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Project Title: A Retrospective Review of High Spinal Anesthesia for Aortic Valve Replacement in Patients with Aortic Stenosis

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Summary (250 words max single spaced):
High spinal anesthesia (HSA) with local anesthetics, as a supplement to general anesthesia, for cardiac surgery has been used in Winnipeg for more than 15 years. It decreases the stress and inflammatory response with cardiac surgery. Aortic stenosis has been traditionally thought of as a contra-indication to the use of spinal anesthesia. However, case series in noncardiac surgery document the use of HSA in patients with aortic stenosis. The goal of this study was to document the local experience with high spinal anesthesia in addition to general anesthesia in patients with aortic stenosis undergoing aortic valve replacement from 2000 to 2015. The primary outcome measure evaluated was time to extubation, either in the operating room or in the intensive care unit. There were also several secondary outcome measures analyzed. The intraoperative glucose levels and insulin use were recorded as a surrogate of the intraoperative stress response. Data on the use of vasopressors and inotropic agents, total analgesia consumption in the first 24 hours, and administration of blood products were also collected for the postoperative time period. We also looked at the re-intubation rate, ICU and total hospital length of stay, major medical complications, and the in-hospital mortality rate. In this retrospective study, it was found that high spinal anesthesia for aortic valve replacement in patients with severe aortic stenosis was associated with an improved postoperative recovery profile as apparent by earlier extubation, shorter ventilation durations, lower inotrope/vasopressor use >24 hours, and less analgesia consumption within 24-hours.

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INTRODUCTION AND BACKGROUND

Aortic Stenosis Epidemiology and Pathophysiology

Aortic stenosis (AS) is the most common valve pathology found in European and North American populations.[1] It affects 2-4% of the population over the age of 65 years and moderate or severe AS affects 13.3% of adults over the age of 75 years.[2,3] The main causes of AS are congenital or acquired. In adults, the most common congenital cause is a bicuspid aortic valve, accounting for over 50% of congenital cases.[4] The most frequent acquired causes of AS are calcific degeneration, infective endocarditis and rheumatic heart disease.[5,6] AS typically develops over many years, with a slowly progressive course in most patients. The classic triad of symptoms of severe AS (valve area <1 cm^2) are syncope, angina, and heart failure.[7,8] As the compensatory mechanisms fail and symptoms develop, the long-term prognosis worsens. For example, in patients with severe symptomatic AS, the annual mortality rate is 25% with an average survival without intervention of 2-3 years.[9]

In aortic stenosis patients, the gradual narrowing of the valve orifice results in chronic obstruction to left ventricular outflow, causing left ventricular pressure overload.[8] In response to the increasing pressure, compensatory concentric left ventricular hypertrophy (LVH) ensues and normalizes the concomitant rise in wall tension secondary to the valvular stenosis.[8,10] The contractility of the left ventricle (LV) is typically preserved, maintaining a normal ejection fraction until the later stages of the disease.[11] There is an inverse relationship between wall tension and the ejection fraction because in the presence of increased afterload, the ejection fraction declines.[10] As the ventricular mass and wall tension increases, the myocardial oxygen demand also increases significantly. The capillary density becomes inadequate in the hypertrophied ventricle and a supply/demand mismatch is created, putting the patient at risk of myocardial ischemia, even in the absence of coronary artery disease.[4,8,12] The augmented chronic afterload burden resulting from the excessively increased impedance to ejection leads to the development of heart failure as cardiac compensatory mechanisms are overwhelmed.[13] The suboptimal LV relaxation also leads to higher left atrial pressures in order to drive early diastolic filling to ensure the LV preload is adequate.[8] The ventricle becomes increasingly dependent on the atrial contribution to maintain preload and atrial systole can account for up to 40% of ventricular filling in patients with severe AS.[8]

Anesthetic Considerations in Patients with Aortic Stenosis Undergoing Noncardiac Surgery

Aortic stenosis has always been considered a critical risk factor for perioperative morbidity and mortality during any noncardiac surgical procedure.[7] Skinner and Pearce were the first to draw the attention to aortic stenosis as a risk factor for noncardiac surgery in 1964.[14] In Goldman's study in 1977, aortic stenosis was one of the eight perioperative factors associated with cardiac complications in noncardiac surgery.[15] A follow up study found a seven fold increase in cardiac complications when aortic stenosis was present. A European study also found a five-fold increase in cardiac complications in patients with aortic stenosis.[16] Thus, patients with severe AS were considered to be at serious risk during noncardiac surgeries, resulting in the avoidance of elective procedures until the aortic valve pathology was corrected.[7] However, newer data suggests that with contemporary surgical and anesthetic techniques, the risks of noncardiac surgery are lower than previously accepted.[7] The improvements in surgical and anesthetic techniques in the past few decades have led to a continual decline in perioperative morbidity and mortality, regardless of valvular heart disease.[7] Nonetheless, the current perioperative mortality risk for patients with aortic stenosis undergoing noncardiac surgery remains approximately 5%.[17]

Echocardiography is highly recommended in any patient in whom AS is suspected. This will provide information on the severity of outflow obstruction and left ventricular systolic function, so that perioperative management can be optimized.[7] The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the management of valvular heart disease supports the deferral of elective noncardiac surgeries in patients requiring aortic valve replacement (AVR).[18] In asymptomatic patients with severe AS, with no evidence of LV dysfunction, the guidelines suggest that moderate-risk noncardiac surgery with careful monitoring can be undertaken.[18]

During the perioperative period, the hemodynamic status of patients with AS must be carefully monitored. The main goals are to maintain a sinus rhythm, a relatively slower heart rate (HR), and adequate preload and systemic vascular resistance (SVR; afterload).[8] A slower HR will decrease the oxygen demand of the myocardial tissue, optimize LV filling by prolonging diastole, and will also increase the coronary perfusion time, which is necessary to prevent supply/demand ischemia.[8] It is important to maintain an adequate blood pressure in patients with aortic stenosis. Hypotension can result in decreased coronary artery perfusion, even in the absence of coronary artery disease, resulting in myocardial ischemia and dysfunction.

Proper cardiac function depends heavily upon the integration of myocardial contractility, preload, resistance, and the heart rate.[13] In aortic stenosis patients, the ventricular function is highly reliant on the inotropic reserve and optimal preload.[13] The main physiological abnormality found in AS patients is the high output resistance produced by the obstructing outlet. Thus, the left ventricle relies heavily on increased preload or accentuated diastolic stretch in order to maintain adequate cardiac output.[13]

Aortic stenosis has been traditionally thought of as a contra-indication to the use of spinal anesthesia for noncardiac surgery. This is because the conventional teaching has been that a stenotic aortic valve creates a fixed obstruction to left ventricular outflow which impairs the ability of the left ventricle to increase stroke volume when there is a decrease in systemic vascular resistance, as occurs with administration of spinal anesthesia.[19] It is feared that the sudden and potentially profound decrease in SVR may cause life-threatening compromise in coronary artery perfusion.[20] The vasodilation would potentially be catastrophic due to the reduction in SVR without a compensatory increase in cardiac output, ultimately leading to hypotension.[21]

However, this belief is an oversimplification of the cardiac hemodynamics present in patients with left ventricular dysfunction. This is because the impedance or resistance across the aortic valve, even though essentially fixed, is not the only factor determining the afterload faced by the left ventricle.[21] Resistance faced by the left ventricle is a sum of the resistance across the aortic valve and the SVR, which are arranged in series, thus making them additive. Hence, decreasing or increasing the SVR directly causes proportional changes in the effective afterload of the left ventricle.[22] A failing heart is highly sensitive to afterload and with nitroprusside administration leading to decreased afterload, there will be a proportional increase in cardiac output preventing hypotension development.[23,24]

A study performed by Awan et al. demonstrated for the first time that systemic vasodilator therapy, via the careful administration of nitroprusside to reduce afterload, can in fact effectively and safely reduce left ventricular systolic hemodynamic overloading in patients with severe AS.[13] They showed that nitroprusside could reduce arterial resistance thus lowering the systemic pressure, while also simultaneously reducing the peak left-ventricular systolic pressure.[13] The study also demonstrated the concomitant decrease of elevated left ventricular end-diastolic pressure (LVEDP), while maintaining cardiac output and reducing the oxygen requirements of the

myocardium.[13] Nitroprusside does decrease preload which is important to maintain an adequate cardiac output. These potential deleterious effects are compensated and balanced by the simultaneous reduction in ejection resistance across the stenotic valve, thus averting dramatic changes in cardiac output.[13]

Khot et al. conducted a study on the use of sodium nitroprusside, a potent intravenous vasodilator, in critically ill patients with end-stage, severe aortic stenosis and congestive heart failure.[21] The study sought to see if nitroprusside could serve as an effective bridge to aortic valve replacement surgery in these critically ill patients.[21] It was found that nitroprusside increased the stroke volume and the mean and peak gradients across the valve, with no change in the aortic valve area.[21] Nitroprusside rapidly and markedly improved cardiac function in patients with decompensated heart failure due to severe left ventricular systolic dysfunction and severe aortic stenosis.[21] It decreased pulmonary edema and provided a safe and effective bridge to aortic valve replacement or oral vasodilator therapy in these critically ill patients.[21]

Even though aortic stenosis is still listed as a relative contra-indication to the use of spinal anesthesia, there have been no prospective, randomized trials evaluating spinal anesthesia in noncardiac surgery. The literature still only consists of case reports and retrospective studies. A case report conducted on literature available to support this traditional view found no contradictory evidence on the use neuraxial blockade in certain patient populations that had neuraxial anesthesia administered successfully.[20] A systematic review by Johansson and Lind found no clinical evidence to support the claim that central regional anesthesia is contra-indicated in patients with AS.[25] Through their literature search, they found no randomized control trials and only four retrospective studies and eight case reports encompassing a total of ten patients.[25] In all of these patients, successful use of neuraxial blockade in patients with aortic stenosis was noted, without significant hemodynamic alterations.[25]

As a consequence, even though the belief in the medical community is that vasodilator therapy is harmful for patients with aortic stenosis, there is surprisingly very little data to support the view. There have actually been several small studies documenting the beneficial hemodynamic effects of vasodilation in asymptomatic patients with severe aortic stenosis with normal or slightly reduced left ventricular function.[13,26] However, the effect of vasodilation in symptomatic aortic stenosis patients with severe ventricular dysfunction is unknown because they are often excluded from studies.[21] Clinical practice instructs that neuraxial anesthesia should actually be considered individually for each patient with AS in the context of their disease severity, left ventricular function, and treatment urgency.[19] A catheter-based neuraxial anesthetic can actually allow for the repeated administration of small doses of local anesthetics, along with more control over hemodynamic changes.[19]

Current recommendations are that spinal anesthesia can be used in patients with aortic stenosis undergoing noncardiac surgery, as long as appropriate monitors and management of hemodynamics are used.

Spinal Anesthesia in Cardiac Surgery

Most reports involving spinal anesthesia in cardiac surgery have only used intrathecal opioids. Intrathecal opioids provide better postoperative analgesia but have no effect on the stress response or other complications.[27–30] The studies by Chaney et al. using intrathecal morphine, 10 micrograms/kg, actually demonstrated an increase in postoperative ventilation time.[27,28] Studies with lower doses of intrathecal morphine showed improved pain scores, alertness and shorter ICU times.[29,31–33]

High spinal anesthesia (HSA) using local anesthetics as a supplement to general anesthesia, was first described in a case series published in 1994.[34] This practice has subsequently been adopted by a number of cardiac anesthesiologists at Winnipeg institutions and elsewhere in Canada. Studies have demonstrated that high spinal anesthesia blunts the stress response to surgery and cardiopulmonary bypass and enhances the anti-inflammatory response to cardiac surgery.[35,36] One study demonstrated that spinal anesthesia with local anesthetics is associated with a decreased risk of delirium in cardiac surgical patients.[37]

A retrospective study conducted in Winnipeg by Goldie et al. (accepted for publication) has shown that spinal anesthesia, in addition to general anesthesia, improved postoperative recovery of cardiac surgical patients as manifested by earlier extubation, shorter ventilation times, better analgesia and fewer ICU readmissions. Another study also conducted in Winnipeg has demonstrated that spinal anesthesia is associated with a decreased risk of delirium in cardiac surgical patients (Odds Ratio of 0.43, 95% confidence interval of 0.20 – 0.94). Spinal anesthesia may be a method to augment enhanced recovery programs after cardiac surgery, which should be evaluated in prospective studies.

The goal of this study was to document the local experience with high spinal anesthesia in addition to general anesthesia, in patients with aortic stenosis undergoing aortic valve replacement.

METHODS

Patients who had aortic valve replacement for aortic stenosis were identified from two previously conducted studies. Both studies had local Institutional Research and Ethics Board approval.

The first study by Goldie et al. was a retrospective case-control series documenting the clinical experience with high spinal anesthesia in patients having all types of cardiac surgery from 2000 to 2010. The privacy and confidentiality of patients was preserved using encrypted, unique identification numbers across data sets. In conjunction with the Manitoba Centre for Health Policy (MCHP), patients who had cardiac surgical procedures with high spinal anesthesia were identified using the billing code of intrathecal opioid administration in conjunction with cardiac surgical billing codes.

MCHP then provided a list of up to ten potential control patients who were matched with the high spinal patients using the following criteria: age (± five years), sex, procedure, date (± six months of index patients), cardiac surgeon, site (St. Boniface General Hospital or Health Sciences Centre). All of these six criteria were successfully matched using the Manitoba provincial administrative database. Afterwards, the charts of the high spinal patients and potential control patients were reviewed for a seventh variable, the preoperative left ventricular ejection fraction to complete the matching process. Once the appropriate cohort of spinal and control patients were identified, patient data was extracted from the charts using a Research and Ethics Board approved data collection sheet.

The second study by Petropolis et al. was a study assessing the effects of high spinal anesthesia on the incidence of delirium in cardiac surgical patients. Patients for this study were identified using the Manitoba Cardiac Sciences (MACS) database, which is a prospectively collected local database of cardiac surgery cases, established in 2010. Database entry is

performed by a trained research technician with previous experience in ICU nursing. Data was extracted from the MACS database by one of the authors (AP) using MySQL, an open-source relational database management system, and PHP, an open-source general purpose scripting language.

Spinal cases and controls were propensity-matched using a 1:1 greedy matching algorithm considering several preoperative and intraoperative variables that were deemed potentially related to delirium. These propensity scores were then used to match similar spinal patients with non-spinal cases.

Local Research and Ethics Board approval was obtained for the reanalysis of these two studies. From these two databases, all patients who had aortic valve replacements for aortic stenosis, both with spinal anesthesia and the controls without spinal anesthesia, were identified. These charts were then reviewed and data was extracted using an approved data collection sheet by one of the authors (MS). Data for preoperative factors (demographics, severity of aortic stenosis, ejection fraction, medications, and medical co-morbidities), intraoperative factors and events, and postoperative course in hospital were collected and entered into a Microsoft Excel Database.

The primary outcome measure evaluated was time to extubation. Patients were identified as being extubated in the operating room at the end of the case or in the intensive care unit (ICU). Patients who were extubated in the ICU had their postoperative duration of intubation documented.

There were also several secondary outcome measures analyzed in our study. The intraoperative glucose levels and insulin use were recorded as a surrogate of the intraoperative stress response. Data on the use of vasopressors and inotropic agents, total analgesia consumption in the first 24 hours, and administration of blood products were also collected for the postoperative time period. Finally, we also looked at the re-intubation rate, ICU and total hospital length of stay (LOS), occurrence of acute kidney injury as reflected by the postoperative rise in creatine (increase in postoperative creatinine by 25%), major medical complications, and the in-hospital mortality rate.

Assuming an operating room extubation rate of 60% in the high spinal anesthetic patients and 40% in the controls, a power calculation with a power of 80% and alpha of 0.05 resulted in a sample size calculation of 97 patients per intervention group. Statistical analysis was conducted using a Student's t test for continuous variables, or a Chi-squared test for non-continuous variables. A two-tailed t test was performed on the data for the postoperative time of intubation, the intraoperative peak glucose levels, and for the 24-hour cumulative analgesia use, along with other variables. A Chi-squared analysis was performed on the number of patients extubated in the operating room, on the number of patients requiring intraoperative insulin, the re-intubation rates, and on patients requiring postoperative inotropes/vasopressors, as well as other variables. Odds ratios and 95% confidence intervals were determined for the extubation rate in the operating room and for patients requiring insulin intraoperatively. A p value less than 0.05 was considered statistically significant. The Wilcoxson rank sum test was used to assess hospital and intensive care unit lengths of stay.

RESULTS

From 2000 to 2015, there were 98 patients who underwent aortic valve replacement for

aortic stenosis with high spinal anesthesia plus general anesthesia. 87 matched control patients who received only general anesthesia during their aortic valve replacements were also found during the same 15-year period. Figure 1 represents a consort diagram of patients included in the study that were recruited from both previous studies.

Spinal Technique

The spinal anesthetic technique is as follows. An arterial line is inserted first and the patient is placed in a lateral position, with the operating table tilted head down between 10 to 15 degrees (Trendelenburg position). The spinal is administered into a lumbar interspace and hyperbaric bupivacaine is utilized. The combination of hyperbaric bupivacaine and being in the head down position for at least 10 minutes ensures that the local anesthetic will reach the high thoracic dermatomes. The level of spinal anesthesia is determined by checking for the onset of cold sensation loss. After the spinal is given, the patient is turned supine and general anesthesia is induced, followed by intubation. During the surgical prep, the patient is kept in a head down position and prior to the surgical incision, the bed is leveled. The head down position enhances the venous return to the heart and helps maintain hemodynamic stability following the extensive sympathetic blockade that is induced by the spinal anesthetic.

In regards to the agents used for the spinal anesthetic, hyperbaric bupivacaine 0.75% with dextrose was used. The average bupivacaine dose was 36.1 $\pm$ 9.5 mg. All patients also received intrathecal preservative free morphine, average dose 239.4 $\pm$ 60.8 mcg. Some patients also received a short-acting opioid, sufentanil, in their spinals, at an average dose of 22.1 $\pm$ 4.6 mg.

Patient Demographics

The two groups were well matched in terms of most of the demographic and co-morbidity categories, as shown in Table 1. No difference was found between groups regarding their sex, age, body mass index, and in most of the medical co-morbidities. However, there were more patients in the high spinal group who had congestive heart failure (40.8% vs 28.7%, $p = 0.01$). This variable, along with other common co-morbidities were not specifically matched for. Preoperative creatinine, blood glucose, and hemoglobin levels were also assessed, with no difference existing amongst groups.

Preoperative Cardiac Variables

The preoperative cardiac characteristics for both groups of patients are shown in Table 2. All patients had severe aortic stenosis with no difference in aortic valve area or peak and mean pressure gradients between groups. The difference in the mean left ventricular ejection fraction for the two groups was not statistically significant (55.1 $\pm$ 11.9% vs 56.0 $\pm$ 11.6%, $p = 0.57$), but more HSA patients had an ejection fraction in the 30-39% range (14.3% vs 5.8%, $p < 0.001$). There was also no difference in the percentage of aortic stenosis patients with concomitant aortic insufficiency in both groups (37.8% for HSA vs 35.6% for control, $p = 0.65$).

Preoperative Medications

A list of preoperative medications taken by patients is shown in Table 3. The medications analyzed were: beta blockers, acetylsalicylic acid, statins, calcium channel blockers, nitrates, digoxin, ACE inhibitors, and diuretics. No significant difference amongst the two groups regarding any of these medications was found.

Surgical Data

Intraoperative surgical data is shown in Table 4. The AVR procedures were categorized as either emergent, urgent, or elective. There was a higher percentage of urgent cases in the HSA group (16.4% vs 9.2%, p = 0.01) and more elective cases in the control group (89.7% vs 81.6%, p = 0.01). There was no statistically significant difference intraoperatively in the total length of the procedures, total cardio-pulmonary bypass times or aortic cross-clamp duration amongst groups. However, there were fewer patients in the HSA group requiring insulin intraoperatively (31.6% vs 47.1%, p = 0.002) and the HSA patients had lower peak blood glucose levels during the procedure (9.2 $\pm$ 2.1 mmol/L vs 10.3 $\pm$ 2.2 mmol/L, p = 0.002). The Odds Ratio for spinal patients requiring insulin intraoperatively was 0.52 with a 95% confidence interval of 0.29 to 0.94.

Postoperative Results

A higher percentage of the high spinal patients were able to be extubated in the operating room following their aortic valve replacement procedures (57.1% vs 31.0%, p < 0.001) (Table 5). The Odds Ratio for HSA patients being extubated in the operating room was 2.96 with a 95% confidence interval of 1.62 to 5.43. For the patients that were not extubated in the operating room, the average time from ICU arrival to extubation (postoperative ventilation) was also shorter in the HSA group (13.3 $\pm$ 16.6 hours vs 25.7 $\pm$ 68.1 hours, p = 0.38). In patients requiring post-operative ventilation, there was no difference in the median [interquartile range] duration of ventilation (12.2 [1.9 – 16.9] hours for spinals vs 12.0 [4.2 – 14.0] hours for controls, p = 0.51).

With regards to other postoperative outcomes (Table 5), there was no difference between groups in ICU length of stay, hospital length of stay, percentage of patients discharged home and in the percentage of patients transferred to another facility. The mean ICU LOS was 2.1 days for the spinal group and 3.3 days for the controls, with the mean hospital LOS being 8.2 days for the spinal group and 8.8 days for the controls. Rearranging the data from shortest to longest duration gave a median [interquartile range] ICU LOS of 1.0 days [1.0 – 2.0] for the spinal group and 1.0 days [1.0 – 4.0] for the controls. Likewise, the median hospital LOS was 6.0 days [5.0 – 8.0] for the spinal group and 7.0 days [5.0 – 10.8] for the controls. Further analyses on these two parameters was conducted using the Wilcoxon rank sum test to determine if a statistically significant difference existed between groups if the outliers were controlled for. For both cases the difference was not significant, yielding a p = 0.22 for hospital LOS and a p = 0.32 for ICU LOS.

Furthermore, no difference was found between groups in re-intubation rate, re-admission to the ICU, and return to the operating room for bleeding. In the spinal group, six patients were re-intubated, either for return to the operating room (4 patients) or for respiratory failure (2 patients). Likewise, in the control group, five patients were re-intubated, either for return to the operating room (1 patient) or for respiratory failure (4 patients). Regarding all patients returning to the operating room, six HSA patients were taken back to the OR for bleeding and four control patients for bleeding. There was one postoperative mortality in the spinal group and three mortalities in the control group. This difference was not statistically significant with a p value of 0.19.

Several major medical complications postoperatively, as shown in Table 5, were also documented. None were found to be statistically different between the two groups.

HSA patients had lower inotrope/vasopressor use >24 hours postoperatively (13.3% vs 17.5%, p = 0.27). A higher percentage of high spinal patients required transfusion when compared to control patients (55.1% vs 47.6%, p = 0.13) (Table 5).

Postoperative Analgesics

There was a discernable difference in the postoperative analgesic requirements amongst the two groups, as shown in Table 6. For the HSA patients, the 24-hour cumulative morphine dose was lower (9.7 ± 7.4 mg vs 17.9 ± 9.4 mg, $p < 0.001$), as was the 24-hour cumulative fentanyl dose (114.9 ± 73.1 mcg vs 334.0 ± 210.4 mcg, $p < 0.001$). Overall, the total 24-hour analgesic cumulative dose, measured in morphine equivalents, was lower in the high spinal group (18.3 ± 12.0 mg vs 37.9 ± 33.0 mg, $p < 0.001$). This included the use of Morphine, Tylenol 3, Fentanyl, Hydromorphone, Percocet, and Meperidine.

DISCUSSION

In this retrospective review, high spinal anesthesia for aortic valve replacement in patients with severe aortic stenosis was associated with an improved postoperative recovery profile as apparent by earlier extubation, shorter ventilation durations, lower inotrope/vasopressor use >24 hours, and less analgesia consumption within 24-hours. This was despite the fact that the high spinal patients were arguably a higher risk population compared to the matched controls, with more spinal patients with a medical history of congestive heart failure, left ventricular ejection fractions in the 30-39% range, and more receiving urgent procedures.

As summarized in Tables 1-3, the preoperative patient characteristics, comorbidities, cardiac factors, and medications were similar for both the HSA and control groups, with the exception of congestive heart failure. It was anticipated that HSA patients would have shorter extubation times, better blood glucose control, and less need for postoperative analgesia. The results of our review indicate that providing HSA to patients with severe aortic stenosis results in a higher proportion of patients being extubated in the operating room following valve replacement procedures. An Odds Ratio of 2.96 with a 95% confidence interval of 1.62 to 5.43 was determined, highlighting the significance of this finding. The HSA patients had shorter periods of postoperative ventilation in the ICU compared to the controls as well, but this difference was not statistically significant. Earlier extubation occurred despite the fact that “fast track” anesthesia is standard of care at institutions in Winnipeg. This is clearly demonstrated by the high rates of operating room extubations for both groups (57.1% and 31.0%). It has been consistently shown that earlier extubation is associated with better postoperative outcomes.[38,39]

To measure the intraoperative stress response, the peak blood glucose level and insulin requirements were used as surrogate measures. Lower epinephrine levels from blocking the stress response, will result in lower blood glucose levels. Almost 33% fewer high spinal patients required intraoperative insulin, relative to the controls, and the peak blood glucose level was approximately one mmol/L lower in the spinal cases. Both of these differences were found to be statistically significant showing that the spinal group demonstrated blunting of the stress response. This phenomenon has been shown previously with both thoracic epidurals and spinal anesthesia.[35,40] As mentioned in Enhanced Recovery After Surgery (ERAS) protocols, a common finding is decreased stress response yielding increased insulin sensitivity and muscle protein breakdown attenuation.[41] By mitigating the stress response leading to lower catecholamine and cortisol levels, high spinal anesthesia can potentially control insulin sensitivity during the perioperative period. Furthermore, fewer spinal patients required insulin postoperatively (59.2% vs 67.8%, $p = 0.07$) (Table 5), highlighting the prolonged attenuation with spinal anesthetics.

The results show that patients receiving HSA had better postoperative pain control as manifest by less analgesic consumption in the 24-hour period following their surgeries. Although

pain scores were not analyzed, the assumption can be made that spinal patients had less postoperative pain. A critical component of ERAS protocols is multimodal analgesia and intrathecal morphine has been used with success in certain programs.[41–43]

No statistically significant difference in mortality was found between groups, as expected with sample sizes this small.

Previous studies of cardiac surgery with regional anesthesia have used thoracic epidurals, with the largest randomized study not showing any major outcome differences.[44] Reports involving the use of spinal anesthesia in cardiac surgical procedures have only used intrathecal opioids, leading to better postoperative analgesia but no effect on the stress response.[29,30] High spinal anesthesia as practiced in Winnipeg institutions, utilizes intrathecal regional anesthetics and opioids. Regional anesthesia blocks nociceptive impulses during the perioperative period, leading to a decreased stress response and modulation of the inflammatory response to surgery.[34,35] The blockade of nociceptive stimuli has the added benefit of possibly contributing to pre-emptive analgesia for the postoperative period. Intrathecal morphine provides prolonged postoperative analgesia as demonstrated in other surgical procedures.[32,33] Furthermore, some patients also were given intrathecal sufentanil, as the use short acting opioids improves intraoperative analgesia in procedures performed under spinal anesthesia.[45,46]

With the use of spinal anesthesia in cardiac surgery, the risk of a spinal hematoma is always a concern.[47] As a consequence, the use of regional anesthetics in patients is highly reliant on the attending anesthesiologist and the patient must agree with the anesthetic plan once all risks are discussed. Clinical practice in Winnipeg has followed the protocol of timing heparin administration for cardio-pulmonary bypass between 1-2 hours post spinal injection, as recommended by the American Society of Regional Anesthesia.[48] Regarding the patients in our review, there were not any complications associated with spinal anesthesia and hematomas, but the sample size of patients were still too small to make a definitive statement on safety.

Limitations

This study has several limitations. The retrospective nature of this report is a weakness. We conducted a review of spinal anesthesia used in clinical practice by certain anesthesiologists. Hence, there may be confounding variables that have not been accounted for.

We were unable to find appropriate controls for all the spinal patients given our predetermined matching criteria. Spinal anesthesia has been administered for many years, so in finding the appropriate matched controls, we looked for cases within six months of each spinal case in order to minimize the effects of time and potential changes in clinical practice. Patients were then matched for age, sex, procedure, ejection fraction and institution. We also attempted to control for cardiac surgeon because some studies have shown differences in perioperative outcomes associated with the attending surgeon.[49] The spinal and control cohort matching was successful for all other pre-determined variables. There were differences between groups in certain unmatched preoperative factors, such as CHF and ejection fraction in the 30-39% range. These were higher in the high spinal patients but did not lead to more complications. Furthermore, the spinal group had more urgent cases, representing patients who were admitted into hospital with an acute coronary event and kept in hospital until they could have their cardiac surgeries.

A difference with the anesthesiologists between groups was found, with only four physicians using spinal anesthesia whereas 20 physicians were in the control cohort. However, the attending anesthesiologist has not been found to be a significant variable in other clinical

studies.[49] Regardless, even in Winnipeg institutions, regional anesthesia for cardiac surgery is used only by a handful of individuals. Other attending anesthesiologists have not used spinals primarily due to the potential risk of hematoma development.

Standardization of the anesthetic technique utilized for either the control patients or the spinal patients was not possible given the retrospective nature of the review. Yet, there were still notable rates of extubation in the operating room (57.1% for the spinals and 31.0% for the controls), highlighting the "fast track" cardiac surgical practice in Winnipeg institutions. The median length of stay in the ICU, for patients admitted to the ICU, was one day in both cohorts. Additionally, this review did not show any significant difference in hospital length of stay for high spinal patients. Several factors other than patient readiness for discharge may have impacted on the actual hospital length of stay, which we cannot control for. Some factors include surgeon's preference and availability of home care, especially in patients from rural areas. As seen in all retrospective reviews, it may not be feasible to control for unknown confounding variables.

Undesirable Drug Effects

Opioids and Local Anesthetics

The four clinically relevant undesirable drug effects of intrathecal opioids are pruritis, nausea and vomiting, urinary retention, and respiratory depression.[50] The incidence of respiratory depression requiring intervention following administration of intrathecal opioids is approximately 1%, the same as the incidence after doses of IV opioids.[50] The most undesirable and dangerous drug effect of intrathecal local anesthetics is hypotension.[50] Spinal anesthesia applied to the upper thoracic dermatomes produces a decrease in mean arterial blood pressure that is accompanied by a parallel decrease in coronary artery blood flow.[51]

Risk of Hematoma Formation:

With the use of HSA, the risk of a spinal hematoma is always a concern.[47] The estimated incidence of a hematoma developing is approximately 1:220,000 after spinal anesthetic injection.[51] This complication has usually occurred when the instrumentation is difficult to perform or in patients with a coagulopathy.[47,51,52] There are several strategies developed to ensure that a spinal anesthetic given to a patient does not put them into undue risk of developing a hematoma. More than 4000 intrathecal and epidural catheterizations were safely performed in patients undergoing peripheral vascular surgery that received IV heparin after catheter insertion.[53] Hematomas were prevented in these patients by delaying surgery for 24 or more hours in the event of a traumatic tap, by delaying heparinization for 60 minutes following catheter insertion, and by maintaining tight perioperative control of anticoagulation.[53] Furthermore, patients that are actively treated with anticoagulation cannot have spinal anesthesia because of the risk of spinal hematoma and permanent neurologic injury.[7]

Conclusion

Advancements in technology over the last few decades have led to a steady decline in the worldwide volume of cardiac surgeries being performed. As the average age of patients and number of comorbidities continues to rise, spinal anesthetics may prove to be a simple but advantageous adjuvant to improve postoperative cardiac surgery recovery. The high spinal anesthesia benefits of earlier extubation, decreased intraoperative stress response and enhanced postoperative analgesia, have the ability to improve Enhanced Recovery After Surgery (ERAS) protocols. Large prospective randomized clinical trials on our current patient populations are

required to evaluate these potential benefits if high spinal anesthesia is to gain wider acceptance in clinical practice. Patients with aortic stenosis should be included in such prospective studies.

REFERENCES

1. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33(19):2451-2496. doi:10.1093/eurheartj/ehs109
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368(9540):1005-1011. doi:10.1016/S0140-6736(06)69208-8
3. Freeman R V., Otto CM. Spectrum of calcific aortic valve disease: Pathogenesis, disease progression, and treatment strategies. *Circulation*. 2005;111(24):3316-3326. doi:10.1161/CIRCULATIONAHA.104.486738
4. Yarmush L. Noncardiac surgery in the patient with valvular heart disease. *Anesthesiol Clin*. 1997;15:69-89.
5. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*. 2005;111(7):920-925. doi:10.1161/01.CIR.0000155623.48408.C5
6. Selzer A. Changing aspects of the natural history of valvular aortic stenosis. *N Engl J Med*. 1987;317(2):91-98.
7. Pislaru S V., Abel MD, Schaff H V., Pellikka PA. Aortic Stenosis and Noncardiac Surgery: Managing the Risk. *Curr Probl Cardiol*. 2015;40(11):483-503. doi:10.1016/j.cpcardiol.2015.06.003
8. Frogel J, Galusca D. Anesthetic Considerations for Patients with Advanced Valvular Heart Disease Undergoing Noncardiac Surgery. *Anesthesiol Clin*. 2010;28(1):67-85. doi:10.1016/j.anclin.2010.01.008
9. Bates ER. Treatment options in severe aortic stenosis. *Circulation*. 2011;124(3):355-359. doi:10.1161/CIRCULATIONAHA.110.974204
10. Zile MR, Gaasch WH. Heart Failure in Aortic Stenosis — Improving Diagnosis and Treatment. *N Engl J Med*. 2003;348(18):1735-1736. doi:10.1056/NEJMp030035
11. Barash P. *Clinical Anesthesia*. 5th editio. Philadelphia (PA): Lippincott Williams Wilkins; 2006.
12. Mittnacht AJC, Fanshawe M, Konstadt S. Anesthetic Considerations in the Patient with Valvular Heart Disease Undergoing Noncardiac Surgery. *Semin Cardiothorac Vasc Anesth*. 2008;12(1):33-59.
13. Awan NA, DeMaria AN, Miller RR, Amsterdam EA, Mason DT. Beneficial effects of nitroprusside administration on left ventricular dysfunction and myocardial ischemia in severe aortic stenosis. *Am Heart J*. 1981;101(4):386-394.
14. Skinner JF, Pearce ML. Surgical risk in the cardiac patient. *J Chronic Dis*. 1964;17:57-72. http://www.ncbi.nlm.nih.gov/pubmed/14107170.
15. Goldman L, Caldera D, Nussbaum S, et al. Multifactorial Index of Cardiac Risk in Noncardiac Surgical Procedures. *N Engl J Med*. 1977;297(16):845-850.
16. Kertai MD, Bountioukos M, Boersma E, et al. Aortic stenosis: An underestimated risk factor for perioperative complications in patients undergoing noncardiac surgery. *Am J Med*. 2004;116(1):8-13. doi:10.1016/j.amjmed.2003.07.012
17. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Can J Cardiol*. 2017;33(1):17-32. doi:10.1016/j.cjca.2016.09.008
18. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol*. 2017;70(2):252-289. doi:10.1016/j.jacc.2017.03.011
19. Nussmeier, NA, Hauser M, Sarwar M, Grigore A SB. Anesthesia for Cardiac Surgery. In: *Miller's Anesthesia*. 7th ed. Philadelphia (PA); 2010:1889-1976.

20. McDonald SB. Is Neuraxial Blockade Contraindicated in the Patient with Aortic Stenosis? *Reg Anesth Pain Med*. 2004;29(5):496-502.
21. Khot UN, Novaro GM, Popović ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med*. 2003;348(18):1756-1763. doi:10.1056/NEJMoa022021
22. Awan N, Vismara LA, Miller RR, Demaria AN, Mason DT. Effects of isometric exercise and increased arterial impedance on left ventricular function in severe aortic valvular stenosis. *Br Heart J*. 1977;39:651-656.
23. Pepine CJ, Nichols WW, Curry RC, Conti CR. Aortic input impedance during nitroprusside infusion. A reconsideration of afterload reduction and beneficial action. *J Clin Invest*. 1979;64(2):643-654. doi:10.1172/JCI109505
24. Francis G. Pathophysiology of the heart failure clinical syndrome. In: *Textbook of Cardiovascular Medicine*. Topol Ej e. Philadelphia (PA): Lippincott-Raven; 1998:2179-2203.
25. Johansson S, Lind MN. Central regional anaesthesia in patients with aortic stenosis - a systematic review. *Dan Med J*. 2017;64(9):1-7.
26. Ikram H, Low CJS, Crozier IG, Shirlaw T. Hemodynamic effects of nitroprusside on valvular aortic stenosis. *Am J Cardiol*. 1992;69(4):361-366. doi:10.1016/0002-9149(92)90234-P
27. Chaney M, Furry P, Fluder E, Slogoff S. Intrathecal Morphine for Coronary Artery Bypass Grafting and Early Extubation. *Anesth Analg*. 1997;84(2):241-248. doi:10.1053/j.jvca.2004.05.023
28. Chaney MA, Smith KR, Barclay JC, Slogoff S. Large-dose intrathecal morphine for coronary artery bypass grafting. *Anesth Analg*. 1996;83(2):215-222.
29. Zangrillo A, Bignami E, Biondi-Zoccai GGL, et al. Spinal Analgesia in Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials. *J Cardiothorac Vasc Anesth*. 2009;23(6):813-821. doi:10.1053/j.jvca.2009.07.002
30. Richardson L, Dunning J, Hunter S. Is intrathecal morphine of benefit to patients undergoing cardiac surgery. *Interact Cardiovasc Thorac Surg*. 2008;8(1):117-122. doi:10.1510/icvts.2008.190686
31. Jacobsohn E, Lee TWR, Amadeo RJ, et al. Low-dose intrathecal morphine does not delay early extubation after cardiac surgery. *Can J Anaesth*. 2005;52(8):848-857. doi:52/8/848 [pii]
32. Parlow JL, Steele RG, O'Reilly D. Low dose intrathecal morphine facilitates early extubation after cardiac surgery: results of a retrospective continuous quality improvement audit. *Can J Anaesth*. 2005;52(1):94-99. doi:10.1007/BF03018588
33. Elgendy H, Helmy HAR. Intrathecal Morphine Improves Hemodynamic Parameters and Analgesia in Patients Undergoing Aortic Valve Replacement Surgery: A Prospective, Double-Blind, Randomized Trial. *Pain Physician*. 2017;20:405-412.
34. Kowalewski RJ, MacAdams CL, Eagle CJ, Archer DP, Bharadwaj B. Anaesthesia for coronary artery bypass surgery supplemented with subarachnoid bupivacaine and morphine: a report of 18 cases. *Can J Anaesth*. 1994;41(12):1189-1195. doi:10.1007/BF03020660
35. Lee TW, Grocott H, Schwinn D, Jacobsohn E. High Spinal Anesthesia for Cardiac Surgery. *Anesthesiology*. 2003;98(2):499-510.
36. Lee TWR, Kowalski S, Falk K, Maguire D, Freed DH, HayGlass KT. High Spinal Anesthesia Enhances Anti-Inflammatory Responses in Patients Undergoing Coronary Artery Bypass Graft Surgery and Aortic Valve Replacement: Randomized Pilot Study. *PLoS One*. 2016;11(3):1-15. doi:10.1371/journal.pone.0149942
37. Tabatabaie O, Matin N, Heidari A, Tabatabaie A, Hadaegh A, Yazdanynejad S. Spinal anesthesia reduces postoperative delirium in opium dependent patients undergoing

coronary artery bypass grafting. *Acta Anaesthesiol Belg*. 2015;66(2):49-54. http://www.arsmbkvbmg.be/ramsb/contact.html%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=2015374464.

38. Noss C, Prusinkiewicz C, Nelson G, Patel PA, Augoustides JG, Gregory AJ. Enhanced Recovery for Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2018;(Fig 1):1-11. doi:10.1053/j.jvca.2018.01.045
39. Cheng DCH, Karski J, Peniston C, et al. Morbidity Outcome in Early Versus Conventional Tracheal Extubation After Coronary Artery Bypass Grafting. *J Thorac Cardiovasc Surg*. 1996;112:755-764. doi:10.1016/S0022-5223(96)70062-4
40. Kirno K, Friberg P, Grzegorczyk A, Milocco I, Ricksten SE, Lundin S. Thoracic epidural anesthesia during coronary artery bypass surgery: effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hemodynamics. *Anesth Analg*. 1994;79(6):1075-1081. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=7978429.
41. Carli F. Physiologic considerations of Enhanced Recovery After Surgery (ERAS) programs: implications of the stress response. *Can J Anesth Can d'anesthésie*. 2015;62(2):110-119. doi:10.1007/s12630-014-0264-0
42. Miralpeix E, Nick AM, Meyer LA, et al. A call for new standard of care in perioperative gynecologic oncology practice: Impact of enhanced recovery after surgery (ERAS) programs. *Gynecol Oncol*. 2016;141(2):371-378. doi:10.1016/j.ygyno.2016.02.019
43. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery a review. *JAMA Surg*. 2017;152(3):292-298. doi:10.1001/jamasurg.2016.4952
44. Svircevic V, Dijk D Van, Ph D, Nierich AP, Bax L. Meta-analysis of Thoracic Epidural Anesthesia versus General Anesthesia for Cardiac Surgery. *Anesthesiology*. 2011;114(2):271-282.
45. Connelly NR, Dunn SM, Ingold V, Villa EA. The use of Fentanyl Added to Morphine-Lidocaine-Epinephrine Spinal Solution in Patients Undergoing Cesarean Section. *Anesth Analg*. 1994;78(5):918-920.
46. Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. *Minerva Anestesiol*. 2014;80(1):96-112.
47. Brem SS, Hafler DA, Van Uitert RL, Ruff RL, Reichert WH. Spinal Subarachnoid Hematoma - A Hazard of Lumbar Puncture Resulting in Reversible Paraplegia. *N Engl J Med*. 1981;303(17):1020-1021.
48. Narouze S, Benzon H, Provenzano D, Buvanendran A, Andres J, Deer T. Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition). *Reg Anesth Pain Med*. 2018;43:225-262.
49. Papachristofi O, Mackay JH, Powell SJ, Nashef SAM, Sharples L. Impact of the anesthesiologist and surgeon on cardiac surgical outcomes. *J Cardiothorac Vasc Anesth*. 2014;28(1):103-109. doi:10.1053/j.jvca.2013.07.004
50. Chaney MA. Intrathecal and Epidural Anesthesia and Analgesia for Cardiac Surgery. *Anesth Analg*. 1997;84:1211-1221.
51. Hackel BDB, Sancetta SM, Klenerman J. Effect of Hypotension due to Spinal Anesthesia on Coronary Blood Flow and Myocardial Metabolism in Man. *Circulation*. 1956;13:92-97.
52. Owens EL, Kasten GW, Hessel EA. Spinal Subarachnoid Hematoma after Lumbar Puncture and Heparinization : A Case Report , Review of the Literature , and Discussion of Anesthetic Implications. *Anesth Analg*. 1986;65(11):1201-1207. doi:10.1213/00000539-198611000-00018
53. Rao TL, El-Etr AA. Anticoagulation Following Placement of Epidural and Subarachnoid Catheters: An Evaluation of Neurological Sequelae. *Anesthesiology*. 1981;55:618-620. doi:10.1167/8.5.1.

APPENDIX

Figure 1. Consort Flow Diagram highlighting patient recruitment.

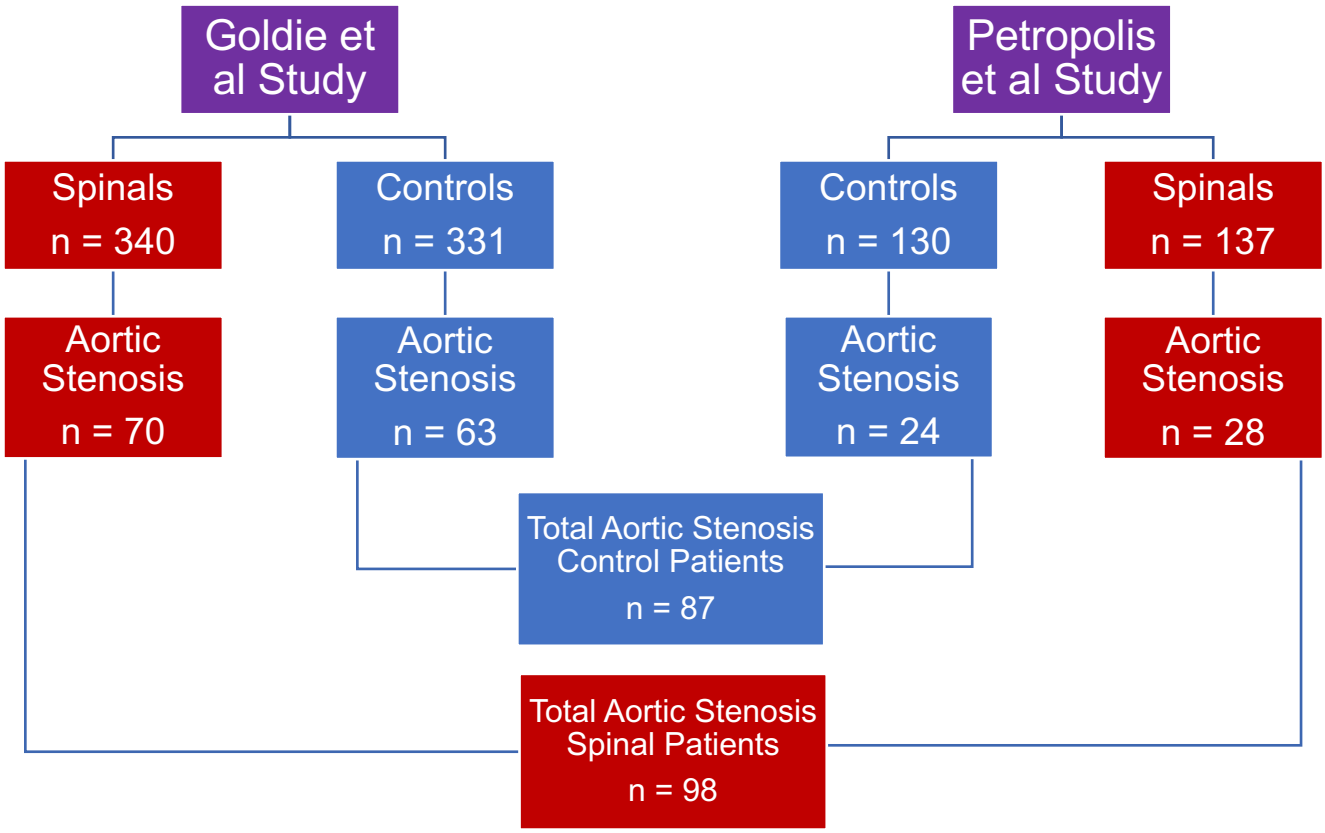

Table 1. Preoperative Patient Demographics

Variable	High Spinal Group	Control Group	P value
Number of Patients	98	87	
Males	72.4	69.0	0.46
Females	27.6	31.0	0.46
Age (years)	68.9 ± 11.0	70.0 ± 10.1	0.45
Body Mass Index	28.8 ± 4.6	29.9 ± 5.7	0.19
Hypertension	64.3	60.9	0.49
Angina	49.0	55.2	0.21
Diabetes	27.6	25.3	0.60
Prior Myocardial Infarction	22.4	29.9	0.10
Atrial Fibrillation	17.3	12.6	0.16
Other Arrhythmias	0.0	1.1	0.29
Congestive Heart Failure	40.8	28.7	0.01*
COPD	12.2	9.2	0.30

Peripheral Vascular Disease	8.2	5.7	0.28
OSA	5.1	2.3	0.06
Pulmonary Hypertension	5.1	4.6	0.81
PE / DVT	1.0	1.1	0.92
Stroke / TIA	9.2	6.9	0.36
Coronary Artery Disease	60.2	67.8	0.10
Current Smokers	10.2	8.0	0.42
Ex-Smokers	50.0	47.1	0.56
Pack-Years Smoking	27.9 ± 17.9	37.9 ± 30.3	0.28
Creatinine (µmol/L)	91.2 ± 32.3	96.3 ± 66.9	0.52
Glucose (mmol/L)	7.8 ± 7.1	6.8 ± 2.6	0.22
Hemoglobin (g/l)	134.8 ± 20.0	135.3 ± 17.6	0.87

[Data shown as Mean ± SD or frequency (%), * = statistically significant difference (p <0.05)]

Table 2. Preoperative Cardiac Characteristics

Variable	High Spinal Group	Control Group	P value
Preoperative LVEF (%)	55.1 ± 11.9	56.0 ± 11.6	0.57
> 60	63.3	67.8	0.34
50 – 59	13.3	16.1	0.45
40 – 49	8.2	6.9	0.61
30 – 39	14.3	5.8	< 0.001*
< 29	1.0	3.4	0.19
Aortic Valve Area (cm^2)	0.86 ± 0.26	0.88 ± 0.30	0.57
Peak Aortic Pressure Gradient (mm Hg)	71.1 ± 32.0	72.3 ± 32.8	0.80
Mean Aortic Pressure Gradient (mm Hg)	43.2 ± 21.2	43.3 ± 20.1	0.97
LVEDP (mm Hg)	21.8 ± 8.0	22.2 ± 6.7	0.77
Aortic Insufficiency	37.8	35.6	0.65

[Data shown as Mean ± SD or frequency (%), * = statistically significant difference (p <0.05)]

Table 3. Preoperative Medications

Medication	High Spinal Group	Control Group	P value
Beta Blockers	49.0	52.9	0.44
ASA	63.3	62.1	0.80
Statins	49.0	52.9	0.44
Calcium Channel Blockers	18.4	24.1	0.18
Nitrates	28.6	20.7	0.05
Digoxin	9.2	8.0	0.66
ACE Inhibitors	37.8	40.2	0.62
Diuretics	36.7	37.9	0.80

[Data shown as frequency (%)]

Table 4. Intraoperative Surgical Information

Variable	High Spinal Group	Control Group	P value
Emergent Procedure	2.0	1.1	0.39
Urgent Procedure	16.4	9.2	0.01*
Elective Procedure	81.6	89.7	0.01*
Length of Procedure (minutes)	234.4 ± 81.5	251.0 ± 108.0	0.26
Total CPB Time (minutes)	124.1 ± 46.9	132.5 ± 54.4	0.26
Aortic XC Time (minutes)	93.3 ± 36.9	102.7 ± 47.3	0.14
Intrathecal Bupivacaine Dose (mg)	36.1 ± 9.5	N/A	N/A
Morphine Dose (mcg)	239.4 ± 60.8	N/A	N/A
Sufentanil Dose (mg)	22.1 ± 4.6	N/A	N/A
Required Insulin Intraoperatively	31.6	47.1	0.002*
Highest Glucose (mmol/L)	9.2 ± 2.1	10.3 ± 2.2	0.002*

[Data shown as Mean ± SD or frequency (%), * = statistically significant difference ($p < 0.05$), N/A = Not Applicable]

Table 5. Postoperative Results

Variable	High Spinal Group	Control Group	P value
n	98	87	
Mean ICU LOS (days)	2.1 ± 2.3	3.3 ± 4.6	0.09
Median ICU LOS[1] (days)	1.0 [1.0 – 2.0]	1.0 [1.0 – 4.0]	0.43
Mean Hospital LOS (days)	8.2 ± 6.2	8.8 ± 5.6	0.48
Median Hospital LOS[1] (days)	6.0 [5.0 – 8.0]	7.0 [5.0 – 10.8]	0.08
Discharged Home	85.7	82.5	0.40
Transferred to Another Facility	10.2	11.1	0.77
Extubated in OR	57.1	31.0	< 0.001*
Time from ICU arrival to extubation (hours)	13.3 ± 16.6	25.7 ± 68.1	0.38
Median time from ICU arrival to extubation[1] (hours)	12.2 [1.9 – 16.9]	12.0 [4.2 – 14.0]	0.51
Re-intubation	6.1	5.7	0.86
Insulin use postoperatively	59.2	67.8	0.07
Re-admission to ICU	0.0	1.1	0.29
Reoperation for Bleeding	6.1	4.6	0.47
Return to OR	8.2	6.9	0.61
In-hospital Mortality	1.0	3.4	0.19
Inotrope/Vasopressor at 12 hours	37.1	27.0	0.02*
Inotrope/Vasopressor at 24 hours	20.0	25.4	0.22
Inotrope/Vasopressor > 24 hours	13.3	17.5	0.27

Atrial Fibrillation	33.7	29.9	0.41
Ventricular Arrhythmias	6.1	4.6	0.47
Renal Failure Requiring Dialysis	0.0	1.1	0.29
Myocardial Infarction	0.0	0.0	N/A
Stroke	1.0	1.1	0.92
TIA	0.0	1.1	0.29
Delirium requiring Haloperidol	12.9	9.5	0.25
Sepsis	1.0	2.3	0.39
Sternal Infection	0.0	0.0	N/A
Pneumonia	6.1	4.6	0.47
Cellulitis	2.0	1.1	0.39
UTI	4.1	4.6	0.81
GI Bleed	2.0	1.1	0.39
Excessive Nausea and Vomiting	37.1	34.9	0.64
Highest Creatinine (μmol/L)	108.2 ± 51.4	119.9 ± 71.5	0.27
Lowest Hemoglobin (g/L)	83.8 ± 14.9	81.9 ± 14.9	0.43
Peak Troponin (μg/L)	0.86 ± 1.39	0.90 ± 1.10	0.84
Transfusion Required	55.1	47.6	0.13
Transfused with RBC (units)	4.2 ± 5.1	3.5 ± 3.3	0.54
Transfused with FFP (Litres)	2.9 ± 3.4	2.4 ± 2.6	0.63
Transfused with Platelets (units)	5.0 ± 4.0	3.5 ± 2.2	0.37
Transfused with Cryoprecipitate (units)	13.0 ± 0.0	10.0 ± 0.0	N/A
Transfused with Albumin (units)	3.7 ± 2.5	4.9 ± 3.7	0.22

[Data shown as Mean ± SD or frequency (%), [1] Median with interquartile range, * = statistically significant difference ($p < 0.05$), N/A = Not Applicable]

Table 6. Postoperative Analgesics

Variable	High Spinal Group	Control Group	P value
n	98	87	
24-hour Cumulative Morphine Dose (mg)	9.7 ± 7.4	17.9 ± 9.4	< 0.001*
24-hour Cumulative Acetaminophen Dose (tabs)	6.8 ± 3.7	7.1 ± 3.9	0.68
24-hour Cumulative Fentanyl Dose (mcg)	114.9 ± 73.1	334.0 ± 210.4	< 0.001*
24-hour Cumulative Hydromorphone Dose (mg)	4.5 ± 3.1	5.8 ± 2.9	0.27
Total 24-hour Analgesic Cumulative Dose (M.E.)	18.3 ± 12.0	37.9 ± 33.0	< 0.001*

[Data shown as Mean ± SD, * = statistically significant difference ($p < 0.05$), M.E. = morphine equivalents]