitions were used during this study.

Hypotension: A decrease in mean arterial pressure of more than 15% from the baseline compared to 10 minutes after the subarachnoid block and also compared to the average at 2, 4, 6, 8 and 10 minutes after the subarachnoid block.

Urgent Caesarean section: A caesarean section the indication for which does not pose an immediate risk to the life of the mother or the fetus. An example would be a caesarean section for a patient who has had a previous caesarean section, is in labour, and is progressing poorly.

Elective Caesarean section: A caesarean section performed at a time convenient to both mother and/or the surgical team on a patient who is not

in labour. An example would be a caesarean section for a patient who has had two previous caesarean sections.

1.6 Study design

This was a prospective open-label observational cross-sectional study.

1.7 Ethical considerations

Ethical appoval Ethical approval was granted by the University of the Witwatersrand, Johannesburg. Human research ethics committee (medical). Ethical clearance certificate protocol number: M071114 (Appendix A).

Post graduate committee approval The study has been approved by the Post-Graduate Committee of the University of the Witwatersrand, Faculty of Health Sciences (Appendix B).

Hospital approval Permission from CHBH Superintendent was also given.

Patient approval Informed consent was obtained from all patients who participated in the study in a language they could understand. The purpose as well as the procedure was explained verbally to all the participants. When this was completed the participants were given a written information sheet (Appendix C) as well as a consent form to sign (Appendix D). The information given to the participants included their right to refuse and their right to withdraw at any time from the study. They were also told that their refusal to participate would not interfere with their treatment.

Declaration of Helsinki The study was performed in accordance with good clinical practice and with the principles outlined in the Declaration of Helsinki [29].

1.8 Summary of Methodology

1.8.1 Study site

Department of Obstetrics, labour ward and theatre, CHBH.

1.8.2 Study population

Participants were selected from patients presenting for caesarean section in the Department of Obstetrics, CHBH.

1.8.3 Sample size

This was a pilot study and the targetted sample size was originally limited to fifty participants: twenty five participants were patients presenting for urgent caesarean sections and twenty five participants were patients presenting for elective caesarean sections.

1.8.4 Study period

Data collection commenced following Post Graduate Committee approval of the protocol. The data collection period began Monday the 22nd of December 2008 and was completed on Saturday the 12th of September 2009.

1.8.5 Methodology

Participants were selected according to the booking list of the CHBH maternity theatre. Consecutive participants were taken on a given data collection day, as booked by the obstetricians. Participants not fitting the criteria of the study were excluded. The elective group was used as a control. Participants on the elective list who had been starved had the duration of starvation noted. Informed consent was obtained from the participants before the samples and data were collected. Consent was confirmed on the first post operative day. The principal investigator obtained consent from all the participants. The participants home language was used where possible. Patients agreeing to participate in the study were interviewed preoperatively. Blood samples were taken in theatre, at the red line. The following data were collected: Age, height, indication for caesarean section and duration of starvation.

Blood and urine was sampled by the principal investigator. The Blood samples were analysed for the following:

1. Haematocrit
2. Haemoglobin
3. Sodium
4. Urea and Creatinine
5. Plasma Osmolality

The urine samples were analysed for:

1. Sodium
2. Creatinine
3. Osmolality

4. Specific Gravity

Intraoperatively, all participants received a standard anaesthetic comprising of a spinal anaesthetic performed by the anaesthetist who had been allocated to the labour ward theatre for that day.

Mean arterial pressure, systolic blood pressure, diastolic pressure as well as pulse rate readings were taken at 2 min intervals after the injection of the local anaesthetic until 10 minutes after the block. The level of the block was tested using loss of sensation to cold and this was noted.

The primary outcome variable was hypotension. Hypotension is defined in this study as a drop of more than 15% from the baseline compared to the 10 minute end point of the study and compared to the average of the readings at 2 minute intervals till the 10 minute end point of the study. Standardised protocols existed for the treatment of hypotension and these were used. Hypotension was managed with colloid or crystalloid boluses as well as phenylephrine or ephedrine boluses. Total amount and type of fluid administered, doses and time of administration of the vasopressors as well as the estimated blood loss during the study period was noted. Surgery was allowed to continue after establishment of an adequate block.

The secondary outcome variable was the Apgar scores of the infant at 1 and 5 minutes after delivery.

1.8.6 The data collection and analysis

After the data collection was complete the results were analysed using a two-sided student t test. If the data were not normally distributed the Mann-Whitney U test was used. Pearson's chi-square test was used for analysis of categorical data. Significance was set at $p < 0.05$.

1.8.7 The significance of the study

The results of the study will be of interest to anaesthetists involved in perioperative care of patients presenting for caesarean section as well as obstetricians and nursing staff involved in the care of these patients. Maternal dehydration during labour can have a number of adverse effects. These include

- A hypercoaguable state as evidenced by a study done by Takashi Watanabe et al [30], in addition, if severe it can compound the hypotensive effect of regional and general anaesthesia.
- Maternal dehydration may also have a role in rising uterine contractions via increased oxytocin release [31], dehydration has however also been implicated in the cessation of labour and decreased uterine contractions
- Maternal dehydration has also been implicated in oligohydramnios [32].

The results have been communicated by means of a presentation at a national congress and will be submitted for publication in the form of a research report for the MMed (Anaesthesia) degree. It is hoped that the results of the study will result in improved patient care as well as safer delivery of anaesthesia.

1.8.8 Inclusion criteria

- Age more than 18 years.
- Women presenting for caesarean section who are able to give consent.
- ASA I and ASA II patients. ASA is an acronym for the American Society of Anaesthetists classification system for assessing fitness of patients for surgery. ASA I patients are normal and healthy patients and ASA II patients are patients with mild systemic disease.
- Elective caesarean sections and urgent caesarean sections only.

1.8.9 Exclusion criteria

- Patients on the following drugs: oxytocin infusions, diuretics, ipradol and cardiovascular active agents such as nifedipine, hydralazine, methyldopa and labetalol. These agents can affect heart rate, some lead to vasodilation and hypotension, potentially confounding the measured variables. Diuretics also alter the urinary concentration of electrolytes.
- Patients given any sedatives in labour as they may not be able to give informed consent.
- Patients with antepartum haemorrhage requiring fluid and/or inotropic resuscitation. These patients might experience large blood pressure drops under spinal anaesthesia.
- Patients with evidence of sepsis (e.g raised white cell count, elevated temperature, unexplained tachycardia or a known source of sepsis). The associated tachycardia and hypotension might be a confounding factor in a study that involves heart rate and blood pressure measurements.
- Hypertensive states of pregnancy.
- Emergency caesarean sections (i.e. procedures that cannot be delayed for the time required to initiate the study e.g cord prolapse and eclampsia).
- Patients requiring general anaesthesia or epidural.
- Patients with overt dehydration. These patients would need to be adequately treated for their fluid deficit before any anaesthetic is administered as they can experience large blood pressure drops after the administration of an intravenous or spinal anaesthetic.

1.8.10 Limitations of the study

1. The small sample size may impact on the significance of the results. This study was aimed to be a pilot study which would hopefully encourage

further research.

2. Intra operative blood loss was variable during the study period. An estimation of the blood loss was recorded in order to be able to comment on this variability.

3. Intra operative hypotension is used as the primary outcome variable, with hypotension being defined as more than a 15% drop from the baseline. The baseline blood pressure may have been influenced by a number of factors such as labour pains, and the anxiety associated with being informed of the need for an urgent caesarean delivery. Therefore participants arriving for urgent caesareans may have had higher baseline blood pressure and heart rate readings.

4. The endpoint of the study is time based, namely ten minutes after initiation of block. Different surgeons will have had different practices. Some had started surgery in this time while others had not.

5. The lack of a gold standard for measuring hydration status meant that investigations from which inferences about hydration status can be made were used. These might not necessarily be the best investigations to use to assess hydration status.

1.9 Outline of report

This research report will comprise of the following chapters:

Chapter one comprises the introduction of the study. The problem statement, aims, objectives, hypothesis and significance of the study are also included.

Chapter two provides the reader with an in depth review of the literature relevant to this study.

In Chapter three the study design, sample, composition and selection are discussed. An explanation of the data collection and statistical analysis is included.

Chapter four contains a presentation of the results

In chapter five the results are discussed, limitations of the study are highlighted and recommendations for further research are made.

Chapter six contains the conclusion.

This chapter provided information on the significance of adequate fluid volume status for maternal and fetal well being. Problems that may arise as a result of inadequate fluid resuscitation pre-operatively were highlighted. The different methods of assessing fluid volume status were addressed and applications of these to our setting at CHBH were mentioned. The problem statement, aims, objectives, hypothesis and significance of the study have been included. Detailed methodology, limitations of the study and ethical considerations are also discusssed. In conclusion an outline of the report was presented.

Chapter 2

Literature Review

This chapter aims to provide the reader with an in-depth discussion of the literature pertaining to this study. The physiology of fluid and electrolyte balance in the human body, normal water and electrolyte distribution, control of water balance and disorders of water balance are discussed. A section on the physiological changes in fluid and electrolyte homeostasis during pregnancy is included.

The different types of fluid loss, their definitions, effect of fluid loss as well as measurement indices are discussed. Special attention is paid to methods of assessing hydration status. The effect of these disorders on the obstetric patient and obstetric anaesthesia is also reviewed.

2.1 Physiology of fluid and electrolyte balance

2.1.1 Normal water distribution

Approximately 60% of body weight in males is water [33]. For females the value is in the range 50-55% due to a greater proportion of body fat [34]. Table 2.1

below illustrates different water distribution according to age and gender.

Table 2.1: Total body water distribution at different ages and between different genders [34].

Age and gender	**Water in % of total body weight**
Infants	75%
Young males	60%
Young females	55%
Elderly males	50%
Elderly females	45 %

Total body water is divided into a number of compartments, the main constituent compartments being intracellular fluid and extracellular fluid [34]. Two thirds of total body water is found in the intracellular fluid compartment and one third in the extracellular fluid compartment [34]. The extracellular fluid compartment is further divided into intravascular and interstitial compartments [34]. This is illustrated in figure 2.1.

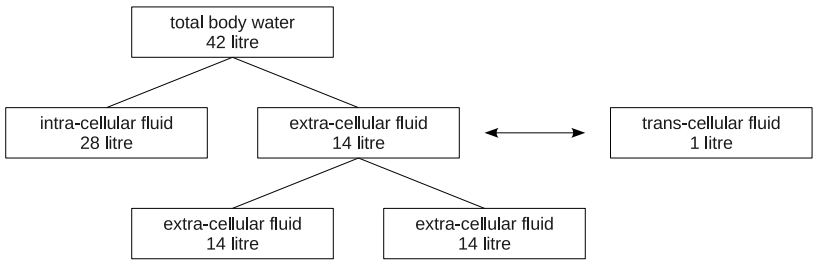


Figure 2.1: Water distribution in the different body compartments.

Approximately one litre is contained within the cerebrospinal fluid, gastrointestinal tract, pleural cavity, eyes etc, and is described as trans-cellular fluid [33].

Normal approximate fluid intake of a 70 kg adult is 1500-2500 ml [34]. Normal output is from the renal tract and gastrointestinal tract as urine and faeces respectively as well as skin and lungs [34]. These are termed obligatory or insensible losses. Insensible water loss can be up to 1200 ml at rest [33, 34].

This component can increase with increased physical exertion, increased body temperature and in tachypnoea [33]. Table 2.2 illustrates the different losses according to organ system. Balance between input and output is tightly regulated to maintain extracellular fluid volume and osmolality[35, 36].

Table 2.2: Normal water intake and output of an average adult [34].

	Obligatory losses (ml)
Skin	500
Lungs	400
Gut	100
Kidneys	500
Total	**1500**
	Fluid Intake (ml)
Diet	1100
Metabolism	400
Total	**1500**

2.1.2 Control of water balance

Water homeostasis is normally maintained by the balance of water intake against water excretion [37]. The sensation of thirst controls water intake and water excretion is controlled by the actions of antidiuretic hormone, atrial natriuretic peptide and the renin/angiotensin system [33]. It is important to note at this point that labouring women may be unable to respond to this thirst sensation due to concerns from the medical team that they may need an operative delivery. Normal plasma osmolality ranges between 280-305mosm/kg and is tightly regulated (rarely changes by more than two percent of baseline) [37]. Most contribution to plasma osmolality is from sodium and its anions glucose and urea; plasma osmolality is thus estimated as (in mosmol/kg):

$$\text{Plasma Osmolality} = [\text{Glucose}] + [\text{Urea}] + 2[\text{Na}]$$

where all concentrations are in mmol/l [33]. Dehydration leads to an increase in plasma osmolality, this activates osmoreceptors in the hypothalamus leading to a sensation of thirst, with resultant fluid intake, increase in body water and return of plasma osmolality to normal [37].This is illustrated in figure 2.2

In this study we also sought to determine if there would be a difference in plasma osmolality between patients planned for elective surgery and patients who had urgent caesarean sections. Presumably women in the urgent group would have been in labour for long and in addition would have had restrictions on their oral intake.

The specialised osmo sensitive neurones are situated in an area of the anterior hypothalamus which lacks the blood brain barrier allowing access to plasma [38].

Stimulation of the osmoreceptors in the anterior hypothalamus also stimulates the paraventricular nucleus and the supraoptic nucleus resulting in the synthesis of a nine amino acid peptide called antidiuretic hormone [39]. The other input to these receptors is via brainstem cardiovascular centres [40]. Barorectors in the aortic arch and carotid arteries stimulate antidiuretic hormone secretion in response to a decrease in mean arterial pressure or blood volume [39]. The antidiuretic hormone synthesised is transported via neural projections to the posterior hypothalamus where it is secreted into the circulation [37].

Antidiuretic hormone is transported via the bloodstream to the kidney where it acts on the V2 receptors of the renal collecting duct cells [41]. The action of antidiuretic hormone on the cells activates adenyl cyclase, generating intracellular cyclic AMP. This causes incorporation of acquaporin-2 water channels on the apical membrane (luminal side) of the collecting duct cell [41]. This increases the duct cell's permeability to water leading to water reabsorption and a decrease in water excretion from the kidneys [41]. Chronically, antidiuretic hormone increases the synthesis of acquaporin 2 in principal cells of the collecting

duct leading to enhanced water permeability and antidiuresis [42].

There are many other factors which influence antidiuretic hormone secretion. Acetycholine, dopamine, prostaglandins, histamine, bradykinin neuropeptide y and angiotensin II are known to stimulate antidiuretic hormone release [43]. Antidiuretic hormone release inhibitors of note include nitric oxide, atrial natriuretic peptide and opioids such as pethidine often given as analgesics during labour. Norepinephrine has both inhibitory and stimulatory effects on antidiuretic hormone release. It stimulates release via alpha 1 adrenoceptors and inhibits its release via alpha 2 adrenoceptors and beta adrenoceptors [44].

A low plasma osmolality results in inhibition of the sensation of thirst and antidiuretic hormone release [45]

2.1.3 Electrolyte distribution

The major extracellular cation is sodium and potassium is the major intracellular cation [33]. The sodium/ potassium ATPase pump constantly pumps sodium against its concentration gradient in exchange for potassium [33–35, 46]. Other cations and anions include magnesium and phosphate which are found both in the extracellular and intracellular space as well as chloride anions which are found predominantly in the extracellular space in association with sodium [34, 35] (see Table 2.3).

2.2 Physiological changes in fluid and electrolyte homeostasis during pregnancy

Pregnancy is a state associated with a number of physiological changes [1]. The changes that pertain to this study are discussed below.

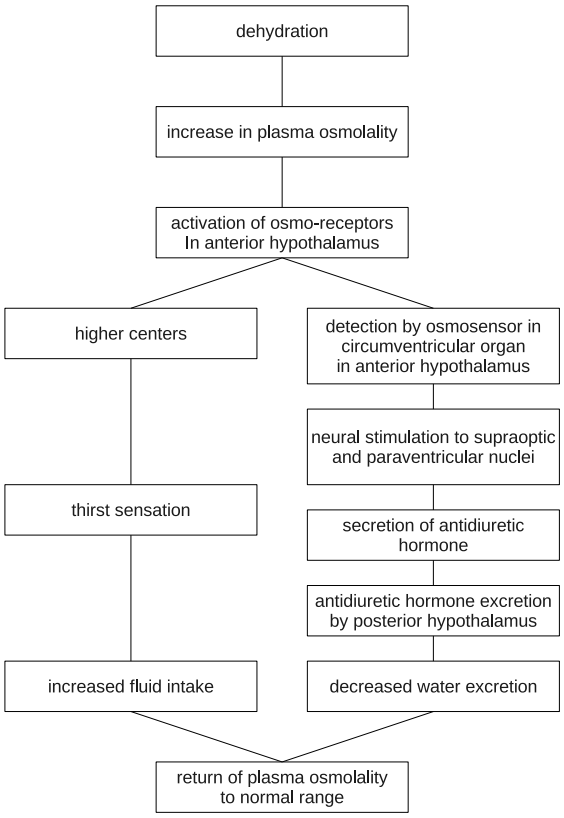


Figure 2.2: Water homeostasis.

Table 2.3: Electrolyte composition of the different body fluids [47].

Electrolyte	**Plasma** mmol/l	**Plasma Water** mmol/kg of H_2O	**Interstitial**	**Intracellular**
Na^+	142	153	145	10
K^+	4	4.3		159
Mg^{2+}	2	2.2	2	40
Total	153	165	154	210
Cl^-	103	111	117	3
HCO_3^-	25	27	28	7
Protein	17	18		45
Others	8	9	9	155
Total	153	165	154	210

2.2.1 Regulation of plasma osmolality

As discussed previously, sodium is the primary determinant of extracellular fluid osmolality. Its importance in water homeostasis has also been mentioned.

There is gradual sodium retention of up to 3-4 mmol per day in pregnancy leading to a total net accumulation of approximately 950 mmol [48]. This sodium is distributed between the products of conception and the maternal extracellular volume [48]. There is however a 4-5 mmol/l decrease in serum sodium [48]. An interplay of factors that lead to natriuresis and factors that are antinatriuresis is involved.

Factors that lead to sodium retention are: mineralocorticoids such as aldosterone, which increase during pregnancy [49]. The concentrations of angiotensin II and oestrogen also increase both of which cause sodium retention [49–51]. The increase in the concentration of natriuretic hormones such as oxytocin [52], atrial natriuretic peptide and effect of progesterone contribute to natriuresis [48].

The action of the Na/K ATPase pump is also altered. The number of enzyme sites increases in the circulating cells and in the kidney [52]. This enzyme is involved in sodium retention by the kidney [53]. Due to a reduction in plasma sodium as well as its anions, plasma osmolality drops by approximately 10mosmol/kg [54]. The osmotic thresholds for thirst and antidiuresis also decrease hence the drop in plasma osmolality does not promote a diuresis by inhibiting antidiuretic hormone secretion [55].

Increases in human chorionic hormone have also been shown to decrease thresholds for thirst and antidiuretic hormone secretion in non pregnant women [56].

2.2.2 Renal effects

An increase in renal blood flow occurs during early pregnancy [1]. Increased renin and aldosterone levels promote sodium retention. Serum creatinine and

blood urea nitrogen may decrease [48].

There is an increase in fluid turnover that results from a combination of factors, some of which include; an increased fluid intake, increased metabolic rate and hyperventilation. An increase in extracellular fluid volume occurs and salt and water are retained [48]. As mentioned previously, plasma osmolality drops by approximately 10mosmol/kg [54] as sodium, chloride and bicarbonate concentration drops [48]. The hypothalamic osmotic receptors are reset with a decrease in the thresholds for thirst and antidiuretic hormone secretion [55]. Renal responsiveness to antidiuretic hormone is also altered [57]. Water excretion depends on the stage of the pregnancy, with an increase in the ability to excrete a water load in the second trimester, which decreases in the third trimester [58].

2.2.3 Cardiovascular changes

There is an increase in cardiac output with a decrease in systemic vascular resistance [1, 48]. The increase in cardiac output is mainly due to an increase in heart rate and stroke volume [48] and occurs early during pregnancy.

There is a change in arterial blood pressure measurement, with relatively little change in systolic pressure but a marked fall in diastolic pressure. The result is a marked widening of the pulse pressure [48]. According to Robson et al, mean blood pressure also rises during labour [59].

2.2.4 Haematological effects

There is an increase in blood volume, mainly plasma volume, which is related to the size of the fetus. Particularly large increases are associated with multiple gestations [48, 60]. There is an increase in the red cell mass. However, the red cell count, haematocrit and haemoglobin concentration decrease as a result of expansion of the plasma volume [1, 48].

A hypercoaguable state develops that may be beneficial in limiting blood loss during delivery [1]. Levels of clotting factors VI, VIII, IX, X and XII as well as levels of fibrinogen increase [1]. A leucocytosis as well as a ten percent increase in platelet count is encountered [1, 48]. Fetal utilization of iron and folate may lead to anaemias associated with their deficiency [48].

2.2.5 Conclusion

In view of the above changes, ranges of haematological and urinary indices that apply to the normal adult population are not necessarily applicable to the pregnant population. It is also important to note the wide variation that may occur amongst pregnant women.

2.3 Disorders of water homeostasis

2.3.1 Types of fluid loss

The type of fluid loss as well as the rapidity of loss influences the effect of fluid loss on the body [34, 35]. Disorders of body water balance can be categorised into hypotonic fluid loss or isotonic fluid loss. Other classifications that have been used include: hypoosmolar disorders, isoosmolar disorder and hyperosmolar disorders of water imbalance [34]. As the main constituent of plasma osmolality is sodium, these disorders are characterised by the amount of water lost in relation to sodium. [61, 62].

2.3.2 Hypotonic fluid loss

In these conditions water in excess of sodium is lost from the extracellular fluid [61, 63]. Examples include; osmotic diuresis (e.g in diabetes mellitus), diabetes insipidus, both nephrogenic and hypothalamic, excessive sweating, fever or exer-

cise in a hot climate, hyperventilation or assisted ventilation with unhumidified air and cessation of water intake with ongoing sensible losses e.g infants, unconscious patients. With hypotonic fluid loss extracellular sodium rises and water moves in from the intracellular fluid compartment [63]. An increase in plasma osmolality will stimulate osmoreceptors resulting in antidiuretic hormone release and a thirst response. Urine becomes concentrated and urine osmolality increases (this does not apply in the case of diabetes insipidus) [61]. These are the types of changes that may occur in labouring mothers who labour for long without adequate fluid intake.

When blood volume has become sufficiently depleted, renal underperfusion results in the activation of the renin angiotensin system, resulting in aldosterone secretion [63]. Aldosterone increases the uptake of sodium in the distal tubule [52]. Less sodium is thus excreted in the urine (urine sodium $<$ 10mM). Note that since water moves in from the intracellular space to the extracellular space, both compartments share the brunt of the water loss and thus the signs of circulatory collapse appear much later and are less dramatic.

2.3.3 Isotonic fluid loss

Examples of isotonic fluid loss include: haemorrhage, burns, gastrointestinal losses from diarrhoea and vomiting, renal loss from polyuric phase of acute renal failure as well as with the use of diuretics and in effusions such as ascites [64]. Though conditions such as peripartum haemorrhage can result in this type of fluid loss in the obstetric population, this type of fluid loss was not the focus of this study.

In this situation, water loss is accompanied by an equivalent loss of sodium (cf with hypotonic fluid loss). There is no compensatory movement of fluid from extracellular space as there is no immediate change in plasma sodium [64]. Circulatory collapse is thus more prominent and patients are more likely

to present with a tachycardia and hypotension [64]. A fall in renal perfusion occurs with a resultant decrease in urine output. Plasma urea and creatinine begin to rise.

The renin angiotensin system is activated early leading to early aldosterone release [64]. Urine is also very concentrated with a very low sodium [64]. Plasma osmolality is however unchanged therefore there is no stimulus for early antidiuretic hormone release. Thirst occurs later when sufficient volume has been lost. Antidiuretic hormone secretion does occur but only when blood volume depletion is severe [64]. Table 2.4 illustrates this discussion.

Table 2.4: Comparison of hypotonic fluid loss to isotonic fluid loss. (DKA= diabetic ketoacidosis, DI= Diabetes insipidus)

	Hypotonic fluid loss	**Isotonic fluid loss**
Definition	loss of water in excess of sodium	loss of water with equivalent amount of sodium loss
Example	Excessive sweating, osmotic diuresis in DKA	Haemorrhage,diarrhoea, burns
Plasma Sodium	↑↑	normal to ↓
Urinary Sodium	↓↓< 10mM	↓↓
ADH Secretion	early	late
Aldosteron Secretion	late	early
Urine Osmolality	↑↑↑ (approaches 1000mosm/kg, except in DI)	↑↑↑
Haematocrit	slightly ↑	↑↑↑
Extracellular fluid volume	↓	↓↓↓
Plasme Urea	normal to ↑	↑
Urine Output	↓↓↓	↓
Thirst	early	late
Tachycardia and hypotension	late	early

2.4 Methods of assessing hydration status

There is currently no gold standard for assessing hydration status [11, 65]. However, a number of methods have been used to determine hydration levels in humans:

2.4.1 Invasive methods

Invasive methods have been mainly used to assess intravascular volume status. These have included pulmonary artery catheter placemement, central venous pressure monitoring as well as arterial waveform pulse pressure variation during mechanical ventilation. These methods have specific indications and the use of each of these methods is associated with known morbidity [12–15].

2.4.2 Clinical parameters in the assessment of hydration status

Numerous other non invasive methods of assessing fluid volume status have been described. These have included the following:

Clinical data, such as changes in body weight [11, 16, 17], skin fold thickness [18], blood pressure and heart rate, changes in heart rate variability [19, 20], orthostatic vital sign changes [21] and bioelectrical impedance [22].

Orthostatic vital sign changes This involves the use of heart rate and blood pressure responses to changes in posture. Dehydration is often associated with a decrease in plasma volume [11]. This can lead to an increase in the heart rate at rest. The change in heart rate and blood pressure to rapid changes in posture can provide information on the degree of orthostatic intolerance, which is often associated with dehydration [66]

Heart rate variability analysis This is a non invasive method that reflects activity of the autonomic nervous system. It has been described by Huang and Kiok and others as a useful non invasive method of predicting hypotension after subarachnoid block [14, 16]. It requires specialised monitoring apparatus.

Body weight changes In this method changes in body weight are used to determine acute water losses. This method can be confounded by factors such as bowel movement as well as fluid and food consumption [11, 16, 17]. A knowledge of a pre dehydration weight is also required for accurate assessment using this method.

Skin fold thickness This method is unreliable as a number of factors can influence this parameter [16]. Such factors include observer subjectivity, age, subcutaneous tissue fat content and pathological skin conditions such as scleroderma [18].

2.4.3 Isotope dilution

The isotope dilution and neutron activation analysis techniques are the accepted standards for measurement of total body water and body fluid spaces [65, 68]. This method is not without fault as body fluids are not stable during daily activities and the method requires three to four hours for the internal equilibration of the isotope and for analysis [65]. Deuterium or tritium labelled water have been traditionally used. However deuterium use is time consuming and tedius whereas tritium use exposes the patient to radiation [67, 68]

2.4.4 Multifrequency bioelectrical impedance analysis

Multifrequency bioelectrical impedance analysis has been used in total body water analysis. In this method the electrical impedence to a current of low amperes is measured [69]. This impedence is affected by the water and electrolyte content of the body [69]. Its usefulness is limited however as the sensitivity and specificity are not known [23, 24]. It is also limited by the fact that various factors including skin temperature and body posture can affect the measurements [69]. Specialised equipment is needed.

2.4.5 Haematological indices

Haemoglobin concentration and the haematocrit may increase with dehydration. Depletion of water results in a rise in the concentrations of large molecules such as proteins and blood cells [10], resulting in an increase in blood haemoglobin concentration and haematocrit [10]. Although these parameters need a baseline measurement in order to be reliable, they can be useful in estimating the percentage change in plasma volume.

This is shown in the equation derived by Dill and Costill [25] for the relative change in plasma volume

$$\frac{[\mathrm{Hb}]_{\mathrm{control}}}{[\mathrm{Hb}]_{\mathrm{incidental}}} \frac{[\mathrm{Hct}]_{\mathrm{incidental}}}{[\mathrm{Hct}]_{\mathrm{control}}} - 1. \tag{2.1}$$

Plasma osmolality and urine osmolality appear to be the most widely used markers of hydration [11, 16, 17]. They may be more useful in diagnosing hydration status than changes in parameters like serum protein and blood urea nitrogen, which are influenced by other factors [26].

2.4.6 Urine parameters

Urine specific gravity is a measure of the weight of dissolved particles in urine, and urine osmolality reflects the number of such particles [27]. They are both useful in the differential diagnosis of oliguria, polyuria or in the syndrome of inappropriate antidiuretic hormone secretion (SIADH). These parameters are easily obtainable measures of concentrating ability but can be unreliable in the presence of glycosuria or other osmotically active substances in urine [27] such as may occur in pregnancy. Diuretics, such as lasix, can also affect the values obtained and for this reason patients on diuretics were excluded from this study [28].

Serum sodium level increases with water depletion, and changes in serum

sodium level most often reflect a change in water balance rather than sodium balance [26]. Hypernatraemia suggests water deficit, except in the face of an increased sodium intake. Similarly, hyponatraemia suggests over hydration [26]. Urine and plasma sodium level have also been used to calculate the fractional excretion of sodium in the diagnosis of pre-renal vs. intra-renal pathology as follows [27]:

$$\frac{[\mathrm{Na}]_{\mathrm{urine}}}{[\mathrm{Na}]_{\mathrm{plasma}}} \frac{[\mathrm{Creat}]_{\mathrm{plasma}}}{[\mathrm{Creat}]_{\mathrm{urine}}} \tag{2.2}$$

The above is a ratio of creatinine clearance to sodium clearance. For a patient with determined renal disease values less than one percent indicate pre-renal pathology and values of more than one percent indicate intra renal pathology [27]. Table 2.5 illustrates the typical ranges that might be found in differentiating pre-renal azotaemia from acute tubular necrosis.

Table 2.5: Table showing the differences between pre-renal azotaemia and acute tubular necrosis.

	pre-renal azotaemia	**acute tubular necrosis**
FeNa	$< 1\%$	$> 1\%$
FeCl	$< 1\%$	$> 1\%$
$[\mathrm{Na}]_{\mathrm{urine}}$	< 10mmol/l	> 20mmol/l
$[\mathrm{Cl}]_{\mathrm{urine}}$	< 25mmol/l	> 25mmol/l
$\frac{[\mathrm{urea}]_{\mathrm{plasma}}}{[\mathrm{creat}]_{\mathrm{plasma}}}$	> 70	< 70
$\frac{\mathrm{osmol(urine)}}{\mathrm{osmol(plasma)}}$	> 1.3	< 1.3
$\frac{[\mathrm{creat}]_{\mathrm{urine}}}{[\mathrm{creat}]_{\mathrm{plasma}}}$	> 14	< 14
$\frac{[\mathrm{urea}]_{\mathrm{urine}}}{[\mathrm{creat}]_{\mathrm{urine}}}$	> 14	< 14

FeNa: Fractional excretion of Sodium. FeCl: Fractional excretion of Chloride [Na] urine: Urine Sodium concentration. [Cl] urine: Urine chloride concentration.

2.4.7 Conclusion

Assessing fluid status is thus a complex process. Current commonly used methods of assessing hydration status are not particularly reliable in adults. There is currently no gold standard for hydration assessment and the available methods have their flaws [11, 16, 65].

2.5 Application to the obstetric patient

2.5.1 Methods of assessing hydration status during pregnancy

Methods of assessing hydration status may be more inaccurate during pregnancy for a number of reasons. The haemodynamic changes that occur during pregnancy may alter haemodynamic parameters such as heart rate and blood pressure. In addition the role of labour must be taken into account. The pain associated with labour may also result in changes to these parameters. Furthermore it may also increase the practical difficulties of a method such as multifrequency bioelectrical impedance (electrodes need to be applied to the patient and a restless patient in pain may not be satisfactorily co-operative). Peripheral oedema common in pregnancy and a result of fluid retention associated with the endocrine changes occuring during pregnancy may make clinical assessment methods such as body weight changes difficult to interpret.

2.5.2 Effect of dehydration on the obstetric patient

Oral intake during labour may decrease, concurrently sensible losses increase due to increased muscle activity [30]. Takashi Watanabe et al highlighted the effect of labour on maternal dehydration, starvation, coagulation, and fibrinolysis in normal parturients during labour [30]. In a study consisting of a total of sixty women they found that urine osmolality, urine creatinine, red blood cell count, haematocrit, thrombin antithrobin III complex and D dimers were significantly increased in normal parturient women. These results indicated that concentrated urine and a hypercoaguable state can develop in parturient women. Their results also indicated that active fluid replacement reduced the degree of the changes.

In the late fifties, Henry JP et al provided evidence from canine models that

rapid fluid administration blocks the release of antidiuretic hormone secretion and oxytocin, suggesting that hypovolaemia may be associated with increased uterine activity as a result of increased antidiuretic hormone and oxytocin release [31]. However to the contrary, a randomised controlled trial suggested that increasing fluid administration for nulliparous women in labor above rates commonly used is associated with a lower frequency of prolonged labor as well as less need for oxytocin. Suggesting that inadequate hydration in labor may be a factor contributing to dysfunctional labor and possibly caesarean delivery [70].

The association of hypovolaemia and preterm labour has also been studied [71], and the administration of fluid to treat pre term contractions has been observed to be frequently effective [72]. Others have however advised caution with the use of this method to treat preterm labour because of the risk of pulmonary oedema [73].

It has been suggested that dehydration can induce oligohydramnios [32, 74].

A Cochrane Review in 2002 sited maternal hydration as a possible strategy to increase amniotic fluid volume. The concern with oligohydramnios is its association with conditions such as malpresentation, failed cephaloversion and umbilical cord presentation [75].

Maternal volume depletion and hypotension can also lead to placental hypoperfusion, adversely affecting the fetus [1–4]. Intravascular volume expansion has been identified as one of the interventions to decrease maternal hypotension [5, 6].

2.5.3 Effect of dehydration on anaesthesia for caesarean section

Fifteen to thirty one percent of births worldwide occur by caesarean section [76]. In 2009, thirty three percent of births at CHBH were by caesarean section [77, 78]

Spinal anaesthesia is the preferred anaesthetic for these procedures [79], the effect of dehydration on spinal anaesthesia is therefore important.

The technique involves the administration of a local anaesthetic solution via the subarachnoid space. The primary cardiovascular effects of spinal anaesthesia are an increase in venous capacitance and a decrease in systemic vascular resistance in the lower limbs, caused by sympathetic outflow blockade to the veins and arterioles [79]. This results in pooling of blood to the lower limbs, which leads to a decrease in venous return and subsequently a decrease in cardiac output [79, 80]. The increase in venous capacitance from the subarachnoid block in the face of an already volume depleted circulatory system can lead to maternal circulatory collapse. General anaesthesia, though itself not a preferred anaesthetic technique for caesarean section, has to sometimes be performed in the case where regional anaesthesia is contra-indicated. The drop in cardiac output as a result of the effects of intravenous and inhalational anaesthetic agents in the setting of maternal volume depletion can be compounded by the effect of volume depletion.

2.5.4 Importance of accurate assessment

Undetected fluid volume depletion maybe responsible for a significant number of intraoperative hypotension. There is thus a need for a method of assessment that is accurate, available and practical to use in the caesarean section theatre.

2.6 Conclusion

In this chapter the physiology of normal water and electrolyte homeostasis has been discussed, as well as the different types of fluid loss and their effects on the human body. A section on the physiological changes in fluid and electrolyte homeostasis during pregnancy has been included as well as the different methods of assessing hydration status. The reviewed literature highlights the possible negative impact of dehydration on the maternal and fetal condition; there is a possible increase in antidiuretic hormone release associated with oxytocin release that may lead to an increase in uterine contractions. Increased muscle activity during labour with a decrease in oral intake can potentiate the hypercoaguable state of pregnancy by resulting in haemoconcentration. Dehydration induced oligohydramnios with its associated complications can also occur. Lastly, severe dehydration can compound the hypotensive effects of both spinal and general anaesthesia. Hence, this literature review supports the need for finding an accurate, simple tool with which to assess the hydration status of a patient prior to caesarean section.

Chapter 3

Materials and methods

This chapter describes the study design, the sample composition and method of selection. The data collection and statistical analysis are explained.

3.1 Problem statement

Maternal dehydration during labour and caesarean section can have a negative impact on both the mother and the fetus. The hypothesis is that patients presenting for urgent caesarean sections after having been in labour will have a higher incidence of covert dehydration as indicated by biochemical parameters, in comparison to patients presenting for elective procedures. In addition this might affect their intra operative cause as measured by the incidence of hypotension between the groups as well as affect the outcome of the newborns as measured by their Apgar scores at birth.

3.2 Ethical considerations

Ethical consent Ethical clearance was obtained from the committee for research on human subjects of the University of the Witwatersrand, protocol clearance number: M071114 (Appendix A).

Hospital consent Permission from CHBH Superintendent was given.

Postgraduate committee approval The study was approved by the Post-Graduate Committee of the University of the Witwatersrand, Faculty of Health Sciences(Appendix B).

Patient consent Informed consent was obtained from all participants who participated in the study. The purpose as well as the procedure was explained verbally to all the participants in a language that they could understand. Participants were approached according to the booking list. When this was completed the participants where given a written information sheet (Appendix C) as well as a consent form to sign (Appendix D). The information given to the participants included their right to refuse and their right to withdraw at any time from the study. They were also told that their refusal to participate would not interfere with their treatment.

3.3 Research methodology

3.3.1 Study design

This was a prospective open-label observational cross-sectional study. The terms are defined as follows:

- Prospective: Only participants giving written informed consent were included in the study. They were then followed forward in time till data collection was complete.
- Open-label: Both the researcher and the participants were aware of which study population they belonged to.
- Observational: Data collection without any intention to intervene. The assignment of participants into a group was outside the control of the investigator. The participants were booked by the attending obstetrician as either urgent or elective.
- Cross-sectional: Data was collected from participants at a single point in time. There was no follow-up of participants following data collection.

Participants were divided into two groups: Elective participants and urgent participants. Each group was further divided into those participants that experienced hypotension intraoperatively and those participants that did not. Figure 3.1 illustrates the group divisions. The biochemical parameters of these groups were analysed for possible causality. It was decided to start with a pilot study in order to estimate statistical parameters which would help to design a larger study if necessary.

3.3.2 Study population

Participants were selected from patients presenting for caesarean section in the Department of Obstetrics, labour ward and theatre Chris Hani Baragwanath Hospital (CHBH). CHBH is located in Soweto, South Africa. It is a state tertiary academic hospital, the largest in sub-saharan Africa with approximately 2800 beds. The hospital and the labour ward serve patients of a predominantly low socio-economic status.

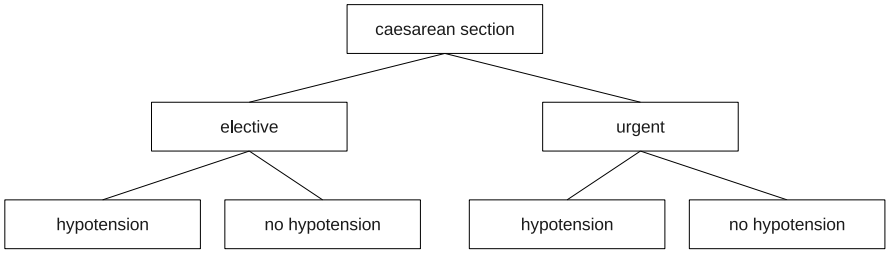


Figure 3.1: Illustration of the group divisions.

3.3.3 Study sample

This was a pilot study which was limited to fifty four participants: twenty seven participants were patients presenting for urgent caesarean sections and twenty seven participants were patients presenting for elective caesarean sections. Initially fifty patients were arbitrarily chosen, twenty five elective and twenty five urgent cases. Due to logistical issues involving the laboratory four additional patients were recruited into the study.

3.3.4 Study period

Data collection commenced following Post Graduate Committee approval of the protocol. The data collection period began Monday the 22nd of December 2008 and was completed on Saturday the 12th of September 2009.

3.3.5 Detailed methodology

Participants were selected sequentially according to the booking list on a given data collection day. This was not necesarily on consecutive days. The elective

group was used as a control. The height and weight was used in the calculation of the body mass index (BMI) to account for the possible effect of a larger mass on hypotension from aortocaval compression. BMI is an index used to estimate total body fat, and is calculated as; weight divided by the square of the height. Aortocaval compression is a phenomenon observed commonly in advanced pregnancy where hypotension occurs on lying supine as a result of the weight of the uterus compressing on the inferior vena cava and or aorta.

Age was recorded to better characterise the population. Participants on the elective list who had been starved had the duration of starvation noted. Prolonged starvation in the elective group could lead to dehydration in this group (control group) which could result in less of a difference in the intraoperative course of the groups. Coincidentally, the groups were matched for age and not for the BMI. Informed consent was obtained from the participants before the samples and data were collected. The investigator met the participants in their cubicles after the booking. The principal investigator obtained consent from all the participants using a language the participants could understand (the principal investigator is multilingual). Patients who agreed to participate in the study were interviewed preoperatively. Blood samples were taken in theatre, at the red line. The following data were collected on the data sheet:

1. Age in years
2. Height in metres
3. Indication for caesarean section
4. ASA status — only ASA I and II participants were included
5. Duration of starvation in hours

Blood and urine were sampled by the researcher. Blood was taken on arrival in theatre at the red line from the antecubital fossa using the arm without the

intravenous cannula in-situ. The skin was cleaned with alcohol and approximately 10 ml of blood was sampled. The urine samples were freshly collected. All participants arrived with a urinary catheter in-situ and a urine bag. The bag was emptied and urine was allowed to collect in a sampling container. After collection the samples were taken immediately to the laboratory by the researcher for immediate analysis. The blood samples were analysed for the following:

1. Haematocrit
2. Haemoglobin
3. Sodium
4. Urea and Creatinine
5. Plasma Osmolality

The urine samples were analysed for:

1. Sodium
2. Creatinine
3. Osmolality
4. Specific Gravity

All the specimens were analysed at the National Health Laboratory System. The haemoglobin and haematocrit were analysed using the cell/dyne 3700 haematology analyser (Abbott Diagnostics). The accuracy of the haemoglobin measurement is less and or equal to 1.2%.and is less and or equal to 1.0% for the haematocrit measurement (Abbot cell/dyne, product details as supplied by Abbott). The urine osmolality and plasma osmolality were analysed using Advanced R model 3320 microosmometer which uses freezing point depression (resolution 1mOsm/kg H_2O). The standard deviation is less or equal to 2

mOsm/kg H_2O between 0 and 400 mOsm/kg H_2O and less or equal to 0.5% of values between 400 and 2000mOsm/kg H_2O (Advanced Instruments Inc).

The Multistix R Siemens reagent strips were used for specific gravity measurement. Inter-individual variation in assessment may possibly affect the results obtained. The test permits determination of urine specific gravity between 1.000 and 1.030. In general it correlates within 0.005 with values obtained with the refractive index method (multistix package insert). The plasma and urine sodium, urea and creatinine were analysed using the Roche Modular system. The system's 'between-day' coefficient of variation has been shown to be less than six percent [81].

Intraoperatively, all participants received the following standard anaesthetic technique performed by the anaesthetist who had been allocated to the labour ward theatre:

The participants were placed in a supine position with a 15 degree left lateral tilt. The tilt is a manoeuvre aimed at decreasing aortocaval compression. Standard monitors (non-invasive blood pressure, electrocardiogram monitor and pulse oximeter) were applied and baseline blood pressure (systolic and diastolic) and heart rate readings were recorded using a study dedicated automated monitor (DINAMAP Pro1000V3 monitor). With regards to accuracy, the monitor meets the AAMI/ANSI standard SP10. The baseline readings were recorded on the data sheet as 'initial supine' readings. These were repeated in the sitting position and recorded on data sheet as 'sitting' readings.

An 18 gauge intravenous cannula was inserted if not already present and participants were given a preload with 500ml of Ringers Lactate over 10-20 minutes. Blood pressure and heart rate readings were repeated 5 minutes after the infusion.

A 25 gauge pencil point needle was inserted at L3/L4 interspace until clear cerebrospinal fluid was obtained indicating the needle's presence in the sub-

arachnoid space. Hyperbaric Bupivacaine (0.5%) was injected intrathecally. Hyperbaric bupivacaine is a local anaesthetic agent mixed with dextrose to increase its baricity. The drug company that manufactures the premixed solution used in this study is Micro Healthcare (Pty) Ltd. All participants received between 2-2.2mls of this solution in the subarachnoid space.

The participants were re-positioned supine with a 15 degree left lateral tilt. Mean arterial pressure, systolic blood pressure, diastolic pressure as well as pulse rate readings were taken immediately and recorded on data sheet as "supine immediately after spinal" readings. These were then repeated at 2 min intervals after the injection of the local anaesthetic until 10 minutes. The highest level of the block achieved was also tested before the skin incision using loss of sensation to cold. This was also noted on the data sheet.

The primary outcome variable was hypotension. Hypotension was defined in this study as a drop of more than 15% from the baseline readings compared to the end point of study (10 minutes after local anaesthetic was injected into the subarachnoid space) and also compared to the average of the readings at 2, 4, 6, 8, and 10 minutes after injection of local anaesthetic into the subarchnoid space. Participants were given a 500ml bolus of colloid or crystalloid as well as phenylephrine in boluses or ephedrine boluses to treat hypotension if it occured at any point in the study. Total amount and type of fluid administered, doses and time of administration of the vasopressors as well as the estimated blood loss during the study period was noted. The study period was limited to 10 minutes after injection of local anaesthetic.

Surgery was allowed to continue after establishment of an adequate block. This was defined as a sensory block tested using cold sensation of a minimal level of T8.

The secondary outcome variable was the Apgar scores of the infant at 1 and 5 minutes after delivery. The Apgar score is a score developed by Dr Virginia

Apgar in 1952 as a method of rapid newborn assessment. It consists of 5 criteria namely; skin colour, tone, heart rate, reflex irritability and respiration. Each criteria is graded 0 to 3. The test is usually done at 1 and 5 minutes after birth [82].

3.3.6 Inclusion criteria

- Pregnant participants booked for caesarean section at CHBH Hospital
- ASA I and II participants only
- Participants over the age of 18 years who are able to give consent

3.3.7 Exclusion criteria

- Patients on the following drugs: oxytocin infusions, diuretics, ipradol and cardiovascular active agents such as nifedipine, hydralazine, methyldopa and labetalol. These drugs have an effect on the cardiovascular system and can thus affect the measured variables.
- Patients given any sedatives in labour.
- ASA III, IV and V patients
- Patients with ante partum haemorrhage requiring fluid and or inotropic resuscitation.
- Patients with evidence of sepsis (raised white cell count, elevated temperature, unexplained tachycardia or a known source of sepsis)
- Patients with hypertensive disorders of pregnancy
- Emergency caesarean sections (i.e. procedures that cannot be delayed for the time required to initiate the study. e.g cord prolapse and eclampsia)
- Patients requiring general anaesthesia or epidural anaesthesia
- Patients with overt dehydration.

3.3.8 The data collection and analysis

Each participants's data were entered onto a data capture sheet (Appendix E) . The following data were entered:

- study number, age, weight, height (weight and height were used to calculate BMI)
- duration of starvation, indication for caesarean section
- haemoglobin, haematocrit
- plasma sodium, urea, creatinine, and osmolality
- urine specific gravity, sodium, creatinine, and osmolality
- the highest level of the subarachnoid block achieved
- Apgar scores of the baby at 1 and 5 minutes
- blood pressure measurements in theatre (systolic, diastolic and mean)
- estimated blood loss during the study period in ml
- vasopressor type and dose given during the study period (ten minutes after subarachnoid block)
- total amount and type of fluid administered

All the data was then entered onto an Open Office spreadsheet. After the data collection was complete the results were analysed. We determined whether the differences in the mean values were statistically significant by using the student t test for normally distributed data and the Mann-Whitney U test if not. The Shapiro-Wilk test was used to test distribution of the data. Pearson's chi-square test was used to analyse categorical data. Significance was set at $p < 0.05$.

3.4 Reliability

The following measures were put in place to ensure the collected data was reliable:

1. All the laboratory tests were performed at the National Health Systems Laboratory at CHBH. As stated previously the haemoglobin and haematocrit were analysed using the cell/dyne 3700 haematology analyser (Abbot diagnostics). The urine osmolality and plasma osmolality were analysed using Advanced R model 3320 microosmometer which uses freezing point depression. The Multistix R Siemens reagent strips were used for specific gravity measurement. The plasma and urine sodium, urea and creatinine were analysed using the Roche Modular system.
2. All participants received a standard anaesthetic.
3. All specimens were analysed immediately
4. The study period was standardised to the first ten minutes after the subarachnoid block.

3.5 Conclusion

In this chapter the problem statement, all the ethical considerations that pertain to the study, the detailed research methodology as well as the reliability of the results obtained have been discussed.

Chapter 4

Results

In this chapter the results of the study are presented. A total of fifty four participants were enrolled into the study. Twenty seven participants from the experimental group and twenty seven participants from the control group. This is notably a slightly higher number than that initially planned for. The reason for this is that some initial results were not recorded by the lab under the study number and could thus not be accessed, these results were later found under the specimen number when other participants had already been enrolled as replacements.

One potential participant refused to give consent, one participant's elective surgery was postponed to another day after recruitment into the study and was thus excluded from the study, and four participants had to be excluded from the study due to laboratory errors relating to the analysis of the blood samples. No patients were excluded as a result of the clinical suspicion of overt dehydration. The reason for this is that overt dehydration should be treated before a spinal anaesthetic is given. A spinal anaesthetic administered to an overtly dehydrated patient can result in severe hypotension.

The data was collected between Monday 22nd of December 2008 and the 12th

of September 2009.

A section on the participants' group characteristics introduces the chapter followed by the laboratory results obtained for each group, blood pressure and heart rate measurements in theatre and intraoperative events. The results will be presented in table format as well as displayed as violin plots (see Appendix F for a description of the various components of a violin plot).

4.1 Participants' groups characteristics

The mean age for the elective group was 28.96 yrs (median, standard deviation) (27, 6.15) and that for the urgent group was 27.41 yrs (27, 5.97). With regards to the BMI; the mean value for the elective group was 32.64 kg/m^2 (30.82, 6.45) and that for the urgent group was 29.68 kg/m^2 (27.27, 5.1). The mean duration of starvation for the elective group was 1014.81 min (1065, 362.97) and that for the urgent group was 1103.93 min (1140, 645.75). The mean for the elective group's ASA status was 1.148 (1, 0.36) and that for the urgent group was 1.370 (1, 0.49).

The age, body mass index, ASA classification as well as duration of starvation of the participants are presented in table 4.1.

The indications for the caesarean sections is presented in table 4.2

Table 4.1: Participant demographics and group characteristics

Characteristic	**Elective** mean/median/SD	**Urgent** mean/median/SD	**p-Value**
Age (yrs)	28.96/27/6.15	27.41/27/5.97	0.414
BMI (kg/m^2)	32.64/30.82/6.45	29.68/27.27/5.1	0.055
DoS (min)	1014.81/1065/362.97	1103.93/1140/645.75	0.535
ASA	1.148/1/0.36	1.370/1/0.49	0.066

SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anaesthesiologists, DoS: Duration of starvation

Figures 4.1, 4.2, 4.3, and 4.4 are violin plots illustrating the differences between the two groups with regards to age, BMI, duration of starvation and ASA status.

Table 4.2: Indication for the Ceasarean Sections

Indication	**Elective**	**Urgent**
Cpd	0	7
Big baby	1	0
Breech elective	2	0
Breech in labour	0	3
Poor progress	0	4
Cpd & big baby	0	1
Twins & decreased liqour	1	0
Twins & placenta praevia	1	0
Prev C/S x1	9	0
Prev C/S x1 & poor progress	0	8
Prev C/S x1 & post dates	1	0
Prev C/S x1 & twins in labour	0	1
Prev C/S x1 & big baby	3	0
Prev C/S x2	9	0
Prev C/S x2 & labour	0	2
Gm & prol rupt of membranes	0	1

Cpd: Cephalopelvic disproportion, C/S: Caesarean section, Gm: Grand multipara, prol rupt of membranes: prolonged rupture of membranes

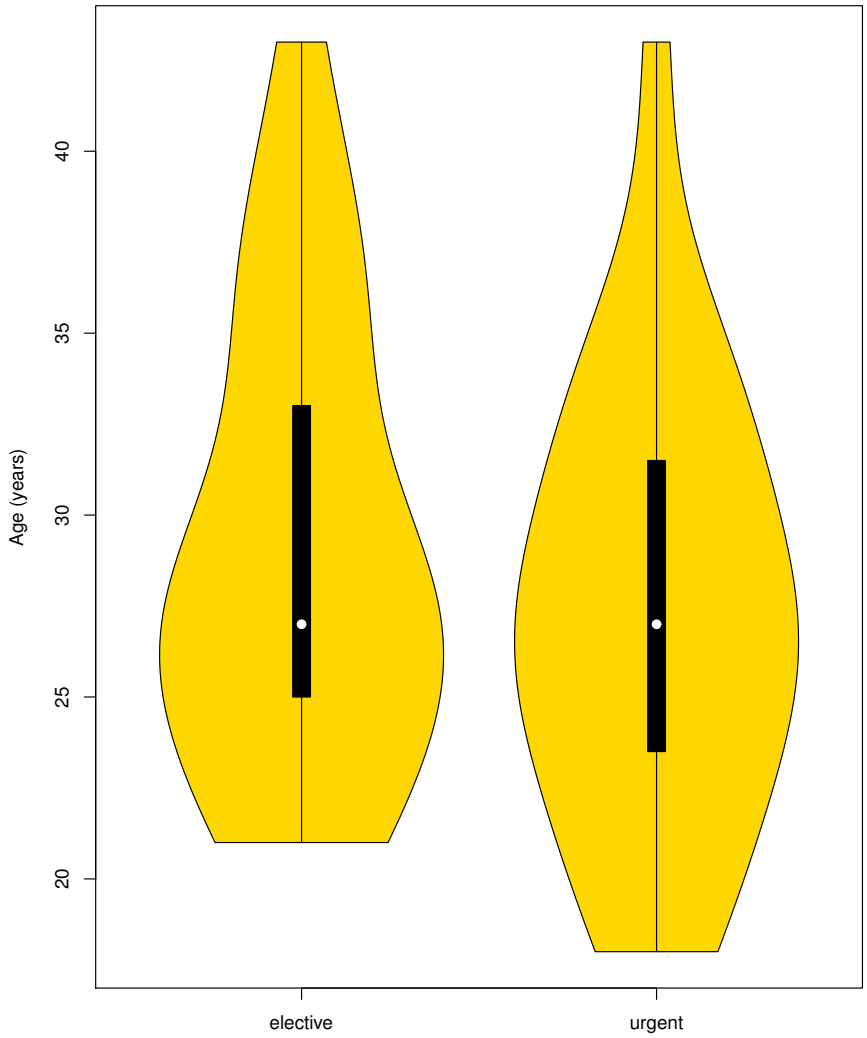


Figure 4.1: Violin-plot illustrating the differences in age distribution between the elective group and the urgent group.

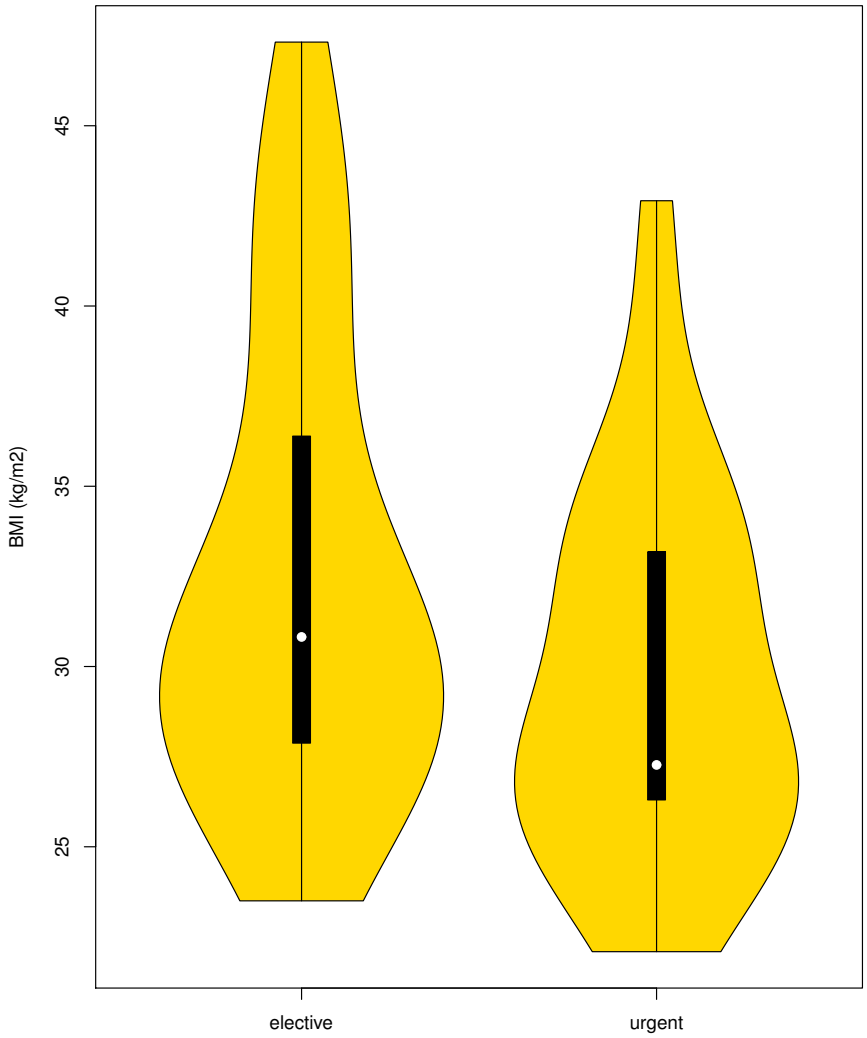


Figure 4.2: Violin-plot illustrating the differences in the BMI between the elective group and the urgent group.

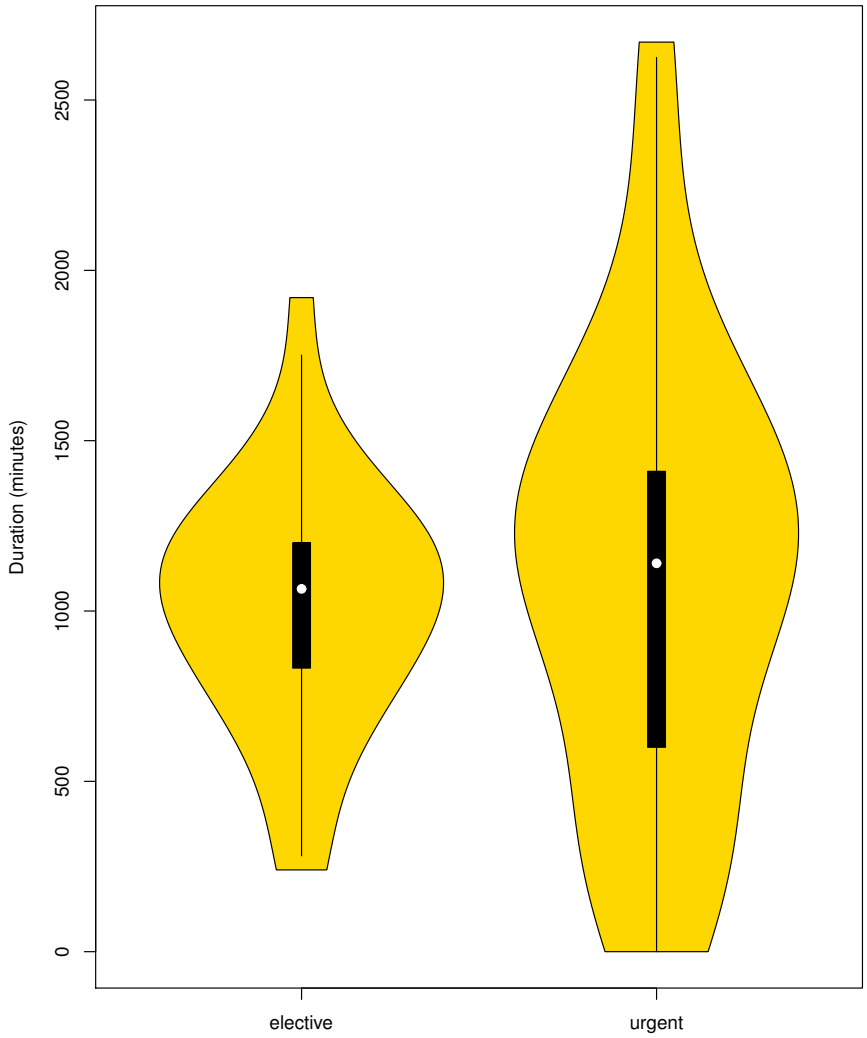


Figure 4.3: Violin-plot illustrating the differences in the duration of starvation between the two groups.

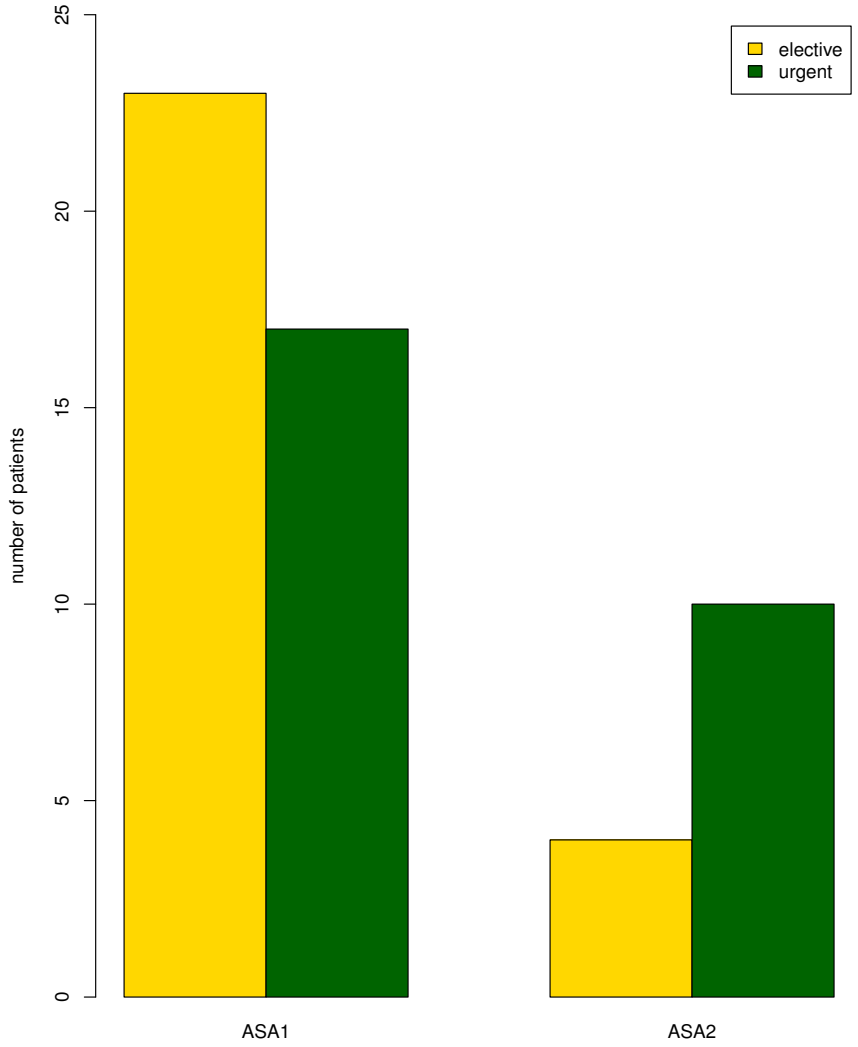


Figure 4.4: Histogram illustrating the ASA score distribution in the elective and the urgent group.

4.2 Laboratory parameters

These consist of haematological and urine results obtained from both the control group (elective) and the experimental group (urgent).

4.2.1 Haematological laboratory parameters

The average haematocrit for both groups was 0.35 l/l (0.34, 0.04) for the elective group and 0.35 l/l (0.35, 0.04) for the urgent group) $p = 0.505$ (see figure 4.5).

The average haemoglobin for the elective group was 11.43 g/dl (11.3, 1.49) and 11.84 g/dl (12.0, 1.51) for the urgent group $p = 0.314$ (see figure 4.6).

4.2.2 Biochemical parameters

The average sodium concentration for the elective group was 139.2 mmol/l (139, 3.1) and 138.2 mmol/l (138, 3.1) for the urgent group $p = 0.099$ (see figure 4.7).

The average urea concentration for the elective group was 2.49 mmol/l (2.6, 0.88) and 2.40 mmol/l (2.5, 0.86) for the urgent group $p = 0.732$ (see figure 4.8).

The average creatinine concentration for the elective group was 47.37 μmol/l (47, 11.44) and 51.48 μmol/l (50, 11.27) for the urgent group $p = 0.158$ (see figure 4.9).

The average plasma osmolality for the elective group was 284 mosm/kg (283, 7.5) and 287 mosm/kg (285, 11.1) for the urgent group $p = 0.136$ (see figure 4.10).

Table 4.3 illustrates the results of the haematological parameters.

Table 4.4 illustrates the results of the biochemical parameters.

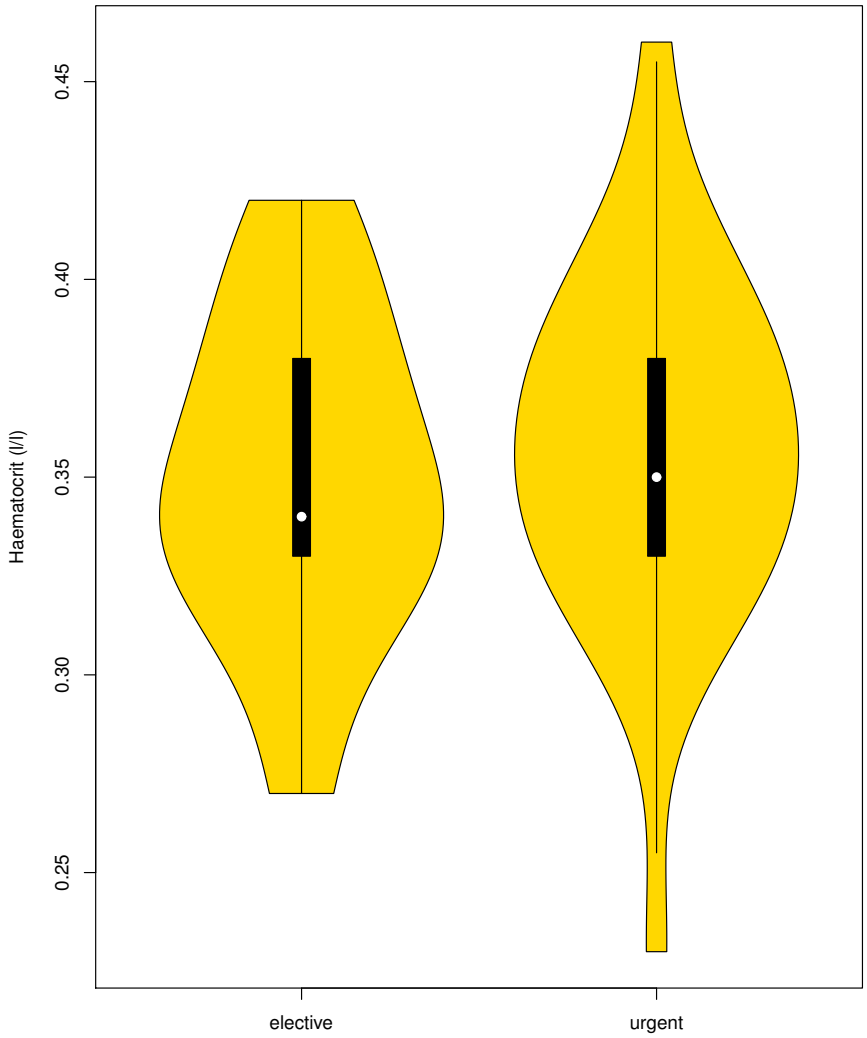


Figure 4.5: Violin-plot illustrating the differences in Hct between the elective and the urgent group.

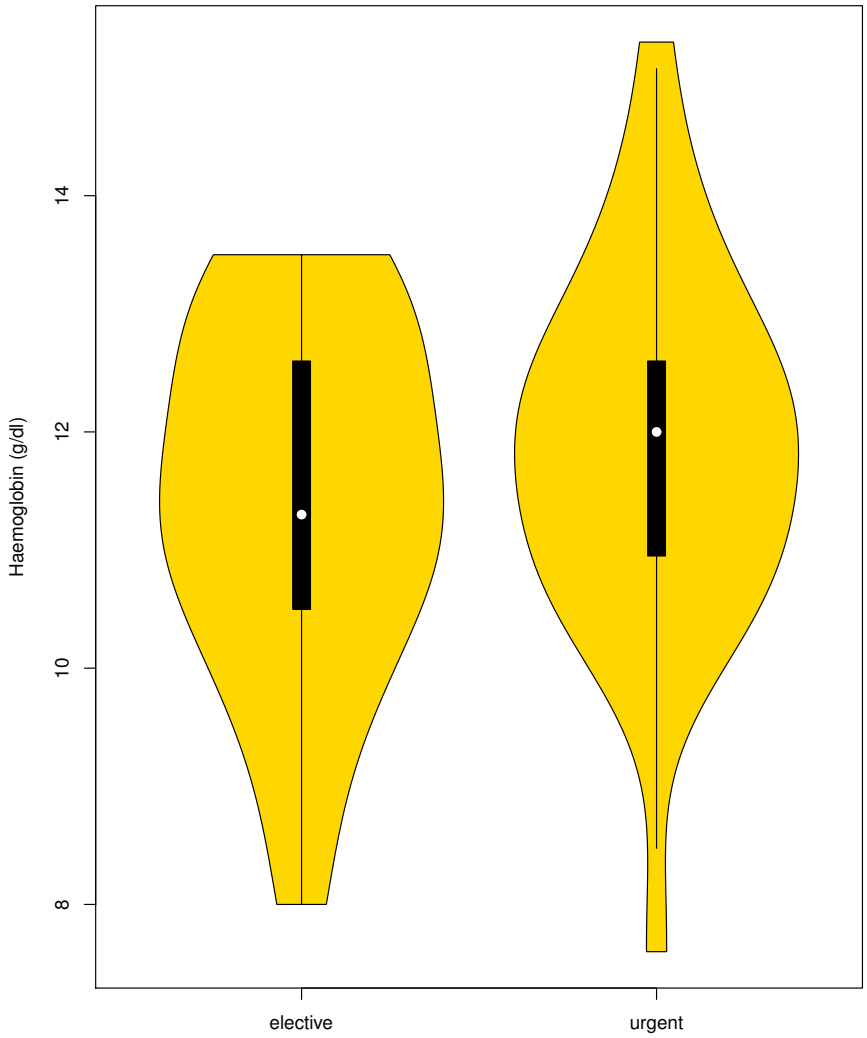


Figure 4.6: Violin-plot illustrating the differences in Hb between the urgent and the elective group.

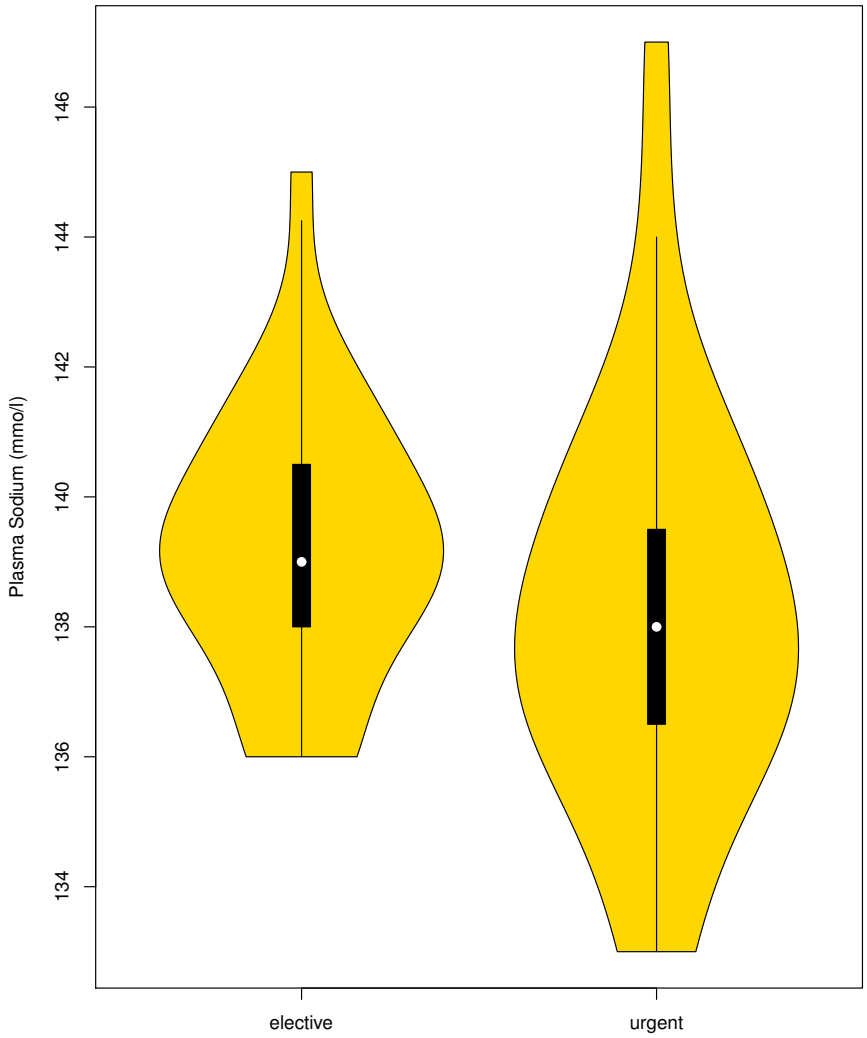


Figure 4.7: Violin-plot illustrating the differences in plasma sodium concentration between the elective and the urgent group.

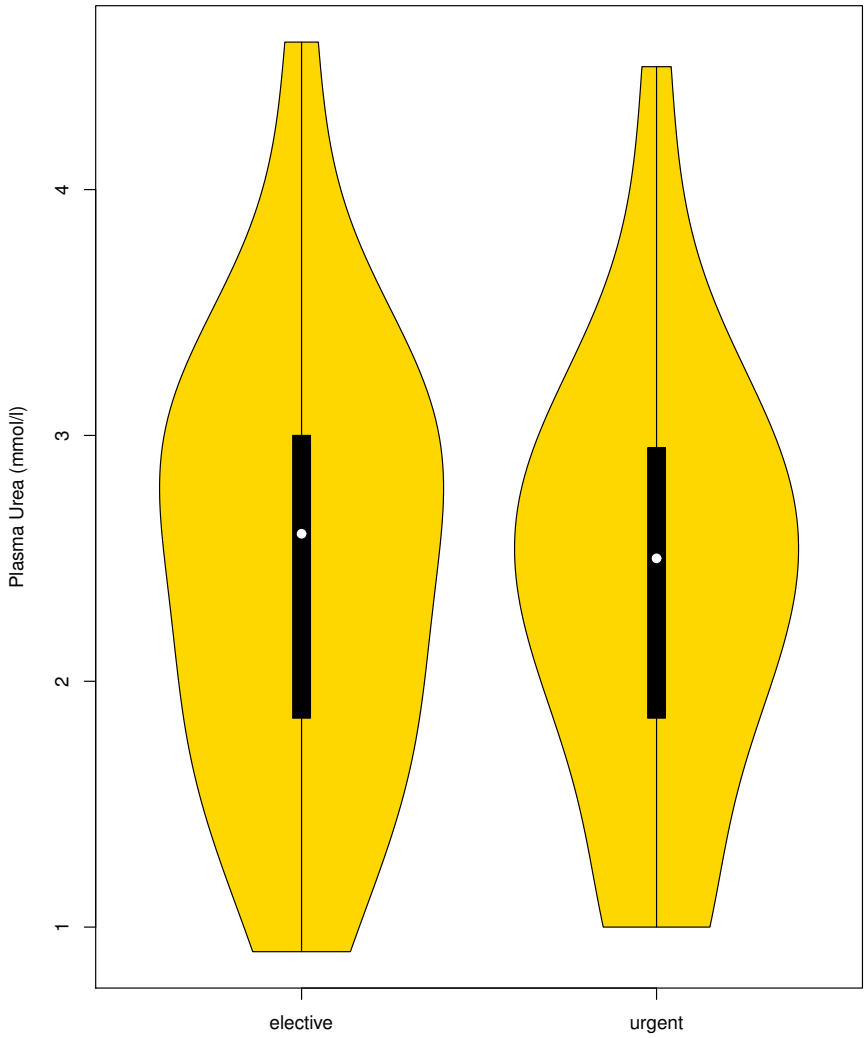


Figure 4.8: Violin-plot illustrating the differences in urea concentration between the elective and the urgent group.

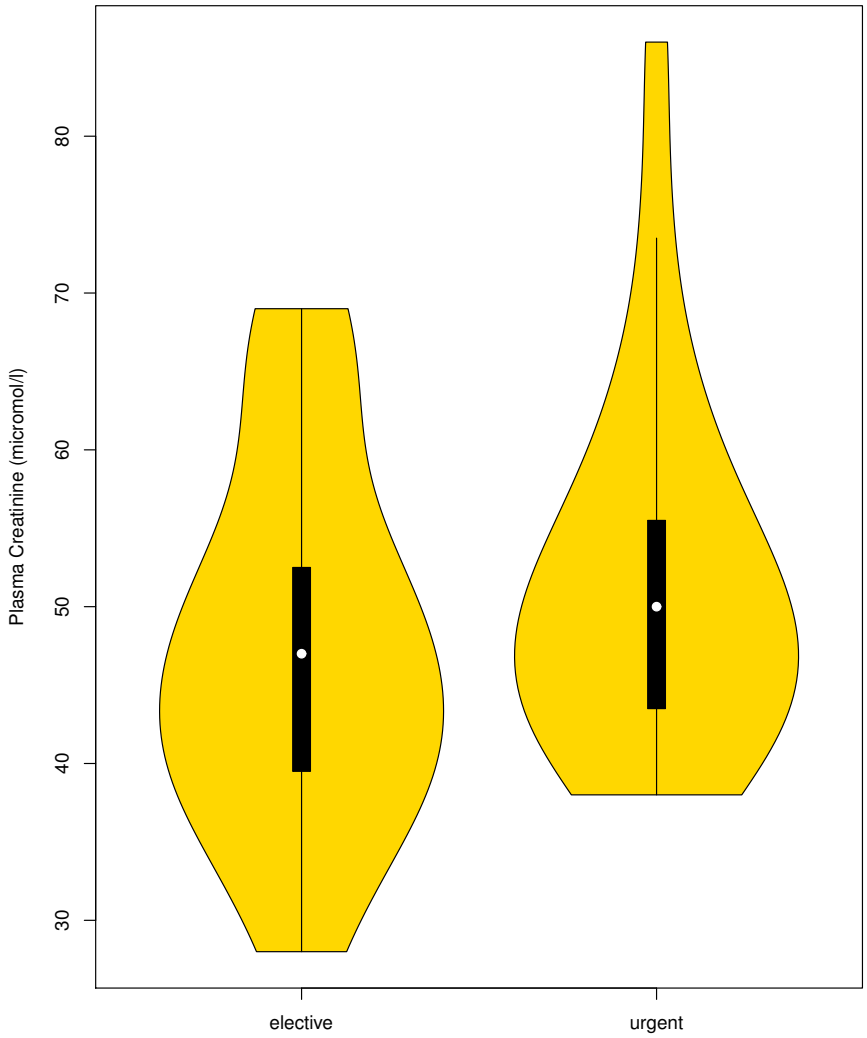


Figure 4.9: Violin-plot illustrating the differences in plasma creatinine between the urgent and elective group.

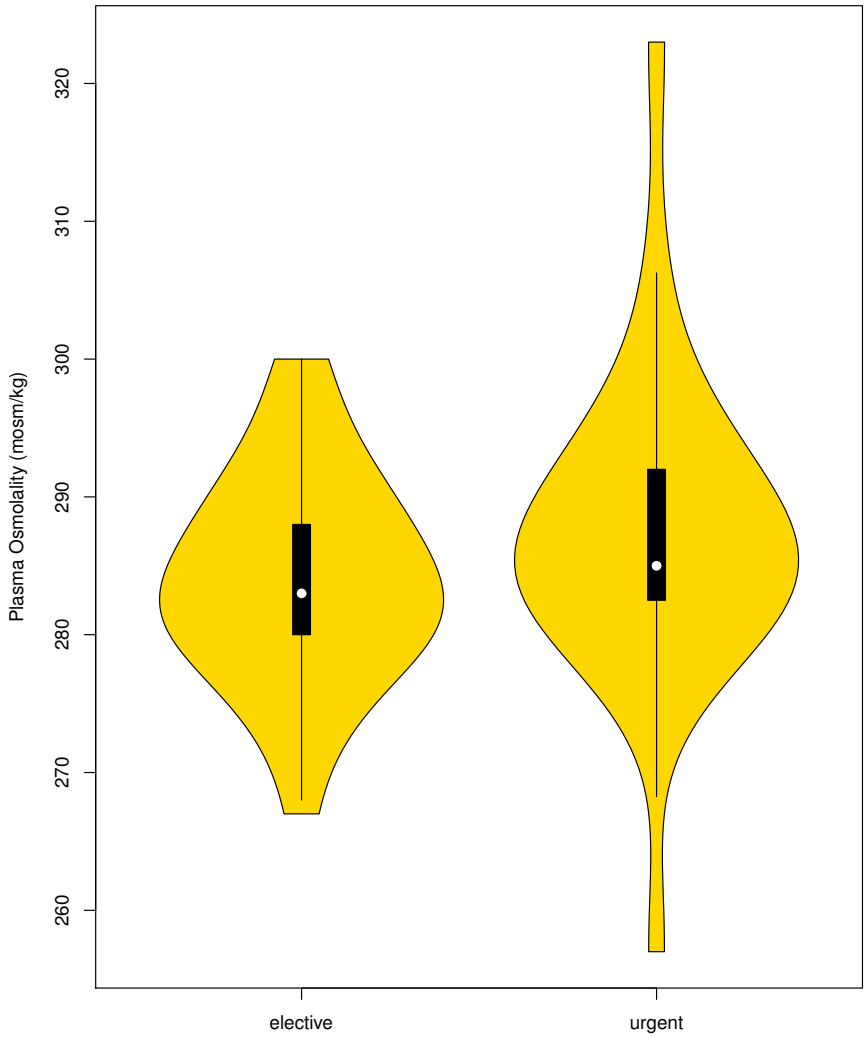


Figure 4.10: Violin-plot illustrating the differences in plasma osmolality between the elective and the urgent group.

Table 4.3: Haematological parameters of participants in the elective and urgent groups

Variable	**Elective** mean/med/std dev	**Urgent** mean/med/std dev	**p-Value**
Haematocrit (l/l)	0.35/0.34/0.04	0.35/0.35/0.04	0.505
Haemoglobin (g/dl)	11.43/11.3/1.49	11.84/12.0/1.51	0.314

Table 4.4: Biochemical parameters of participants in the elective and urgent groups

Variable	**Elective** mean/med/std dev	**Urgent** mean/med/std dev	**p-Value**
Sodium (mmol/l)	139.2/139/2.1	138.2/138/3.1	0.099
Urea (mmol/l)	2.49/2.6/0.88	2.40/2.5/0.86	0.732
Creatinine (μmol/l)	47.37/47/11.44	51.48/50/11.27	0.158
Plasma osmolality (mosm/kg)	284/283/7.5	287/285/11.1	0.136

4.2.3 Urine laboratory parameters

The average creatinine for the elective group was 11.51 μmol/l (7.7, 13.16) for the elective group and 11.40 μmol/l (10.5, 6.15) for the urgent group $p = 0.97$ (see figure 4.11).

The average sodium for the elective group was 164.26 mmol/l (168, 80.41) and 152.19 mmol/l (159, 71.66) for the urgent group $p = 0.56$ (see figure 4.12).

The average osmolality for the elective group was 602.07 mosm/kg (577, 283.61) and 635.44 mosm/kg (611, 272.14) for the urgent group $p = 0.66$ (see figure 4.13).

The average specific gravity for the elective group was 1.01 (1.010, 0.01) and 1.02 (1.015, 0.01) for the urgent group $p = 0.06$ (see figure 4.14).

Table 4.5 illustrates the results of the urine parameters.

Table 4.5: Results for the urine parameters in the elective and urgent groups

Variable	**Elective** mean/median/std dev	**Urgent** mean/median/std dev	**p-Value**
Creatinine (μmol/l)	11.51/7.7/13.16	11.40/10.5/6.15	0.97
Sodium (mmol/l)	164.26/168/80.41	152.19/159/71.66	0.56
Osmolality (mosm/kg)	602.07/577/283.61	635.44/611/272.14	0.66
Specific gravity	1.01/1.010/0.01	1.02/1.015/0.01	0.06

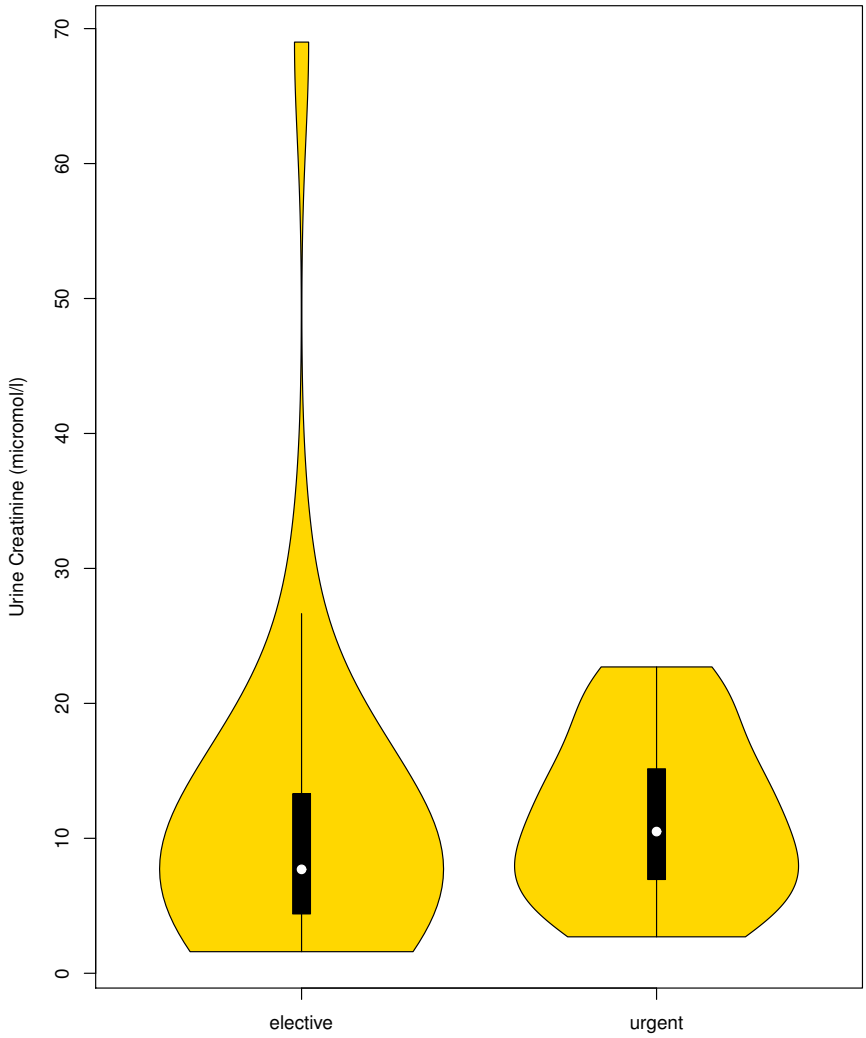


Figure 4.11: Violin-plot illustrating the differences in urine creatinine between the elective and the urgent group.

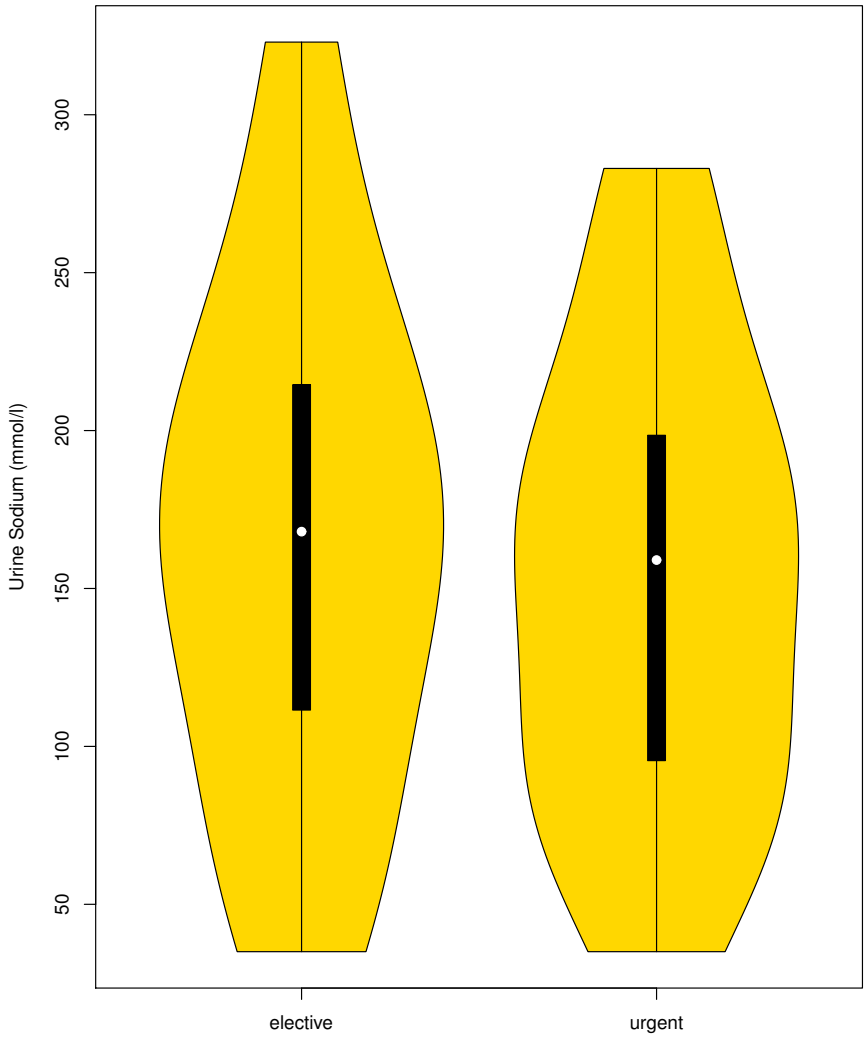


Figure 4.12: Violin-plot illustrating the differences in urine sodium concentration between the elective and the urgent group.

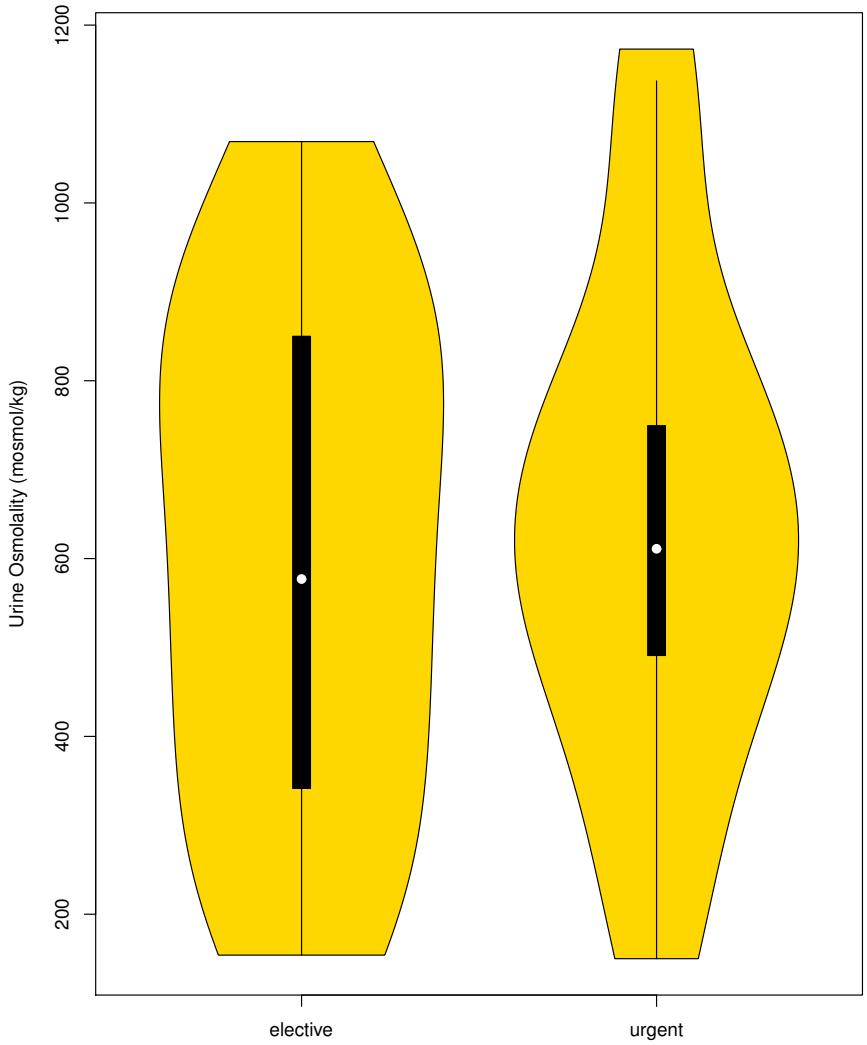


Figure 4.13: Violin-plot illustrating the differences in urine osmolality between the urgent and the elective group.

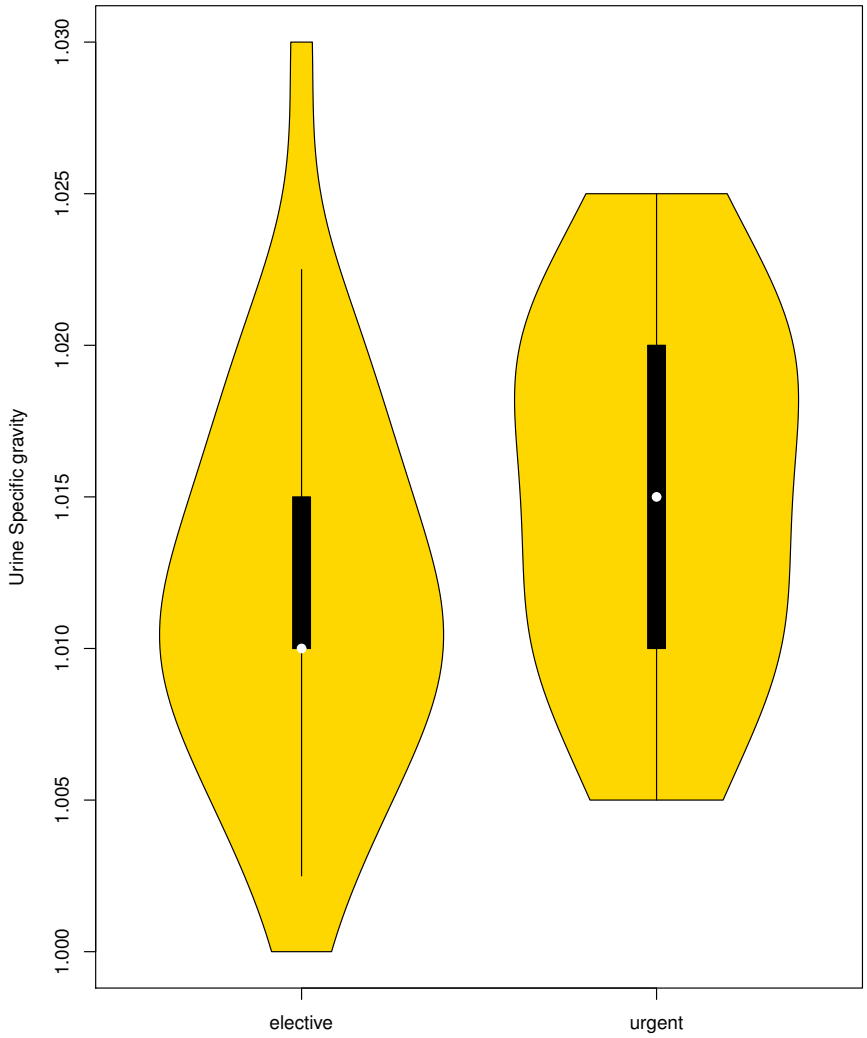


Figure 4.14: Violin-plot illustrating the differences in urine specific gravity between the elective and the urgent group.

4.3 Blood pressure and heart rate measurements in theatre

Participants were divided into two groups: elective and urgent. For each participant the blood pressure and heart rate were recorded initially and in two minute intervals up to ten minutes. Table 4.6 shows the average mean blood pressure and average heart rate readings obtained intraoperatively for each group. These are further illustrated graphically in Figure 4.15 (x axis time, y axis blood pressure change and heart rate. Elective in blue, urgent in red. On the x-axis -2 represents the initial supine measurement, -1 represents the measurement taken sitting for administration of the spinal anaesthetic and 0 min represents the measurement taken supine immediately after administration of the spinal anaesthetic.).

Table 4.6: Average heart rate and average of the mean arterial pressure over time.

	Heart Rate			
time	**elective**	**std dev**	**urgent**	**std dev**
-2	83.48	10.71	91.26	15.91
-1	89.60	10.62	97.37	15.66
0	96.53	19.95	99.37	24.79
2	96.11	17.96	101.30	25.92
4	92.07	20.82	97.52	21.85
6	84.52	19.00	93.41	24.81
8	80.67	20.44	87.07	21.49
10	78.74	17.18	87.67	19.27
	Mean Arterial Pressure			
	elective	**std dev**	**urgent**	**std dev**
-2	93.84	14.70	97.89	16.84
-1	97.63	15.13	100.88	13.60
0	91.83	15.32	93.30	15.80
2	84.93	16.49	82.37	15.80
4	78.55	19.82	79.93	16.68
6	83.41	18.12	81.40	15.34
8	82.21	17.64	82.70	14.48
10	84.28	15.77	80.96	13.66

The relative blood pressure change to end point of study was -9.6% (-9, 12.7)

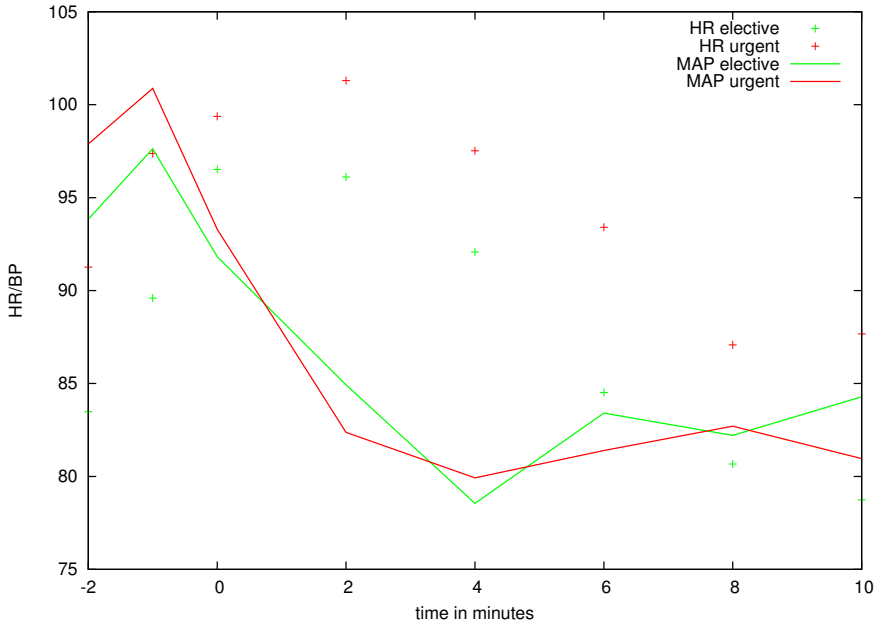


Figure 4.15: Heart-rate and (mean-arterial) blood pressure against time. -2 initial supine, 0 supine after administration of the spinal anaesthetic.

for the elective group and -15.4% (-17, 17.6) $p = 0.17$. Figure 4.17 illustrates this.

The average relative blood pressure change was -11,7% (median, standard deviation) (-12.4, 11.1) for the elective group and -15.1% (-14.9, 15.1) $p = 0.36$. This is illustarted in Figure 4.18.

The number of cases of hypotension in each group was recorded. Hypotension was defined in this study as a blood pressure drop of more than 15 percent from the baseline compared to the 10 minute end point mean arterial blood pressure (10 minutes after the suarachnoid block) as well as to the average of the readings at 2, 4, 6, 8 and 10 minute intervals.

When comparing baseline blood pressure and heart rate measurements to the ten minute end point measurements then 15 (out of the 27) experienced hypotension in the urgent group compared to 9 participants in the elective group $p = 0.17$. When comparing baseline blood pressure and heart rate measurements

to the average (average of 2, 4, 6, 8 and 10 minute readings) then 13 participants from the urgent group experienced hypotension compared to 9 participants in the elective group $p = 0.40$.

Table 4.7 shows the number of occurences of hypotension in the two groups.

Table 4.7: Number of occurences of hypotension between elective and urgent groups. The first row contains the number of cases of hypotension observed when the baseline readings were compared to the readings obtained at the 10 minute end point of the study, whereas the second row contains the number of cases of hypotension observed when the baseline readings were compared to the average of the readings obtained at 2, 4, 6, 8 and 10 minute intervals.

	elective	urgent
10 min	9	15
Average	9	13

Figure 4.16 shows the resulting probability distribution for the estimate of the true occurance rate of hypotension in each group. (The graphs were derived under the assumption of a flat prior-distribution.)

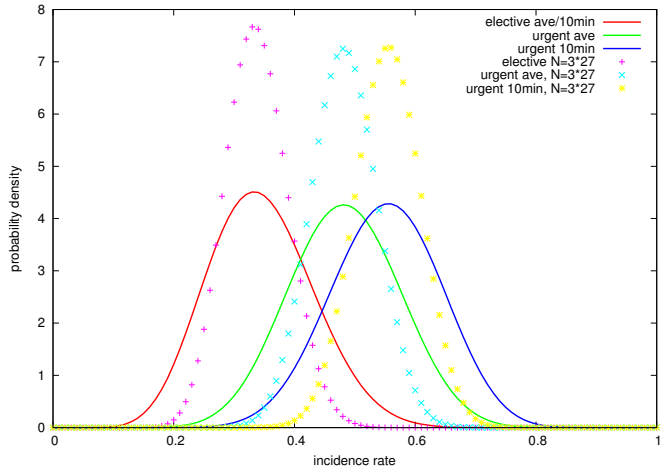


Figure 4.16: .
The doted line shows how the certainty would improve if the same incidence rates would have been found with a three-fold increase in the sample size

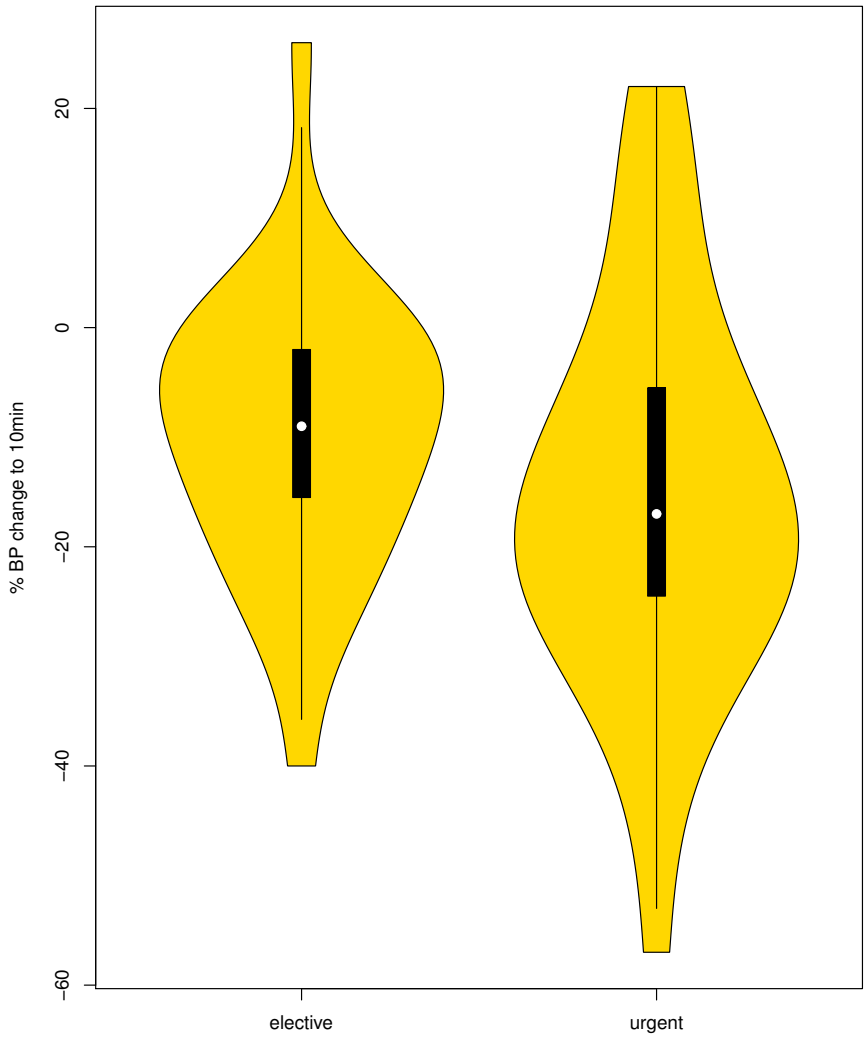


Figure 4.17: Violin-plot illustrating the distributions of the relative blood pressure after 10 minutes.

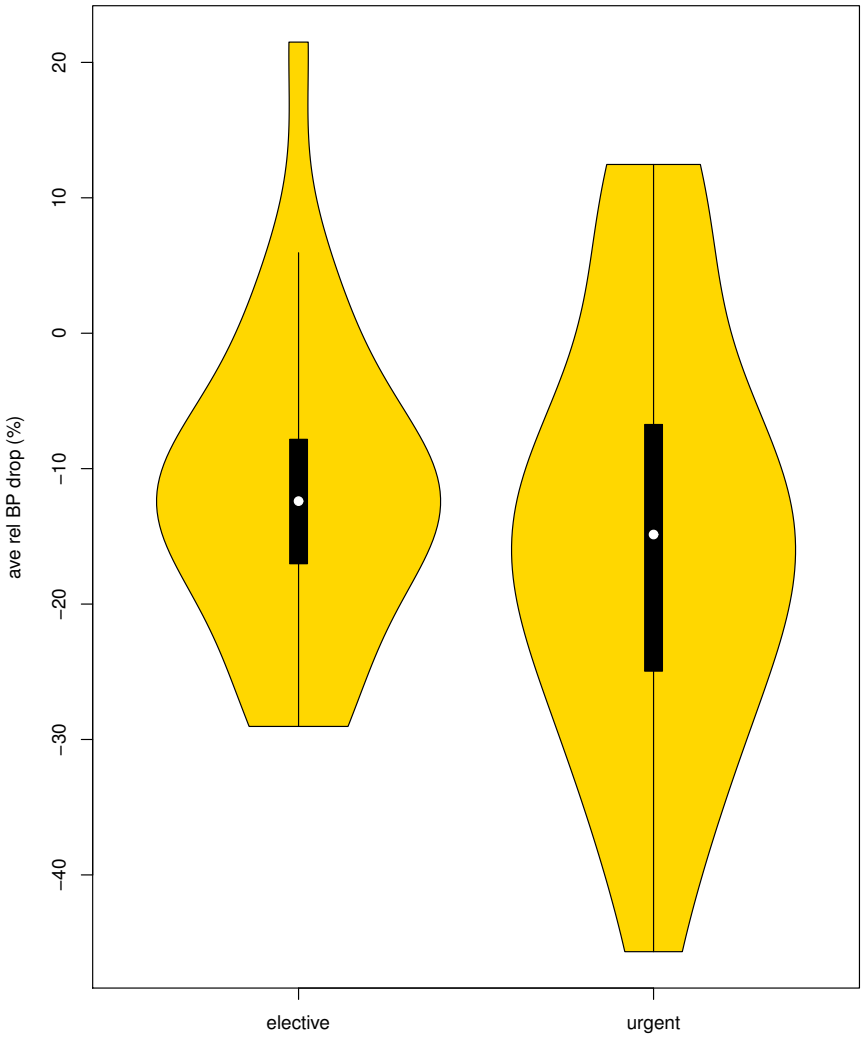


Figure 4.18: Violin-plot illustrating the distributions of the average relative blood pressure.

4.4 Intraoperative events

4.4.1 Level of block

The level of the block achieved and the number of participants who had a certain level of blockade are shown in Table 4.8.

Table 4.8: Number of participants for each level of block.

Level of block	**elective**	**urgent**
T2	1	0
T3	1	3
T4	8	8
T5	2	0
T6	8	7
T7	0	1
T8	5	5
T10	2	3

4.4.2 Apgar scores

The mean Apgar scores at 1 minute for the elective and urgent groups were 8.89 (median, standard deviation) (9.00, 0.32) and 8.37 (9.00, 0.93), respectively $p = 0.01$. The 5 minute Apgar scores for both groups were 10.

Table 4.9 shows the Apgar scores of the infants at 1 and 5 minutes after birth. Figure 4.19 illustrates these statistical quantities.

Table 4.9: Apgar scores of infants delivered in the two groups.

Apgar Score	**Elective** mean/median/std dev	**Urgent** mean/median/std dev	**p-Value**
Apgar score at 1 minute	8.89/9.00/0.32	8.37/9.00/0.93	0.01
Apgar score at 5 minute	10/10/0	9.81/10/0.48	n/a

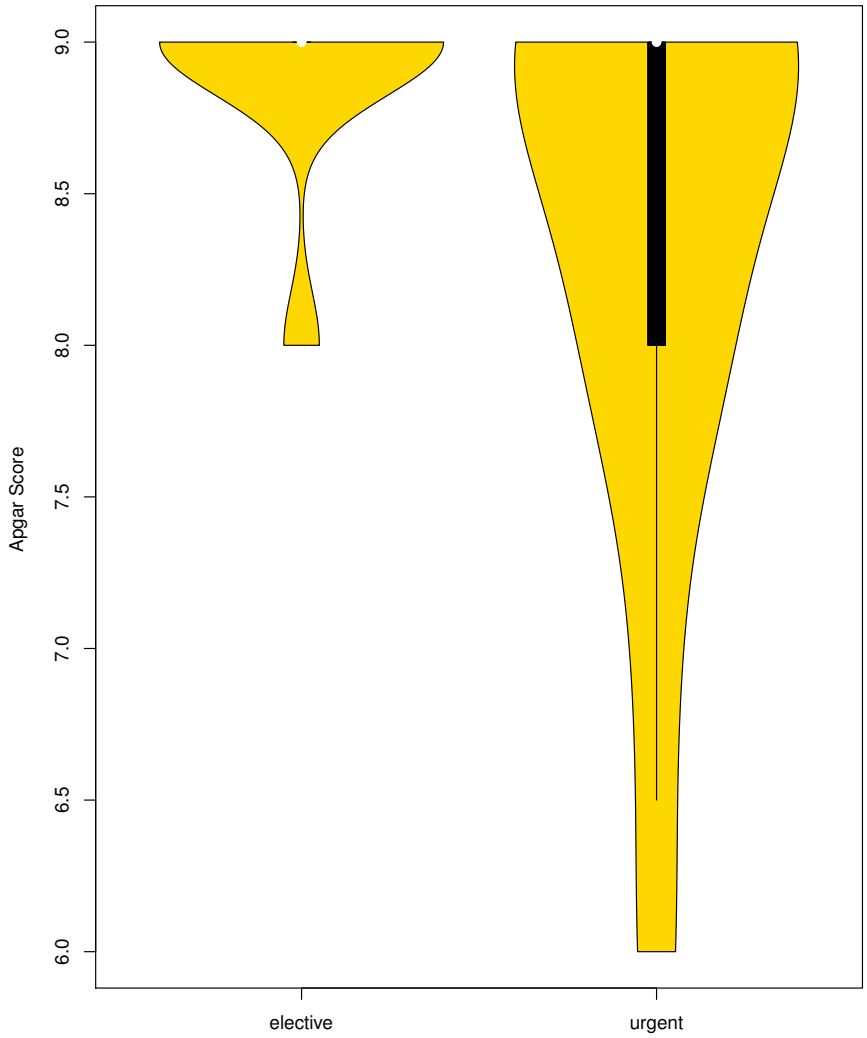


Figure 4.19: Violin-plot of Apgar scores illustrating the difference between the elective and the urgent group.

4.4.3 Amount and type of fluid given

The average amount of colloid given to the elective group (in ml) was 162.96 (0, 206.90) and 79.63 for the urgent group (0, 161.28) $p = 0.08$. The average amount of crystalloid given to the elective group (in ml) was 540.74 (600, 472.72) and 948.15 for the urgent group (700, 1457.44) $p = 0.29$. The total average amount of fluid given to the elective group (in ml) was 833.33 (650, 448.93) and 1027.78 for the urgent group (70, 1432.14) $p = 0.57$.

Table 4.10 shows the type of fluid administered as well the total amount of fluid administered between the two groups

Table 4.10: Average amount of fluid given.

Fluid	**Elective** mean/median/std dev	**Urgent** mean/median/std dev	**p-Value**
colloids (ml)	162.96/0/206.90	79.63/0/161.28	0.08
crystaloids (ml)	540.74/600/472.72	948.15/700/1457.44	0.29
total (ml)	833.33/650/448.93	1027.78/700/1432.14	0.57

4.4.4 Amount and type of vasopressor given

The average amount of ephedrine (in mg) given to the elective group was 2.96 (0,7.37) and 0 (0,0) (p value undefined) for the urgent group. The average amount of phenylephrine given to the elective group (in μg) was 66.67 (0,86.60) and 35.10 (0,51.54) $p = 0.29$ for the urgent group.

Table 4.11 shows the total amount and type of vasopressor given

4.4.5 Estimated blood loss during the study period

The mean bloodloss (ml) for the elective group was 128.15 (0,216.54) and 140.37 (20,206.96) $p = 0.47$. Table 4.11 also shows the estimated blood loss during the

Table 4.11: Average intra-operative vasopressor use and blood loss.

Vasopressor	**Elective** mean/median/std dev	**Urgent** mean/median/std dev	**p-Value**
ephedrine (mg)	2.96/0/7.37	0/0/0	n/a
phenylephrine (μg)	66.67/0/86.60	35.10/0/51.54	0.29
blood loss (ml)	128.15/0/216.54	140.37/20/206.96	0.47

study period. Figure 4.20 illustrates the statistical quantities.

4.5 Conclusion

In this chapter the results of the study which include the demographic and laboratory parameters were presented as well as the statistical analysis.

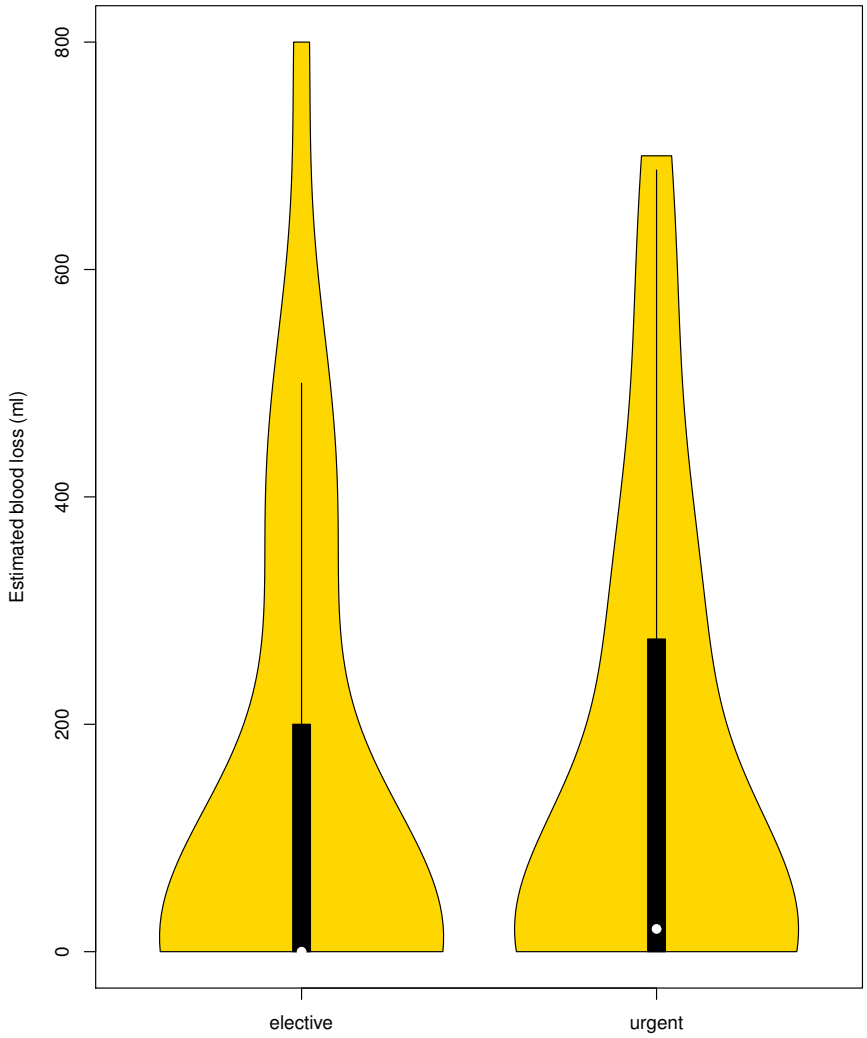


Figure 4.20: Violin-plot of estimated blood loss between the elective and the urgent group.

Chapter 5

Discussion

This chapter contains a detailed discussion of the results as well as the limitations of the study. The implications that these results may have will also be discussed.

5.1 Discussion of results

5.1.1 Demographic data and group characteristics

Age There were no statistically significant differences between the two groups with regards to age. The mean age (in yrs) was 28.96 in the urgent group and 27.41 in the elective group $p = 0.414$. This lack of difference might possibly be because most women who deliver either vaginally or by caesarean section are obviously of child bearing age.

BMI The two groups were not matched with regards to BMI. The mean BMI (in kg/m2) in the elective group was 32.64 and 29.68 in the urgent group $p = 0.055$. The importance of BMI is that aortocaval compression can be possibly influenced by the mass above the vessels. Women with a higher BMI might

experience a significantly higher amount of compression, which can influence the blood pressure changes on lying supine. The height of the block can also be influenced by obesity. Thus BMI could have been a confounding factor as women with a higher BMI could possibly have experienced a greater blood pressure drop than women with a lower BMI. In this study the urgent group had a lower BMI. Of note is that there were more twin pregnancies in the elective group than in the urgent group. This could possibly explain this difference in BMI between the groups.

Duration of starvation A startling finding was the very prolonged duration of starvation in both groups, which did not differ significantly between the two groups. This averaged 16.9 hours in the elective group and 18.4 hours in the urgent group $p = 0.535$. Prolonged starvation can potentially influence hydration status perioperatively. This may have a played a role in the lack of difference between the two groups as the elective groups' prolonged duration of starvation placed them closer to the urgent group with regards to hydration status. The high volume of caesarean sections performed at CHBH labour ward could result in the postponement of less urgent caesarean sections leading to this observation of a very prolonged duration of starvation. A possible solution would be to allow clear oral fluid supplementation to labouring mothers till the decision for a caesarean birth is made.

Indication for caesarean section Emergency caesarean sections were excluded from this study as mentioned earlier in the methodology section as the time needed to obtain consent might have compromised the prospective mother and her fetus. The commonest indications in the urgent group were previous caesar x 1 (eight participants) and cephalopelvic disproportion (seven participants) and that in the elective group was previous caesar x 1 (nine participants) and previous caesar x 2 (nine participants) . Patients with cephalopelvic disproportion in particular might have spent a longer time in labour with a higher

amount of sensible losses than patients having an urgent caesarean section for prolonged latent phase of labour.

5.1.2 Laboratory parameters

Haematological There were no significant differences between the two groups with regards to haematocrit, haemoglobin and osmolality. The average haematocrit (in l/l) was 0.35 for the elective group and 0.35 for the urgent group $p = 0.505$. The average haemoglobin in the elective group (in g/dl) was 11.43 and was 11.84 in the urgent group $p = 0.314$.

This may be attributed to the fact that with dehydration, there is compensation in the form of water and sodium reabsorption resulting in the ability to maintain intravascular volume.

Biochemical There were no significant differences between the two groups with regards to plasma sodium, plasma urea, plasma creatinine and plasma osmolality.

Urinary There were no significant differences in urine creatinine (μmol/l), urine sodium (mmol/l) and urine osmolality (mosm/kg). The mean creatinine for the elective group was 11.51 and that for the urgent group was 11.40 $p = 0.97$. The same values for the urine sodium and urine osmolality were 164.26, 152.19 $p = 0.56$ and 602.07, 635.44 $p = 0.66$.

There was a trend toward a higher urine Specific Gravity (Usg) in the urgent group. The mean for the elective group was 1.010 and urgent 1.020 however this was not found to be statistically significant $p = 0.06$. This strong trend may be suggestive of a lower state of hydration in the urgent group, due to the fact that with progressive dehydration there is activation of the renin-angiotensin system as described in the literature review, resulting in sodium and water reabsorption

and urine which is more concentrated. This may result in higher urine osmolality and higher Usg. It is, however, important to note that a higher urine osmolality was not noted in the urgent group. Causes of a higher urine sg difference between the two groups with less of a difference in the urine osmolality may be as a result of the presence of cells, casts, bacteria, etc. While there is inter observer variability with regards to specific gravity measurements, this applied to both groups and will be indirectly captured by the standard deviation of the observed results.

5.1.3 Blood pressure and heart rate measurements in theater

There were more occurences of hypotension in the urgent group.

When comparing baseline blood pressure and heart rate measurements to the ten minutes end point measurements then 15 (out of the twenty seven) experienced hypotension in the urgent group compared to nine in the elective group $p = 0.17$. When comparing baseline blood pressure and heart rate measurements to the average (average at 2, 4, 6, 8 and 10 minutes) then 13 patients from the urgent group experienced hypotension compared to 9 participants in the elective group $p = 0.36$. Though the difference in mean arterial pressure was not statistically significant between the groups, the width of the distribution (standard deviation) was wider for the urgent group. This means that even though the means of the mean arterial pressure readings were not significantly different between the groups there were however more cases of hypotension in the urgent group as seen in the observed number of occurences of hypotension in the groups.

The reason for more cases of hypotension in the urgent group is possibly because the urgent cases began with a higher mean arterial pressure average than the elective group as illustrated in figure 4.15, possibly a result of factors such

as labour pain as well as the associated stress of needing to have an urgent caesarean section, and so the drop at 10 minutes and the average drop at 2, 4, 6, 8 and 10 minutes seemed higher.

Figure 4.16 in chapter 4 shows the resulting probability distribution for the estimate of the true occurance rate of hypertension in each group. This also illustrated how the certainty would improve if the same incident rates would have been found with three times as many cases.

A larger sample will thus be necessary to explore this further.

5.1.4 Intraoperative events

Highest level of subarachnoid block achieved The highest level of subarachnoid block achieved in the total sample was recorded as T2 in the elective group. This is a level notably higher than that necessary for anaesthesia for a caesarean section. As previously stated in the methods the spinal anaesthetic was performed by an anaesthetist assigned to labour ward for that day, who also recorded the data concerning their specific participant on a data sheet.

A high sensory block may be an indicator of a high subarachnoid block which can lead to various cardiac and respiratory sequelae. A sequelae most pertinent to this study would be hypotension. Reasons for a high block can include; drug factors such as the total volume of local anaesthetic injected in the subarachnoid space (a high volume can lead to a high block), patient factors such as obesity (obesity can lead to a higher block) and technique factors such as level of insertion of the spinal needle (a high level of insertion can lead to a higher block). With regards to Bupivacaine the dose in the methodolgy was 2-2.2mls, possible inaccuracies in dosing could have occured. Both groups got their dose in the same manner therefore the possible inaccuracy should apply to both groups.

Type and total amount of fluid given The average colloids (in ml) given in the elective group were 162.96 and 79.63 in the urgent group $p = 0.08$. Participants in the elective group were given 83.33 ml more colloid than in the urgent group. The average amount of crystalloids (in ml) given to participants in the elective group was 540.74 compared to 948.15 in the urgent group $p = 0.29$. The urgent group was given 407.41 ml more crystalloids on average. The total amount of fluid given was 194.45 ml more in the urgent group $p = 0.57$. Women arriving for urgent caesarean sections may have been assessed on clinical grounds as needing more fluid or this might be due to chance as the p Value does not show significance.

Type and total amount of vasopressor given The average intraoperative vasopressor use between the two groups was as follows; with regards to ephedrine the average amount given during the ten minute study period, defined as ten minutes after injection of the local anaesthetic agent to the subarachnoid space, to the elective group was 2.96mg and 0mg to the urgent group. It is interesting to note that in this study women arriving for urgent caesarean sections were not given any ephedrine. The tachycardia associated presumably with anxiety associated with labour pain may have played a role as women with a tachycardia are more likely to be given phenylephrine (phenylephrine causes a reflex bradycardia). As no women in the urgent group received any ephedrine the p Value could not be calculated.

The elective group was given an average of 66.67 μg of phenylephrine compared to the average of 35.10 μg given to the urgent group $p = 0.29$. Interestingly the elective group was given 31.57 μg more phenylephrine, however the high p Value suggests a possible chance event. The possible reason for more vasopressor use in the elective group is not clear. One possibility could be the indication for the caesarean sections in the elective group. Nine patients had twin pregnancies. The prolonged duration of starvation as well as a heavier mass causing aortocaval compression may have resulted in the need for more phenylephrine in this group.

Estimated blood loss during the study period In this study some surgeons had not started surgery at the endpoint of the study, therefore the blood loss would have been recorded as 0 mls. The estimated blood loss between the two groups (at ten minutes after injection of the spinal anaesthetic) was 128.15ml for the elective group and 140.37ml for the urgent group $p = 0.47$. A major difference in blood loss could have led to a higher blood pressure drop in the group with more blood loss. There were no reported cases of significant blood loss during the study period.

Apgar scores of the infants at one and five minutes after birth The average Apgar score at one minute was 8.89 (8-9) for the elective group and 8.37 (6-9) for the urgent group $p = 0.01$. There was a lower Apgar score at 1 min in the urgent group. This may be because of the nature of the pathology that necessitated the urgency of the caesarean section. It is however important to note that urgent in this group was defined as a caesarean section the indication for which does not pose an immediate threat to the wellbeing of the child or mother. The ten minute Apgar score for both groups was 10. The reason for including the calculation of the Apgar scores of the infants was to see if there would be a difference in immediate outcome of the infants of elective versus urgent groups. It is however notable that even thought the Apgar score numbers might have differed significantly, this might be of limited clinical significance. Cord blood pH might have been more useful in the immediate assesment of peripartum events on the fetus. This would have meant an additional investigation at an additional cost. It is however a possible investigation to include in a future study.

5.2 Limitations of the study

1. The small sample size may impact on the significance of the results. This study was aimed to be a pilot study which will hopefully encourage ongoing

research.

2. Different anaesthetists where involved in the intraoperative management of the participants. An attempt at standardising management was made by informing the attending anaesthetists about the methods of the study.

3. Intraoperative blood loss may be variable during the study period. An estimation of the blood loss was however recorded. The urgent group was estimated to have lost only 12.2mls more blood than the elective group.

4. Intra operative hypotension is used as the primary outcome variable, with hypotension being defined as more than a 15% drop from the baseline. The baseline blood pressure may have been influenced by a number of factors such as labour pains, and the anxiety associated with being informed of the need for an urgent caesarean delivery. Therefore participants arriving for urgent caesareans may have had higher baseline blood pressure and heart rate readings.

5. The endpoint of the study is time based, namely ten minutes after initiation of the block. Different surgeons have different practices. Some had started surgery in this time while others had not.

6. As there is no gold standard in the assessment of hydration status, variables most suitable and feasible to our setting were chosen to asses hydration status.

5.3 Recommendations

1. A larger study with a larger sample size might yield more significant results and may possibly find the use of urine specific gravity helpful. Such a study might prove less costly and thus allow for the larger numbers needed to show significant results.

2. There is a need to re evaluate nil per os orders for women in labour at CHBH. A possible solution would be to categorise patients on admission into low, medium and high risk. Low risk patients could be allowed clear fluid intake in labour.s

3. Closer attention should be paid to the duration period of waiting for surgery.

4. A review into our practice to determine whether there has been a change of practice following presentation of these results might prove insightful.

Chapter 6

Conclusion

This was a pilot study aimed to investigate the possibility of using biochemical parameters as a means of assessing the preoperative hydration status in two groups of patients coming for caesarean section. In addition it aimed to determine if there is a difference in their intra operative course with regards to the incidence of hypotension between the groups and the outcome of the newborns as measured by Apgar scores of the infants.

The results showed the following;

There was no significant difference in haematological and urinary indices between participants presenting for elective versus those presenting for urgent caesarean sections. There was however a finding of a strong trend toward a higher urine specific gravity in the urgent group $p = 0.06$.

More participants in the urgent group experienced hypotension, however due to the small sample size this could not to be shown be to statistically significant. A bayesian analysis illustrated how a three-fold increase in the sample size might prove useful.

The elective group was given on average more ephedrine than the urgent group.

Interestingly the elective group was also give more phenylephrine. With regards to fluids given, participants arriving for urgent caesarean sections received on average more total fluid intraoperatively than those arriving for elective caesarean sections.

There was a significantly lower 1 minute Apgar score in the urgent group $p = 0.01$, which was discussed in chapter 5.

While it was not an objective of the study, it was interesting to note the very prolonged duration of starvation of participants in both groups. The study thus highlighted this pitfall in their management. The perioperative management with regards to the starvation period of patients presenting for caesarean section at CHBH will as a result need to be urgently reviewed.

One of the objectives of a pilot study is to determine and investigate possible relationships between variables, in order to allow for the planning of a larger study. In this study a limited number of participants were arbitrarily chosen in order to investigate this. The study could thus not be expected to significantly prove the hypothesis that patients presenting for urgent caesarean sections after having been in labour would have a higher incidence of covert dehydration as indicated by biochemical parameters, in comparison to patients presenting for elective caesarean sections. It did however highlight variables that should be investigated further by a larger study as well as highlight a potential pitfall in the management of patients presenting for caesarean sections at CHBH.

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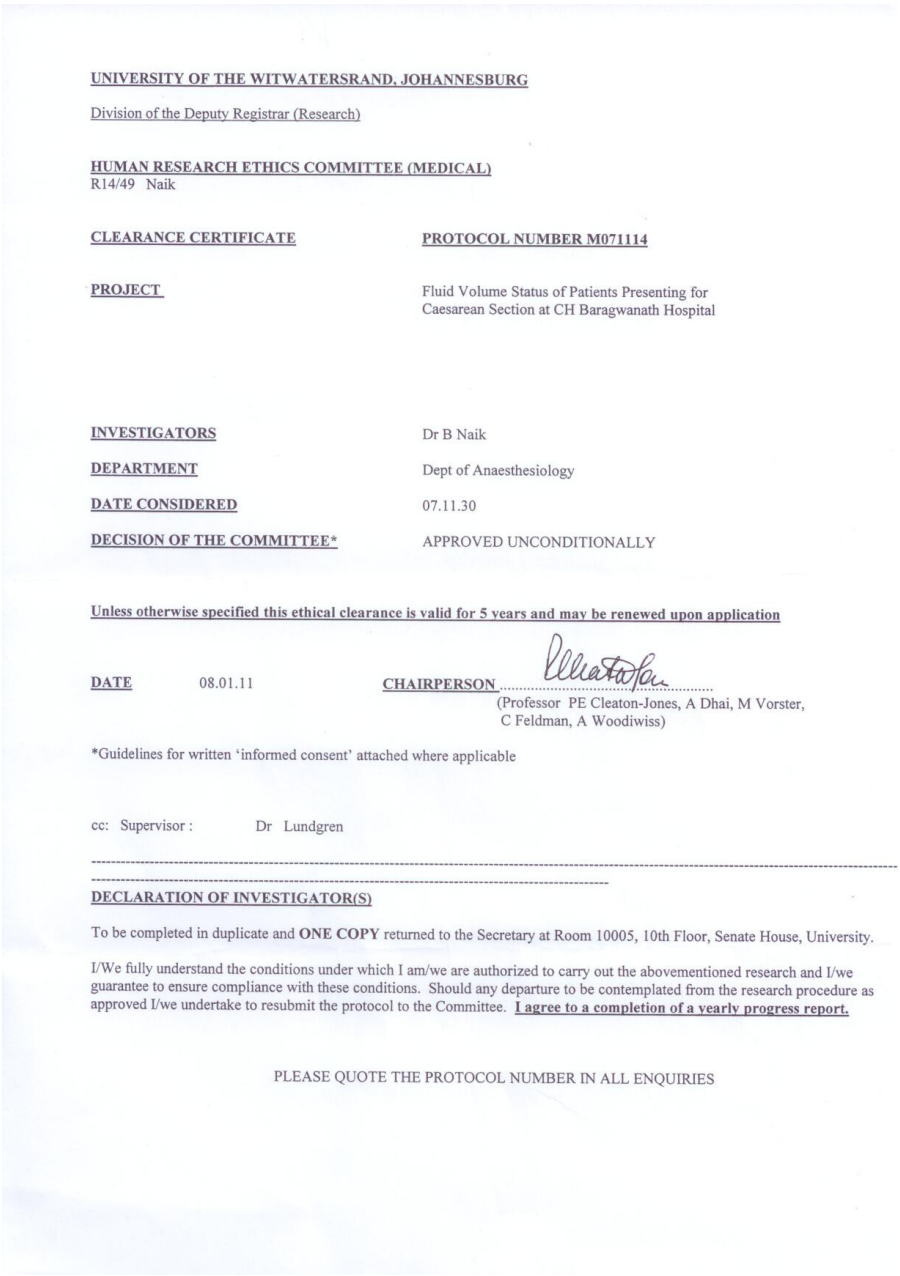
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Appendix A

Ethics clearance certificate



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Naik

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M071114**
PROJECT	Fluid Volume Status of Patients Presenting for Caesarean Section at CH Baragwanath Hospital
INVESTIGATORS	Dr B Naik
DEPARTMENT	Dept of Anaesthesiology
DATE CONSIDERED	07.11.30
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application

DATE 08.01.11 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr Lundgren

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

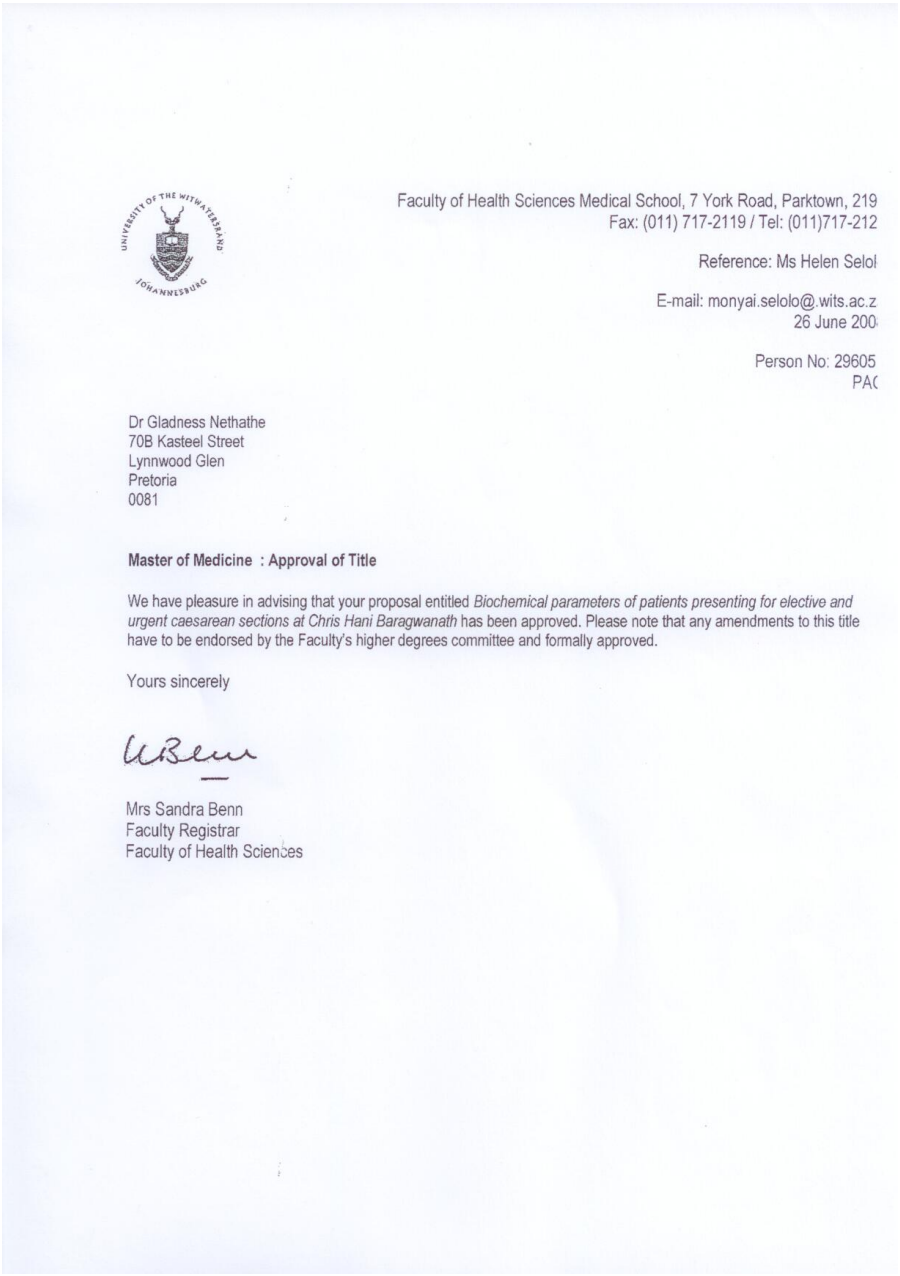
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Figure A.1: Ethics approval document

Appendix B

Postgraduate Committee Approval



Faculty of Health Sciences Medical School, 7 York Road, Parktown, 219
Fax: (011) 717-2119 / Tel: (011)717-212

Reference: Ms Helen Selol

E-mail: monyai.selolo@.wits.ac.z
26 June 200

Person No: 29605
PA(

Dr Gladness Nethathe
70B Kasteel Street
Lynnwood Glen
Pretoria
0081

Master of Medicine : Approval of Title

We have pleasure in advising that your proposal entitled *Biochemical parameters of patients presenting for elective and urgent caesarean sections at Chris Hani Baragwanath* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Figure B.1: Approval document.

Appendix C

Patient information

Information sheet for participants

Good day. My name is Dr Nethathe. I am a Doctor in the Department of Anaesthesia at Chris Hani Baragwanath Hospital. I am doing a study to find out the amount of fluid in patients who are coming to theatre for Caesarean sections (the name of the operation you are going to have) at this Hospital.

The amount of fluid in your body may have an influence on your well being as well as that of your baby, especially around the operation time. I am inviting you to participate in this study.

If you agree a small amount of blood (about two teaspoons, about 10ml) and urine will be collected from you. I will also record your blood pressure, how fast your heart is beating and how fast you are breathing. Other information that will be collected about you is the reason for your operation and any medical problems you have as well as the weight and Apgar scores of your baby. The Apgar score is a score that Doctors use to see how well your newborn baby is. It uses observations like the colour of your baby, how active your baby is from birth and measurements like how fast your babys heart is beating. This I will collect from your file. Please note that the collection of the blood sample may cause you to feel pain at the injection site as well as some minor bleeding.

The results of the samples collected from you as well as the information about you will remain confidential. Your information will be allocated a secret code and your name will not be used. Only people involved in the study will have access to this information and no one else.

Your participation in this study is voluntary and you may withdraw at any stage. If you do not participate in the study or if you withdraw from the study your treatment will not be affected and you will still receive standard treatment and care. Studies such as this can only be done if the Ethics Committee has approved them. Feel free to contact them if you need any information regarding your right as a participant in research. The contact number for the Ethics Committee Chairman is: 011-717 2301 You are welcome to ask as many questions as you like about the study. My 24 hour contact number is 083-7438279 and you may contact me if you have any questions.

Appendix D

Consent form

I _____ have been informed about the reasons for the study. The methods and the possible complications have been explained to me. I agree to participate in this study which will involve the collection of urine and blood as well as information about me. I have been told that this information will be handled in a confidential manner. My participation in this study is voluntary and I can withdraw at any stage.

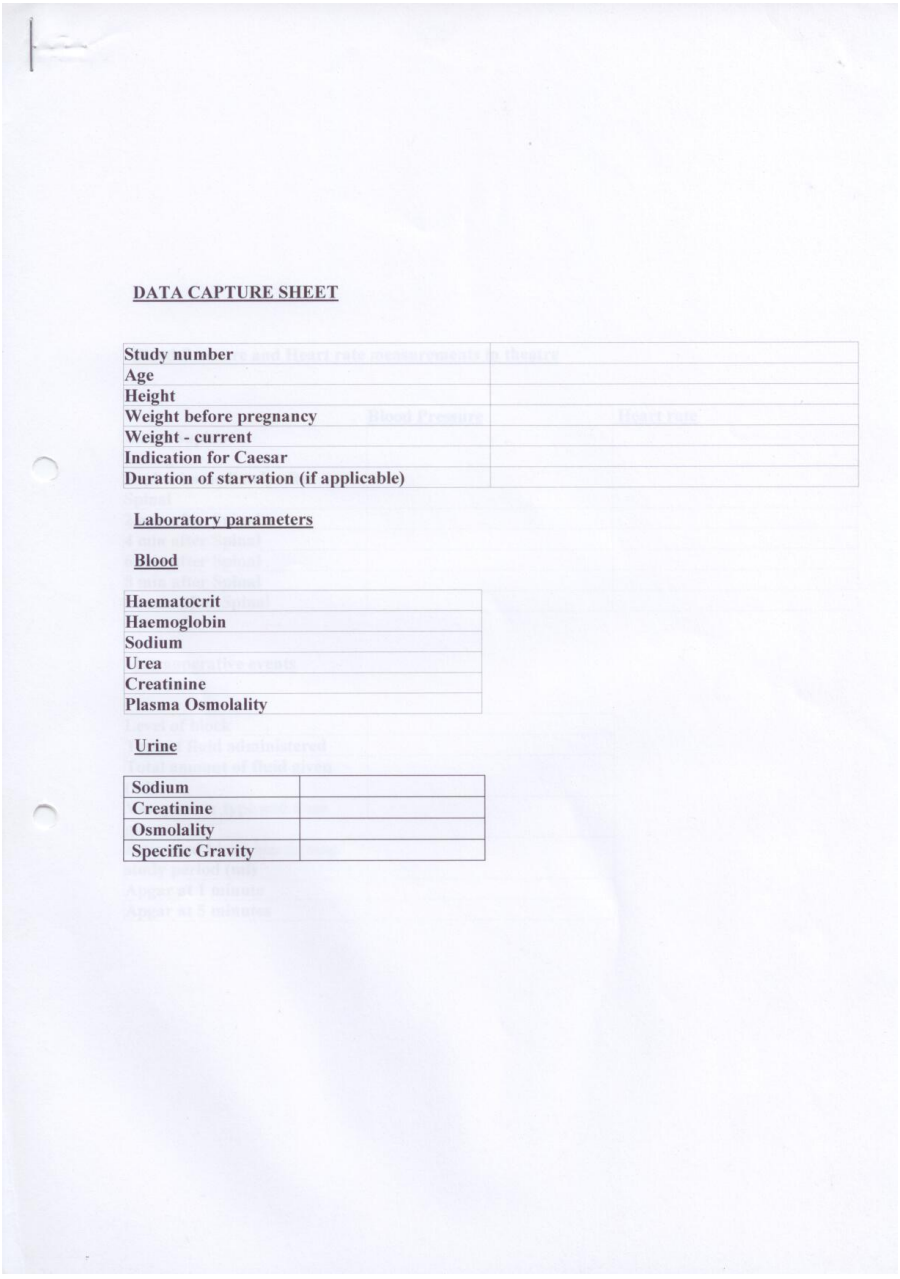
Signed at _____ on _____

_____

Signature

Appendix E

Data capture sheet



DATA CAPTURE SHEET

Study number	
Age	
Height	
Weight before pregnancy	
Weight - current	
Indication for Caesar	
Duration of starvation (if applicable)	

Laboratory parameters

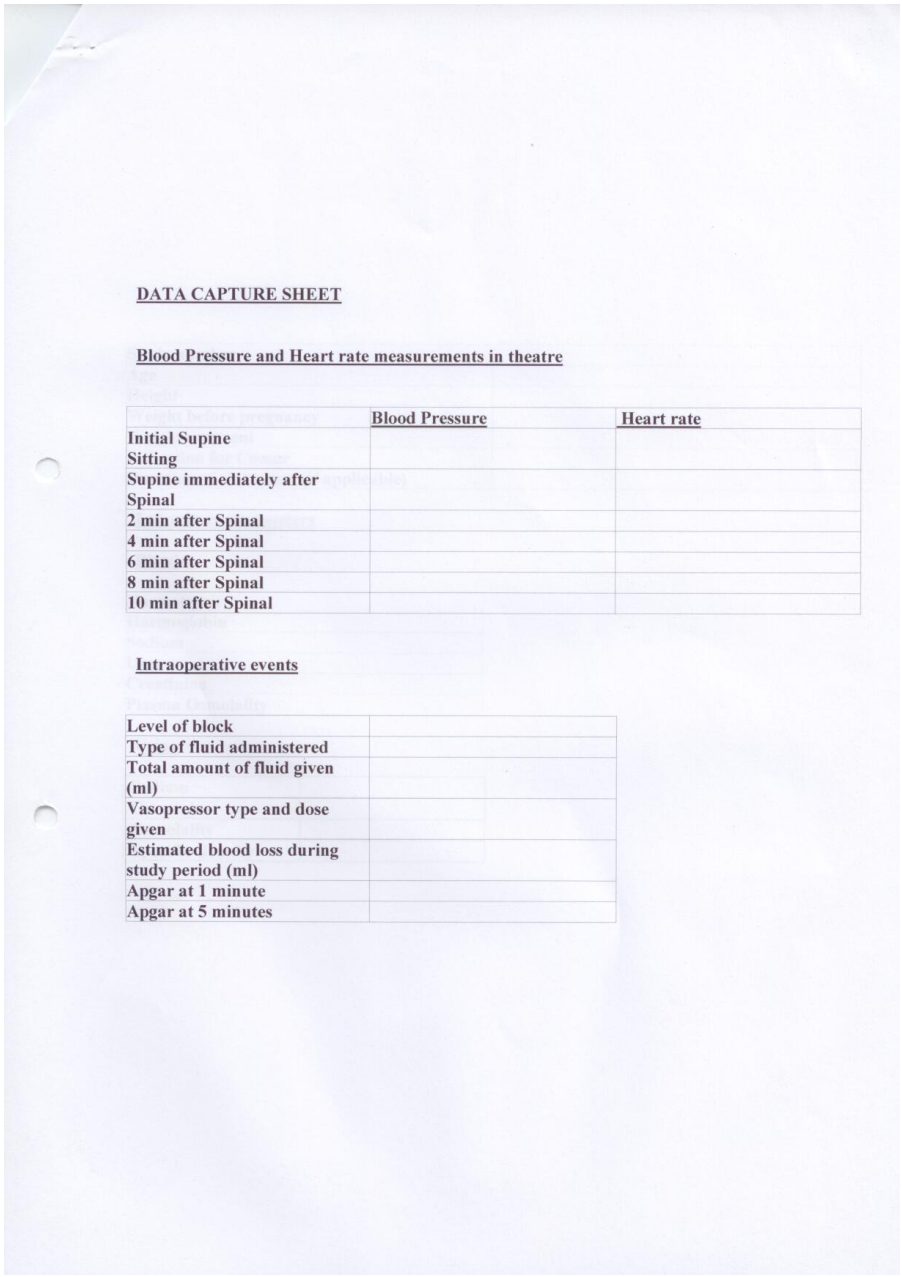
Blood

Haematocrit
Haemoglobin
Sodium
Urea
Creatinine
Plasma Osmolality

Urine

Sodium	
Creatinine	
Osmolality	
Specific Gravity	

Figure E.1: First page of the data capture sheet.



DATA CAPTURE SHEET

Blood Pressure and Heart rate measurements in theatre

	Blood Pressure	Heart rate
Initial Supine Sitting		
Supine immediately after Spinal		
2 min after Spinal		
4 min after Spinal		
6 min after Spinal		
8 min after Spinal		
10 min after Spinal		

Intraoperative events

Level of block	
Type of fluid administered	
Total amount of fluid given (ml)	
Vasopressor type and dose given	
Estimated blood loss during study period (ml)	
Apgar at 1 minute	
Apgar at 5 minutes	

Figure E.2: Second page of the data capture sheet.

Appendix F

Description of Violin Plot Components

A violin plot is a box plot augmented with a (vertical) kernel density function plot on each side. Figure F.1 gives a typical example. The median value is indicated with the white point in the middle. The black box shows the 25%-75% range. The thin black line indicates the range of the data. On each side is a vertical plot of the estimated kernel density, giving it a violin shape.

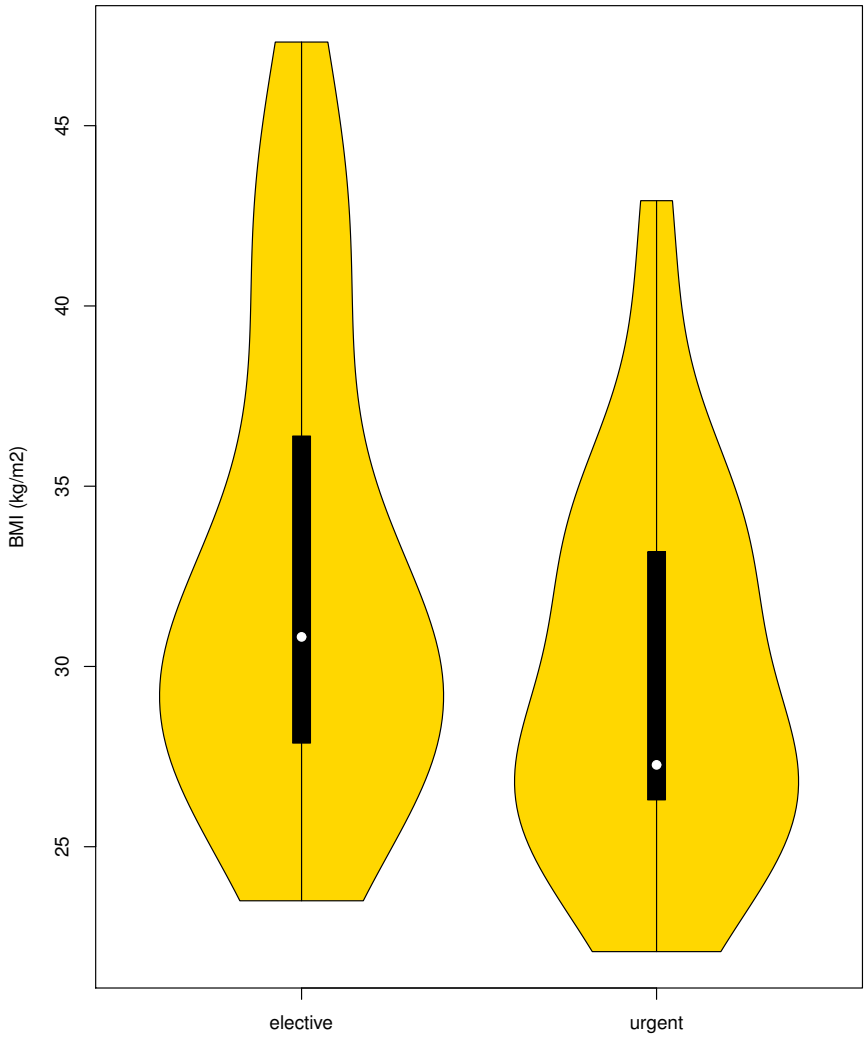


Figure F.1: An example of a violin-plot.