ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE

DEPARTMENT OF ANESTHESIA

PROSPECTIVE COHORT STUDY ON PROPHYLACTIC USE OF INTRAVENOUS ATROPINE IN PREVENTION OF SPINAL ANESTHESIA INDUCED HYPOTENSION AND BRADYCARDIA IN FIFTY YEARS AND ABOVE PATIENTS UNDERGOING UROLOGICAL SURGERY AT TIKUR ANBESA SPECIALIZED HOSPITAL

BY: MOGES GELAW (BSc)

A THESIS IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR MASTERS OF SCIENCE IN ADVANCED CLINICAL ANESTHESIA; ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF ANESTHESIA.

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JUNE, 2018

ADDIS ABABA, ETHIOPIA

CERTIFICATION

The undersigned people certify that the research entitled **Prospective cohort study on Prophylactic use of intravenous atropine for prevention of Spinal anesthesia induced hypotension and bradycardia in elderly patients undergoing elective urological surgery at Tikur Anbesa Specialized Hospital, from December 1, 2017 to February 30, 2018 G.C;** A hospital based study is my original work and any literature and/or data cited in this article were listed in the reference section. Any assist done for this work has been given an acknowledgement.

Author Name _____ Signature _____ Date _____

Approval of the Board of Examiners

Advisors:

1. _____ Signature _____ Date _____
2. _____Signature _____ Date _____

Internal Examiner

Name _____Signature _____ Date _____

External Examiner

Name _____ Signature _____ Date _____

Abstract

Background: Spinal anesthesia induced hypotension is common and hazardous in elderly patients. Many techniques are being used to prevent and treat spinal anesthesia induced hypotension and bradycardia; including preloading, coloading, and vasopressors. Elderly cannot tolerate aggressive fluid challenges and the reflex tachycardia secondary to vasopressor use. Besides their adverse effects vasopressors are not easily available in most Ethiopian hospitals. The current study investigated whether prophylactic use of atropine helps in prevention of spinal anesthesia induced hypotension and bradycardia in elderly.

Objective: To assess the effect of prophylactic atropine in preventing spinal anesthesia induced hypotension and bradycardia in elderly patients undergoing urological surgery at Tikur Anbesa Specialized hospital from December 1, 2017 to February 30, 2018 G.C.

Methodology: Hospital based prospective cohort study was employed on 76 elderly patients with American Society of Anesthesiologists class I & II underwent urologic surgery under spinal anesthesia at Tikur Anbesa Specialized hospital during the study period. Samples were selected using systematic random sampling technique. Hemodynamic parameters and total vasopressor consumption were compared between the exposed and un-exposed groups. Descriptive data were displayed using tables and figures. Continuous data were analyzed using independent samples t test and Mann Whitey U test. Chi-square test and fisher exact test was used to analyze categorical data. P Value < 0.05 was considered statistically significant.

Results: A total of 76 patients were included in this study. Patients were comparable in age, sex weight and other demographics. There was no significant difference in baseline heart rate, mean arterial pressure, type & duration of surgery and total fluid administrations. There was a statistically significant difference in mean heart rate and mean arterial pressure between the atropine exposed and un-exposed groups. As compared to exposed group (7.9%), total vasopressor consumption was high in un- exposed group (28.9%) with P = 0.038.

Conclusion: The use of prophylactic atropine IV with in one minute of induction of spinal anesthesia maintains mean arterial pressure and heart rate in elderly patients thereby reducing incidence of hypotension and bradycardia.

Acknowledgements

First, I would like to express my heartfelt gratitude to my advisors, Mrs. Lidya Haddis and Mrs. Meron Abrar for their invaluable supports by giving constructive comments and suggestions. My appreciation extends to Bethlehem Ayele, Sr. Addisalem Abera, Sr. Kinde Hafte, Sr. Eyerusalem Lakew and Sr. Tigist Zewdie who participated in the data collection. I would also like to extend my special acknowledge to Mr. Adugna Aregawi (Lecturer, AAU) for his professional advices and suggestions in my work. Mr. Eyayalem Melese, Mr. Abateneh Melkamayehu, Mr. Mulualem Sitot and my colleagues Mr. Abebe Tiruneh & Mr. Bedilu Abebe really thank you for your invaluable supports. The major gratitude goes to my lovely wife Sr. Tesfaye Getnet for her patience and strength to help me reach at this achievement. Finally, I would like to thank department of anesthesia and Addis Ababa University for giving the chance and funding for this thesis.

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Acronyms and Abbreviations

AAU	Addis Ababa University
ASA PS	American Society of Anesthesiologists Physical Status
BJR	Bezold Jarish reflex
BMI	Body Mass Index
BP	Blood Pressure
Bpm	beats per minute
CSF	Cerebrospinal Fluid
DBP	Diastolic Blood Pressure
HR	Heart Rate
IV	Intravenous
LAs	Local Anesthetics
MAP	Mean Arterial Pressure
mmHg	millimeter mercury
SA	Spinal Anesthesia
SBP	Systolic Blood Pressure
TASH	Tikur Anbesa Specialized Hospital
TURBT	Transurethral resection of bladder tumor
TURP	Transurethral Resection of prostate
URS	Uretroscopic removal of stone

Chapter one: Background of the study

1.1 Introduction

Spinal anesthesia (SA) is one of the neuraxial blocks with a massive and temporary interruption of nerve transmission within the subarachnoid space produced by injection of a local anesthetic solution into cerebrospinal fluid (CSF) (1). Local anesthetics (LAs) administered in the subarachnoid space block sensory, autonomic, and motor impulses as the anterior and posterior nerve roots pass through the CSF. The site of action includes the spinal nerve roots and dorsal root ganglion. Spinal anesthesia has been widely used and continues to be popular for surgeries involving the lower abdomen, perineum and lower limbs. It is major regional technique with a long history of effective use for many urological procedures (2).

When compared with general anesthesia spinal anesthesia has many advantages including; few adverse effects on the respiratory system as long as unduly high blocks are avoided, a reduced risk of airway obstruction or aspiration, little risk of unrecognized hypoglycemia in an awake diabetic patient, less sedation, less nausea and vomiting, decreased blood loss, less immunosuppression, less cognitive impairment (especially in the elderly), easy to perform for well trained, reliable and provides excellent operating conditions, less costly, normal gastrointestinal function returns faster, decreased incidence of deep vein thrombosis and pulmonary emboli formation (1),(3),(4).

Spinal anesthesia is associated with many complications among which the most common side effects are hypotension and bradycardia (5),(6),(7). Systemic vasodilation induced by sympathetic blockade after SA, resulting in venous pooling of blood and reduction in systemic vascular resistance, has been regarded as the predominant mechanism for hypotension.

In addition, the blunted reflex tachycardia following hypotension in elderly also play important role in persistence of hypotension (8). This phenomenon may result from the blockade of cardioaccelerator sympathetic fibers at the first to fourth thoracic (T1 to T4) nerve roots, and possibly the “reverse” of the Bainbridge reflex (9),(10). Bainbridge reflex, also called atrial reflex, is increment of the heart rate resulting from distension of large systemic veins or the right

atrium. This reflex was first described by the British physiologist Francis Arthur Bainbridge in 1915 that prevents the pooling of blood in the venous system (11).

Special pressure sensors called baroreceptors (or venoatrial stretch receptors) located in the right atrium of the heart detects increases in the volume and pressure of blood returned to the heart. These receptors transmit information along the vagus nerve (10^{th} cranial nerve) to the central nervous system. This response results in the activation of sympathetic nerve pathways that serve to increase the strength of the heart muscle contraction and to increase heart rate (tachycardia) (9).

The following factors were identified as having association with a higher incidence of early hypotension and bradycardia: age greater than forty, female gender, weight, height, body mass index > 30 kg/m^2, ASA physical status II and above, history of hypertension, history of antihypertensive therapy, diabetes mellitus, anemia, higher baseline heart rate, blood pressure < 90/60 mmHg, highest level of sensory blockade more than or equal to T6 (8),(12).

Atropine is esters of an aromatic acid combined with an organic base. It competitively blocks acetylcholine binding to its receptor and prevents receptor activation thus cellular effects of acetylcholine are inhibited (13). In general, atropine lowers the parasympathetic activity of all muscles and glands regulated by the parasympathetic nervous system and increase heart rate via abolishing the vagal tone acting on M2 receptor at heart.

Mild hypotension or bradycardia may be treated with volume expansion, ephedrine, or atropine. However, severe and/or rapidly progressing bradycardia demands aggressive treatment with epinephrine, followed by cardiopulmonary resuscitation if appropriate (14).

1.2 Statement of the problem

The incidence of hypotension and bradycardia in non-obstetric patients has been reported to be 33%-54% and 0.05-13%, respectively (5),(7),(9). Relative dominance of parasympathetic system, activation of Bezold Jarish reflex (BJR) and increased baroreceptor activity may lead to bradycardia and some degree of hypotension. The responsible receptors for the BJR are mechanoreceptors located in the heart walls which participate in systemic responses to hyper and hypovolemia. They also include chemoreceptors sensitive to serotonin (5-HT3 receptors) (12).

Spinal anesthesia induced hypotension is believed to occur due to two possible mechanisms. The first and widely accepted mechanism is systemic vasodilation induced by sympathetic blockade after spinal anesthesia, resulting in venous pooling of blood and reduction in systemic vascular resistance (11). Based on this mechanism many scholars argue that the spinal anesthesia induced hypotension could be treated by administering peripheral vasoconstrictors thereby increasing the systemic vascular resistance and facilitating the venous return (8).

On the other hand, the cause for spinal anesthesia induced hypotension is believed to be the blunted reflex tachycardia. This phenomenon may result from the blockade of cardioaccelerator sympathetic fibers at T1 to T4, and possibly the "reverse" of the Bainbridge reflex. To prevent this mechanism, some scholars argue that prophylactic use of intravenous (IV) atropine is of great importance (10).

Currently various techniques are being used for the prevention of hypotension and bradycardia which include pre or co-loading of IV fluid, vasopressors, and physical methods such as table tilt, leg binders, and compression devices (14). However, none of these techniques alone are effective and there is a search for a technique or combinations of techniques for the proper prevention of spinal anesthesia induced hypotension and bradycardia (15).

Elderly patients are prone to spinal anesthesia induced hypotension and bradycardia than young adults. This is because they may have coexisting degenerative cardiovascular diseases with deranged reflex compensatory mechanisms for hypotension and bradycardia. They are also sensitive for both fluid resuscitation and sympathomimetic drugs. So, aggressive fluid therapy may end up with pulmonary edema and congestive heart failure. Vasoactive agents may also increase myocardial workload and ischemic injuries in elderly (16),(17),(18).

The purpose of the current study was to assess the effect of prophylactic atropine in preventing spinal anesthesia induced hypotension and bradycardia in elderly patients undergoing urological surgery.

1.3 Significance of the study

Hypotension and bradycardia are the common complications in spinal anesthesia. Their prevention and symptomatic treatment is still unsatisfactory.

In most clinical settings spinal anesthesia induced hypotension and bradycardia are managed by using pre &/or coloading, vasopressors or other physical methods like reverse trundelenberge position. But elderly patients cannot tolerate fluid challenges and vasopressors my lead to sudden myocardial infarction. In addition, compared to atropine, vasopressors are not easily available in most Ethiopian hospitals.

Another rational of choosing atropine is that elderly have blunted cardiac reflexes. Atropine helps in preventing the blunted reflexes, thus, helping in increasing heart rate and cardiac output, and finally blood pressure (19).

Atropine is more easily available and cost effective than vasopressors and IV fluids. Therefore, the results of the current study could be easily applicable in any hospital setups. Researches showing the effect of atropine to prevent spinal anesthesia induced hypotension are limited. As far as my search, there is no published study in Ethiopia that assessed the effect of atropine in preventing hypotension and bradycardia.

Another reason why we did this research is that it is difficult to generalize research results from other countries, because management style also varies due to economic and technological difference from our study area. It may generate information that may help program planners to develop effective preventive strategies, to select the best alternative solution and to evaluate the effectiveness of implemented preventive interventions targeted to these problems.

The findings may contribute to Tikur Anbesa Specialized Hospital anesthetic management protocols and will be an input for future researches. The primary outcome of the present study was to compare the heart rate and mean arterial pressure between patients exposed to atropine and those un-exposed. We also compared the vasopressor consumption in the first hour.

Chapter two: Literature review

2.1. Literature review

Hypotension and bradycardia commonly occur after spinal anesthesia. Dinesh Singla and his colleagues assessed the following factors were independently associated with the development of early hypotension: age, female sex, body mass index >30 kg/m^2, history of hypertension, diabetes mellitus, anemia, baseline heart rate, systolic and diastolic blood pressure, pulse pressure, rate pressure product, vascular overload index, sensory level of blockade higher than or equal to T6 (12).

Chinachoti et.al prospectively assed the incidence of hypotension and bradycardia and associated risk factors at Siriraj Hospital from 1st July 2004 to 31st December 2004. They found that the incidence of hypotension (20% or more decrease in systolic blood pressure) was 57.9%. The highest incidence was in cesarean section. They identified four non-modifiable factors for higher incidence of spinal anesthesia induced hypotension which included females, age more than 50 years, body mass index more than 35 and type of operation. Based on their findings the two modifiable risk factors included high dose of heavy bupivacaine and level of sensory blockage equal to or higher than T5 (5).

Intramuscular atropine 0.5 mg as an anticholinergic premedicant for spinal anesthesia was studied in Jichi Medical School, Tochigi; Japan showing no significant difference between the atropine and non-atropine groups with regard to changes in blood pressure during spinal anesthesia whose analgesic level reached T4. A significant difference was found between the groups with regard to changes in heart rate during spinal anesthesia, but the incidence of bradycardia below 60 beats per minute was similar between the two groups. They showed that intramuscular atropine 0.5 mg as a premedicant offered little vagal blockade of the heart during spinal anesthesia (20).

A study done in Ireland showed that there is no difference in the incidence of spinal anesthesia induced hypotension between colloid and/or crystalloid preloading in elderly patients undergoing elective procedures. Withholding prehydration is not associated with any greater degree of hypotension or need for vasopressor therapy compared with crystalloid or colloid prehydration (21).

On the other hand a randomized controlled trial done in Hong Kong, China in 2000 showed that IV atropine increases heart rate in a dose-dependent manner in elderly patients undergoing spinal anesthesia. It reduces the incidence of hypotension and the dose of ephedrine required. This study also recommended that small-dose atropine may be a useful supplement in preventing spinal anesthesia-induced hypotension in elderly patients (6).

A study in Shahid Beheshti University, Iran in 2009 randomly assigned sixty-four candidates for urological laparoscopic surgery into 2 groups to receive either atropine sulfate or hypertonic saline solution (as placebo). This study showed that a significant decreasing trend was seen in the heart rates during the operation in patients without atropine sulfate, while none of the patients with atropine sulfate prophylaxis had bradycardia perioperatively (22).

A randomized controlled trial done at Tribhuvan University Teaching Hospital, Nepal in 2015 on a total of 40 patients undergoing urological surgery showed that Compared to baseline, mean HR and MAP were significantly reduced in placebo group most of the study times. Comparing between groups, HR and MAP were also significantly decreased in placebo group. The incidence of hypotension was high in placebo (60%) compared to atropine group (5%). Thus, requirement of vasopressor for the management of hypotension was significantly high in placebo (60%) than atropine group (5%) (10).

Another randomized controlled trail done at Tribhuvan University Teaching Hospital, Nepal in 2015 that compared prophylactic use of atropine and ephedrine showed that administration of intravenous atropine 0.6 mg or IV ephedrine (12 mg) one minute after induction of spinal anesthesia in elderly patients was safe and effective in the prevention of spinal anesthesia induced hypotension and bradycardia. This study also showed that the requirement of vasopressors was decreased without clinically significant side effects (23).

A randomized, double-blind, placebo-controlled study was done at Seoul Paik Hospital of Inje University, Republic of Korea, in 2016. This study grouped the patients into atropine (A) and normal saline (N) groups. Then they were administered a bolus of 0.5 mg atropine and normal saline respectively. This study showed that the incidence of bradycardia requiring atropine treatment was significantly higher in group N than group A. However, the incidence of hypotension needing ephedrine treatment showed no significant difference between the 2 groups.

Systolic blood pressure and heart rate showed no significant differences between the 2 groups. However, group A showed significant increases in DBP and MAP, and group N did not (24).

2.2. Hypotheses

1. **H0**: There is no difference in mean heart rate after spinal anesthesia between the atropine exposed and non-exposed groups.

   HA: There is a difference in mean heart rate after spinal anesthesia between the atropine exposed and non-exposed groups.
2. **H0**: There is no difference in mean arterial pressure after spinal anesthesia between the atropine exposed and non-exposed groups.

   HA: The mean arterial pressure after spinal anesthesia is different between atropine exposed and non-exposed groups.
3. **H0**: Vasopressor consumption is equal between the two groups.

   HA: Vasopressor consumption is not equal between the two groups.

2.3. Conceptual framework

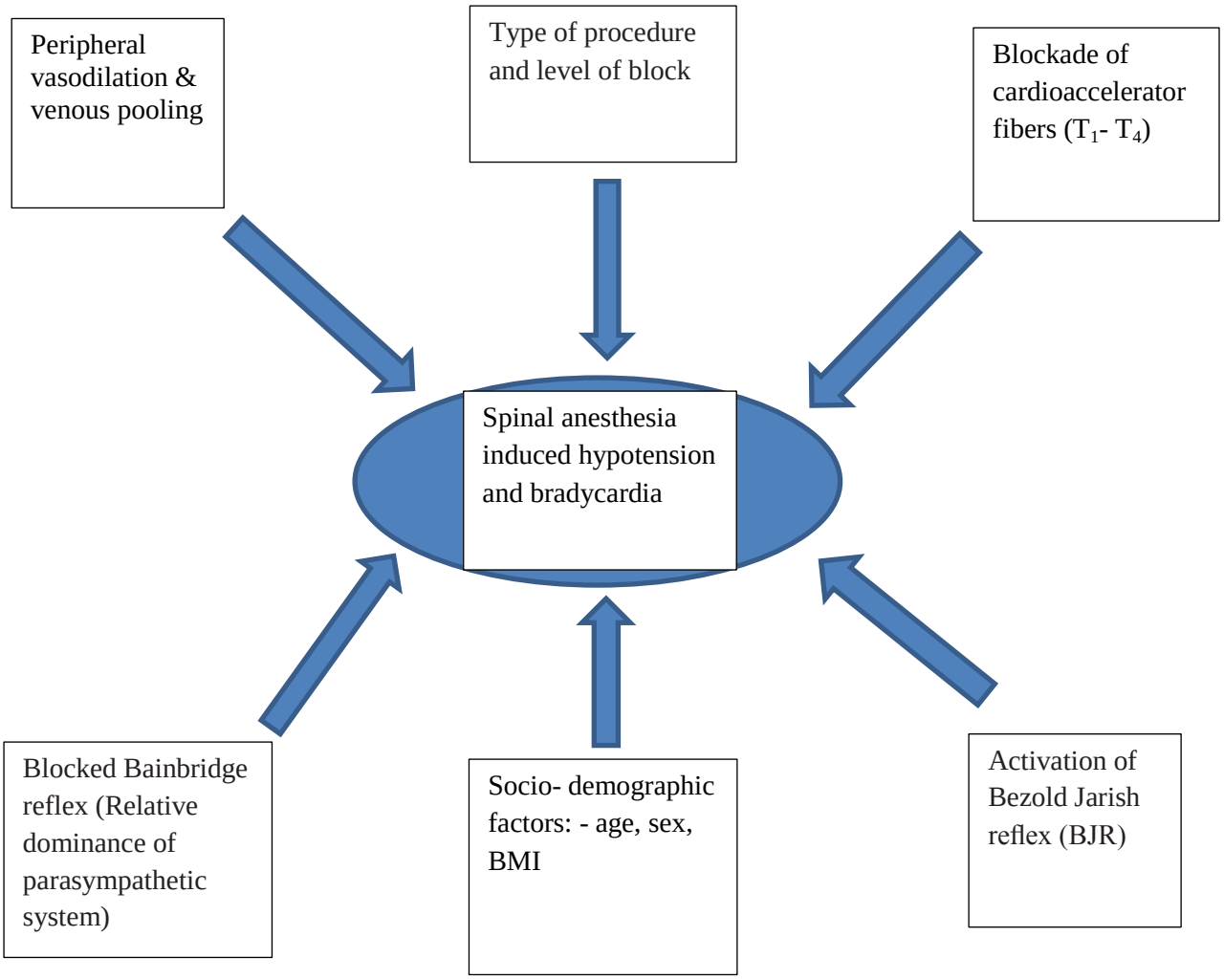


Figure 1: Factors affecting spinal anesthesia induced hypotension and bradycardia:

Chapter three: Objectives

1.1. General objective

To assess the effect of prophylactic atropine in preventing spinal anesthesia induced hypotension and bradycardia in elderly patients undergoing urological surgery at Tikur Anbesa Specialized hospital from December 1, 2017 to February 30, 2018 G.C.

1.2. Specific objectives

- To compare the heart rate after spinal anesthesia between atropine exposed and un-exposed groups.
- To compare the mean arterial pressure after spinal anesthesia between atropine exposed and un- exposed groups.
- To compare the vasopressor consumption between atropine exposed and un- exposed groups.

Chapter four: Method and Materials

4.1. Study area and period

The study was conducted at Tikur Anbesa Specialized Hospital (TASH) urology operation theatre. TASH is a governmental hospital under Addis Ababa University. It has about 800 beds and 17 operation theatres out of which the two operation rooms are for urological procedures. Approximately 7000-9000 patients undergo surgery in a year. This study was conducted from December 1, 2017 to February 30, 2018 G.C.

4.2. Study design

Institutional based prospective cohort study was conducted.

4.3. Population

4.3.1. Source population:

All patients with age 50 and above years who underwent urological surgery under spinal anesthesia at Tikur Anbesa Specialized Hospital

4.3.2. Study population

Selected patients with age 50 and above years who underwent urological surgery under spinal anesthesia at Tikur Anbesa Specialized Hospital during the study period

4.4. Variables:

4.4.1. Independent variables:

Age, sex, Body Mass Index (BMI), American Society of Anesthesiologists Physical status (ASA PS), type of procedure, duration of surgery, IV fluid, volume of local anesthetics, level of autonomic block

4.4.2. Dependent variables:

- ✓ Heart rate
- ✓ Mean arterial pressure
- ✓ Vasopressor consumption

4.5. Sample size and sampling technique:

4.5.1. Sample size:

By using Epiinfo-7 statistical calculator for independent cohort and considering one to one ratio of the atropine exposed and un-exposed groups with the assumption of a P value <0.05 as statistically significant and a power of 80%, the sample size was calculated to be 68 (34 patients each). Adding 10% nonresponse rate the total sample size was 76 (38 subjects to each group). The sample size was calculated based on a previous study in Nepal that showed the incidence of hypotension in atropine exposed and un-exposed groups was 5% and 60% respectively (10).

4.5.2. Sampling technique:

Systematic random sampling was used from daily schedule lists. In TASH, some anesthetists preload with 5-10ml/kg crystalloid solution & give 10µg/kg atropine IV one minute after spinal anesthesia; while others give only 5-10ml/kg fluid preloading to prevent hypotension. The patients were grouped based on their exposure to atropine; i.e. if the anesthetist decides to give atropine, that patient has been followed under the exposed group; if not, he/she has been grouped under un-exposed group and followed for one hour.

4.6. Inclusion and exclusion criteria:

4.6.1. Inclusion criteria:

All patients with age above 50 years and above (12), American Society of Anesthesiologists Physical status I and II (ASA PS I & II) undergoing urological surgery under spinal anesthesia during the study period were included in this study.

4.6.2. Exclusion criteria:

- Failed spinal,
- Heart block greater than first degree, left bundle branch block,
- Hypertension (SBP > 140 mmHg or DBP > 90 mmHg) (10).
- Preoperative tachycardia (HR > 120 bpm),
- Taking β-adrenergic blockers (10).
- Open urological surgeries

- Combinations of spinal block with other type of anesthesia (epidural block, inhalational or intravenous sedation and general anesthesia).
- Prior anticholinergic use within 2 hours before entering the operating room,
- supplementation with strong opioids (morphine, pethidine, fentanyl) (10).

4.7. Ethical Consideration:

Ethical clearance and approval was obtained from Institutional Review Board, college of health sciences, Addis Ababa University. Permission to conduct the research was obtained from Tikur Anbesa Specialized Hospital managements. Written consent was taken from all study participants and data were coded to secure confidentiality of patient information.

4.8. Operational definitions:

1. Spinal Anesthesia: Administration of local anesthetics into the subarachnoid space.
2. Elderly : age greater than or equal to 50 years (10),(25),(26).
3. Hypotension: SBP < 90mmHg or DBP < 60mmHg (10).
4. Hypertension: >20% increase from baseline BP (27).
5. Bradycardia: HR < 50 beats per minute (10).
6. Tachycardia: >20% increase from baseline heart rate (10),(28).

4.9. Data quality control:

To keep the quality of the data:

1. The checklist was pretested on small group samples at Minelik II memorial hospital before the actual data collection commenced.
2. Data collectors were Anesthesia professionals who are familiar for recording perioperative data.
3. Training and orientation about the objective and process of data collection was provided for data collectors.
4. Close supervisions were undertaken during the data collection.
5. The supervisor checked each questionnaire daily and reported to the principal investigator on the same day.
6. Collected data were being checked every day by the principal investigator.

4.10. Data collection:

Four anesthetists were given training by the principal investigator about how to collect the data. After written consent taken from each patient to participate in the study, the patients' socio-demographic data (age, sex, weight, BMI,), ASA PS, type of procedure, total amount of IV fluid, and duration of surgery were recorded. MAP and HR were recorded at 0 (baseline), 5, 10, 15, 20, 30, 40, 50 and 60 minutes intraoperatively in both exposed and un-atropine groups. Requirement for vasopressors was studied for the 1st hour intra/postoperatively.

4.11. Data analysis and interpretation:

The collected data was checked manually for completeness and entered into Epiinfo-7 then exported to SPSS version 20.0 windows for analysis. Descriptive data were presented as mean, standard deviation, median and interquartile range. Continuous data were tested for normality by using Shapiro-Wilk's test. We used Levene's test to assess homogeneity of variance and independent samples t test was used to analyze all continuous data except total volume of local anesthetic which was analyzed by Mann-Whitney U test. Paired sample t test was used to compare the values with the baseline within either group. The data for Sex, ASA, incidence of hypotension & bradycardia and vasopressor consumption were analyzed by using Chi-square test and Fisher's exact test. P-value < 0.05 was considered statistically significant.

Chapter five: Results

5.1. Comparison of Demographic data

A total of 76 (38 exposed and 38 un-exposed) patients were included in this study. There was no statistically significant difference in age between exposed and un-exposed groups with a P value of 0.656. The two groups were comparable in other demographic data (***Table 1***).

Table 1: *Comparison of demographic data between the two groups: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018*

		Exposed (n=38)	**Un-exposed(n=38)**	**P value**
Age in years (Mean +SD)		62.95 ± 7.392	62.21 ± 6.975	.656
BMI in Kg/m^2 (Mean +SD)		21.08 ± 2.136	20.11 ± 2.275	.058
Sex	Male [f (%)]	28 (73.7%)	23 (60.5%)	.222
	Female [f (%)]	10 (26.3%)	15 (59.5%)	
ASA class	I [f (%)]	20 (52.6%)	21 (55.3%)	.818
	II [f (%)]	17 (47.4%)	18 (44.7%)	
Type of surgery	TURP [f (%)]	15 (38.5%)	11 (28.9%)	.626
	TURBT [f (%)]	11 (28.9%)	13 (34.3%)	
	URS [f (%)]	12 (31.6%)	14 (36.8%)	

ASA: American Society of Anesthesiologists, BMI: Body Mass Index, TURP/BT: Transurethral Resection of prostate/ Bladder Tumor; URS: Uretroscopic Removal of stone; f: frequency

5.2. Comparison of baseline hemodynamics and fluid management

There was no significant difference in the type, baricity and volume of local anesthetic used, size of spinal needle and level of autonomic block between the two groups. Preload, total IV fluids in the first hour and baseline hemodynamics were also comparable (***Table 2***).

Table 2: *Comparison of baseline hemodynamics and fluid management between the two groups: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018*

	Exposed (n=38)		**Un-Exposed (n=38)**		
	Mean	Std. Deviation	Mean	Std. Deviation	P value
Preload (ml)*	444.74	148.319	455.26	169.972	.774
Total fluid in 1st hrs. (ml)*	1039.47	440.847	1221.05	559.033	.120
Duration of surgery (minute)*	64.21	20.253	65.53	24.489	.799
Baseline HR (bpm)*	76.16	11.988	78.18	11.359	.452
Baseline MAP (mmHg)*	94.66	7.528	94.16	6.310	.755
Volume of LA in ml [median (IQR)]**	3.5 (3.0-3.5)		3.0 (3.0-3.5)		.507

*HR: Heart Rate, MAP: Mean Arterial Pressure. *: Independent samples t test,*

***: Mann Whitney U test.*

5.3. Comparison of mean heart rate

The mean baseline heart rate was comparable between the two groups. There was a statistically significant difference in mean heart rate records between exposed and un-exposed groups at all measurements in the 1st hour (***Table 3***).

As compared to the baseline, mean heart rate was significantly low in un-exposed group with the lowest mean HR of 65.84 ± 8.964 bpm at 15th minute. While in exposed group; all the mean records of HR were higher than the baseline with the highest to be 93.63 ± 16.210 at the 10th minute (***Table 3***).

Table 3: Comparison of mean heart rate within and between the two groups: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018

	Exposed (n=38)		**Un-exposed (n=38)**		**P value (between groups)****
	Mean +SD	P value (within group)*	Mean +SD	P value (within group)*	
Baseline HR	76.16+11.988	…	78.18+11.359	…	.452
HR 5	89.18+10.221	< .001	73.82+9.543	.003	< .001
HR 10	93.63+16.210	< .001	66.53+10.830	< .001	< .001
HR 15	85.95+11.116	< .001	65.84+8.964	< .001	< .001
HR 20	85.18+11.982	< .001	69.34+12.312	.002	< .001
HR 30	84.29+12.256	< .001	70.11+12.661	.007	< .001
HR 40	81.82+12.623	.003	69.89+12.078	.004	< .001
HR 50	77.89+7.777	.314	68.45+7.999	< .001	< .001
HR 60	76.58+9.105	.806	69.92+8.264	< .001	.001

*HR: Heart Rate, SD: Standard Deviation. *: Paired sample t test, **:Independent samples t test*

5.4. Comparison of Mean MAP

The mean baseline MAP was comparable between the two groups (94.66 ± 7.528 in exposed and 94.16 ± 6.310 in un-exposed). M AP in exposed group was significantly greater than the non-exposed group throughout the whole times of measurement with P values < 0.001 (**Table 4**).

Table 4: Comparison of Mean MAP within and between the two groups: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018

	Exposed (n=38)		**Un-exposed (n=38)**		**P value (between groups)****
	Mean +SD	P value (within group)*	Mean +SD	P value (within group)*	
Baseline MAP	94.66+7.528	…	94.16+6.310	…	.755
MAP 5	94.82+10.717	.922	79.95+12.559	< .001	<.001
MAP 10	94.97+9.048	.843	74.32+8.690	< .001	<.001
MAP 15	94.55+11.086	.955	73.21+10.351	< .001	<.001
MAP 20	94.21+11.630	.830	74.55+8.186	< .001	<.001
MAP 30	90.32+7.447	.010	74.61+8.189	< .001	<.001
MAP 40	90.47+9.443	.015	77.53+8.320	< .001	<.001
MAP 50	90.55+8.193	.010	78.74+8.275	< .001	<.001
MAP 60	91.68+8.650	.110	80.58+8.314	< .001	<.001

*MAP: Mean Arterial Pressure, SD: Standard Deviation. *: Paired sample t test, **:Independent samples t test*

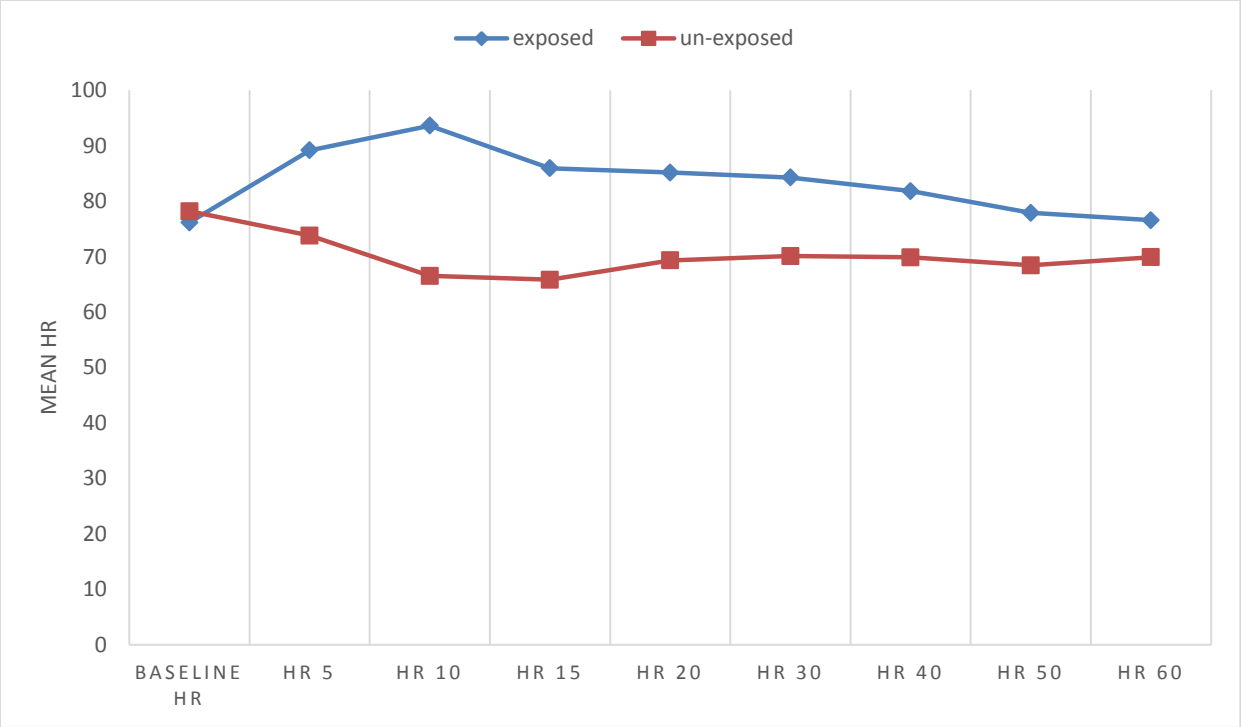
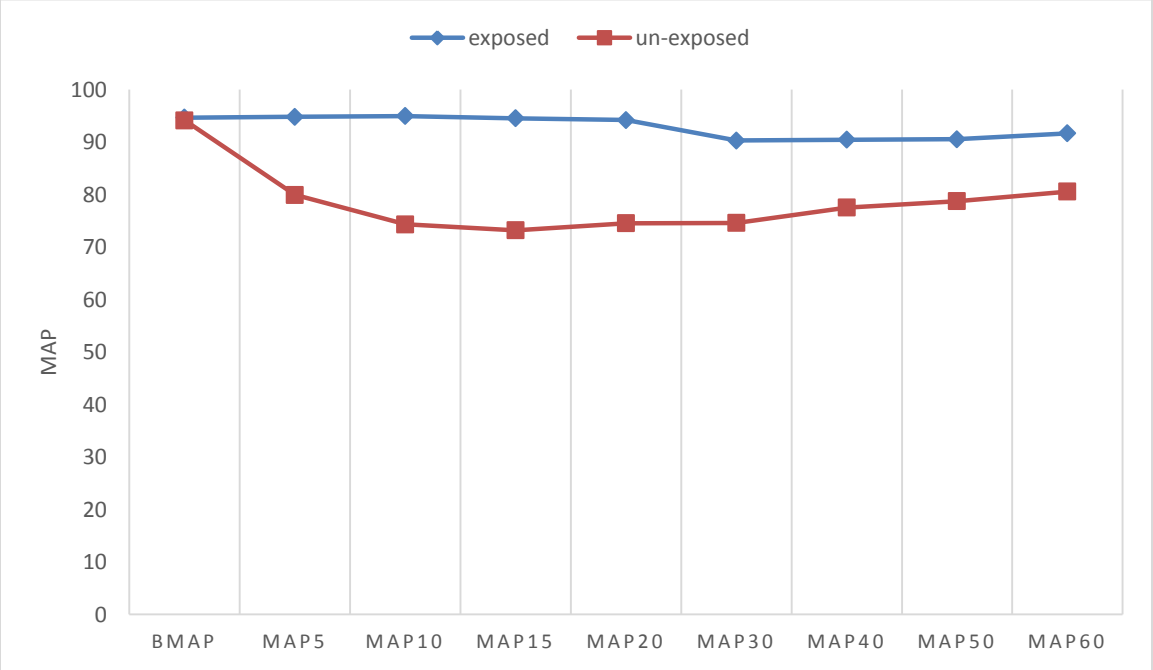


***Figure 2**: Trends of **mean heart** rate in exposed and un-exposed groups: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018*

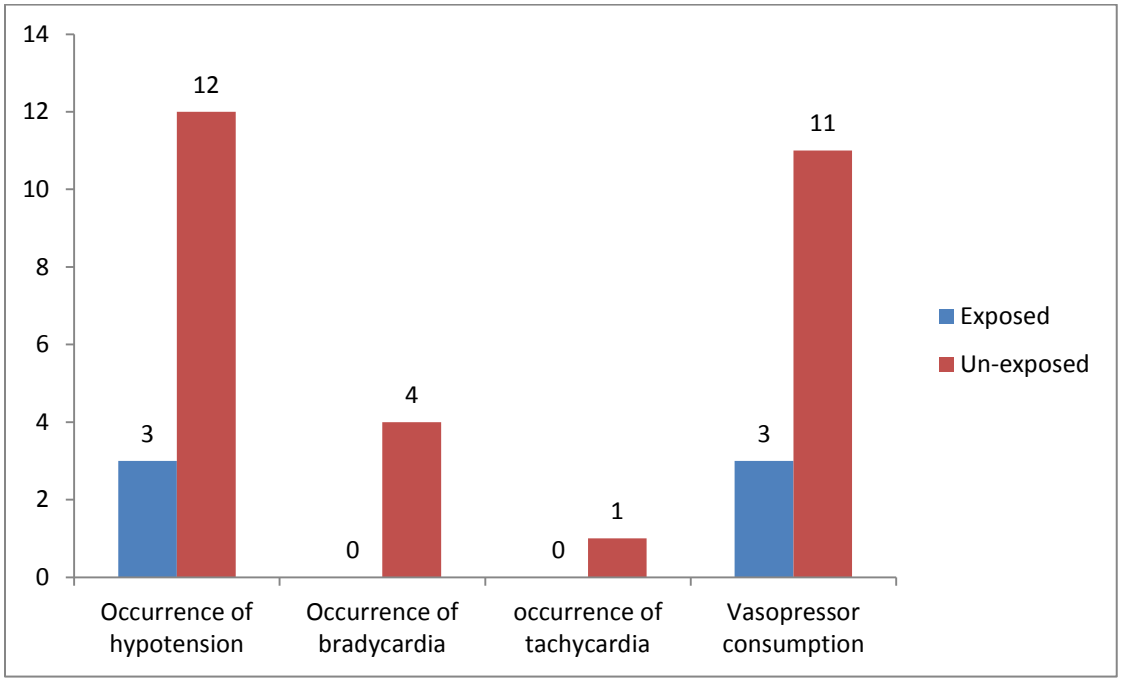


BMAP: Baseline Mean Arterial Pressure; MAP5-60: Mean Arterial Pressure at 5th- 60th minute.

***Figure 3:** Trends of **mean MAP** exposed and un-exposed groups: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018*

5.5. Comparison of Vasopressor consumption

The frequency of vasopressor consumption was significantly different between the exposed and un-exposed groups with a P value of 0.038 (***Figure 3***). The overall occurrence of hypotension (BP<90/60mmHg) was 3(7.9%) and 12(31.6%) in exposed and un-exposed groups respectively. There were four patients (10.5%) with heart rate <50 bpm in un-exposed group, but this was not statistically significant (***Figure 3***). A Chi-square test for independence (with Yates Continuity Correction) indicated that there is a significant association between atropine prophylaxis and intraoperative vasopressor consumption, $\chi 2$ (1, n = 76) = 4.290, P = 0.038, phi = 0.272.



-Hypotension – Blood pressure < 90/60 mmHg. Bradycardia – HR < 50 bpm, Tachycardia >20% increase in baseline heart rate.
-P was 0.021 for hypotension and 0.038 for vasopressor consumption.

Figure 4: *Occurrence of hypotension & bradycardia and total vasopressor consumption in the first hour after spinal anesthesia: Tikur Anbesa Specialized Hospital, December 1, 2017 – February 30, 2018*

Chapter Six: Discussion

Hypotension and bradycardia are the two most common complications of spinal anesthesia (5),(6). There are various techniques to prevent these complications which may include fluid loading, vasopressors, leg up positioning, low dose local anesthetic combined with opioid additives and others (9),(24),(27). However none of these techniques are sufficient for proper prevention of hypotension and bradycardia after spinal anesthesia (7),(9),(15),(29).

Systemic vasodilation induced by sympathetic blockade, resulting in venous pooling of blood and reduction in systemic vascular resistance, has been regarded as the predominant mechanism for hypotension induced by SA (7). However, the absence of reflex tachycardia after spinal anesthesia induced hypotension has been observed to contribute by Hwee H. Lim et al (6). We postulate that the absence of reflex tachycardia may be an important component in the pathogenesis of hypotension induced by SA in addition to effects of venous and arterial dilation.

The current study showed that there was a statistically significant difference in heart rate between the exposed and un-exposed groups throughout all the measurements with P values less than 0.001 (**Table 3**). The increase in HR was statistically significant but no patient required treatment for tachycardia (>20% increase from baseline heart rate). Compared with the baseline, the heart rate was significantly decreased in the non-exposed group and significantly increased in exposed group (**Figure 1**). The possible justification for this difference could be due to the vagolytic effect of atropine which increased the heart rate in the exposed group.

These findings were in line with other studies. A Randomized Controlled Trial done in Nepal in 2015 compared mean heart rate between a group of 20 patients given a single dose of 0.6 mg atropine and a placebo group of equal number. This study showed that the mean heart rate was significantly different between the atropine premedicated and the control groups at all the times they measure (10).

Another RCT that compares the prophylactic effect of atropine and ephedrine with a placebo group also showed that as compared to the placebo, mean heart rate was significantly increased in atropine and ephedrine groups at all the times. This study also showed that maximum heart rate in atropine group was 89.30 ± 14.62 bpm at 5^{th} minute (23).

A study done in Chai Wan, Hong Kong to assess the effect of different doses of atropine in prevention of spinal anesthesia induced hypotension showed that the heart rate in both small dose (5mcg/Kg) and large dose (10mcg/Kg) groups was significantly different from that of the placebo group (6).

In contrast to our findings of increased mean heart rate in the exposed group in all times, a study in Seoul Paik Hospital of Inje University, Republic of Korea showed that as compared to the baseline, there was a significant decrease in heart rate at 5, 10, 15, 20, 25, and 30 minutes in the atropine group (24). This difference may be due to the administration of dexmedetomidine for sedation at a loading dose of 0.6 mcg/kg for 10 minutes followed by an infusion at 0.25 mcg/(kg h) in their study. Dexmedetomidine decreases sympathetic out flow from the central nervous system which may result in bradycardia.

So we have enough evidence to reject the hypothesis that says there is no difference in mean heart rate between the exposed and un-exposed groups at a 99.9% confidence level.

The current study showed that the mean MAP was significantly different between the two groups throughout the whole measurements with $P < 0.001$ (**T*able 4***). Compared to the baseline the mean MAP in un-exposed group showed a significant decrease. There was not a statistically significant difference in MAP from baseline until the 30^{th} minute in exposed group (**F*igure 2***).

The possible explanation for the maintenance of MAP in the exposed group may be due to the increased heart rate which again increases the cardiac output and mean arterial pressure by the anticholinergic effect of atropine.

A study done in Nepal that compared patients premedicated with a fixed dose of 0.6mg atropine with a placebo showed a significant increase in MAP at the first minute in the atropine group and significant decrease at the 5^{th}, 10^{th}, 15^{th}, 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minute in placebo. To the contrary to the current study, they found that the mean MAP in the atropine group was not significantly different from the baseline throughout the whole times (10). While our study showed a significant decrease in MAP at the 30^{th}, 40^{th} and 50^{th} minute in exposed group. This difference may be due to variations in study designs.

Another RCT that compares atropine and ephedrine with a placebo showed MAP was comparable between atropine and ephedrine groups but in placebo group MAP was significantly

low compared to other groups (23). This is also in line with our findings showing a better maintenance of MAP after spinal anesthesia in the atropine exposed group than un-exposed group especially in the first 30 minutes.

A comparative study done by Jain and Kaushik in India that compared the effect of atropine and ephedrine in the prevention of spinal anesthesia induced hypotension in elderly patients who undergo surgery under spinal anesthesia showed that as compared to placebo group both atropine and ephedrine groups had a significantly different mean MAP from the placebo in all times they measured (30).

Based on our findings we are 99.9% confident that there is a significant difference in the mean arterial pressure of exposed and un-exposed groups.

In the current study there was a significant difference in the occurrence of hypotension and frequency of vasopressor consumption between exposed and un-exposed groups (with P values of 0.021 and 0.038 respectively) (***Figure 3***). Adrenaline was required in 28.9% of un-exposed and 7.9% of exposed groups. This result was also in line with other studies.

Possible explanation for the reduced incidence of hypotension and decreased vasopressor consumption with the prophylactic use of atropine may be the help in preventing the blunted Bainbridge reflex thus increasing heart rate and cardiac output.

In a randomized controlled trial that compared occurrence of hypotension and vasopressor consumption in a group of patients given 0.6mg of atropine one minute after administration of spinal anesthesia with a placebo group the occurrence of hypotension and total vasopressor consumption was significantly different between the two groups. They showed that 60% of placebo and 5% of atropine groups developed hypotension that required mephentermine (10). While in our study the occurrence of hypotension in un-exposed group was 31.6% which is significant with a P value of 0.021. The variation in percentage may be due to difference in study design.

Another study done in India that compared vasopressor consumption between three groups of patients (atropine, ephedrine and placebo) showed that as compared to the atropine and ephedrine groups, there was a significant increase of vasopressor consumption in the placebo group (P = 0.02). Based on their findings mephentermine was required in more than 50 percent,

5 percent and 5 percent of the patients of the placebo, ephedrine and atropine groups respectively (30).

This result was also in line with a study done in Hong Kong that compared the incidence of hypotension between three groups of small dose atropine (5mcg/Kg), large dose atropine (10mcg/Kg) and placebo that showed the incidence of hypotension to be 76%, 50% and 40% in placebo, small dose and large dose atropine groups respectively (6).

In contrast to our findings, a study done at Seoul Paik Hospital of Inje University, Republic of Korea, in 2016 showed that the incidence of hypotension needing ephedrine treatment showed no significant difference between atropine pretreated and placebo groups. This variation could be due to the difference in study design and they used a fixed dose of 0.5mg atropine for all patients (24).

In the current study the occurrence of tachycardia had no significant difference between exposed and un-exposed groups. This was also in line with other studies that showed the reflex tachycardia after atropine prophylaxis in patients undergoing urological procedures under spinal anesthesia is not statistically significant (23),(6) ,(10).

Based on our findings, we can reject the null hypothesis that says the total vasopressor consumption is equal in exposed and un-exposed groups at 95% confidence level.

Chapter Six: Strength and limitations

Strength of the study:

- We had no incomplete data with missing values.
- The calculated sample size was adequate and was attained on the planned schedule of time.
- Study participants were homogenous between the two groups.

Limitation of the study:

- Lack of randomization and control
- Lack of blinding
- Unable to get articles with similar study design

Chapter Seven: Conclusion and Recommendation

Conclusion: The use of prophylactic atropine IV with in one minute of induction of spinal anesthesia maintains mean arterial pressure and heart rate in elderly patients thereby reducing incidence of hypotension and bradycardia.

Recommendation: prophylactic atropine can be used to prevent spinal anesthesia induced hypotension and bradycardia in patients with age 50 years and above undergoing urological surgeries. Further randomized clinical trials should be done.

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Annexes:

I. Consent and questionnaire

Informed consent form

Dear Sir /Madam

This is _____. I am a member of a research team of anesthesia department at Addis Ababa University. We are studying on how to prevent spinal anesthesia induced hypotension and bradycardia. We will not intervene on any of your anesthetic or surgical management. We just follow your vital signs like blood pressure and heart rate during the perioperative period. I confidently can assure you that our study will not compromise your anesthetic and surgical management nor it will cause any adverse effects on your life. If you feel that this study affects you negatively, feel free to stop your participation in the study at any time. I would like to remind you that the results of this study will hopefully improve our clinical management of patients like you. So, don't you feel that you are saving life of others with no harm and hazard happening on you? The results of the study will be announced in statistical generalization that means the data from you will not be reported individually. If you feel that this study is essential, please put your signature on the space below. Since the date is secured with code none of your personal data will be disclosed to anybody. You are not supposed to write your name, just put your own signature below. Thank you for your cooperation.

Sign_____ Date _____

የስምምነት ፎርም

_____ እባላለሁ፡፡ በአዲስ አበባ ዩኒበርሲቲ የአንስቴቨርያ ት/ት ክፍል የጥናትና ምርምር አባል ነኝ፡፡ ከወገብ በታች ማደንዘዣ ከተወሰደ በኋላ የሚከሰት የደም ግፊትና የልብ ምት መቀነስ እንጌት መከላከል እንደሚቻል እያጠናን እንገኛለን፡፡ በጥናቱ ምክንያት በርእሰዎ ላይ ምንም አይነት የሚቀነስበዎት የህክምና አገልግሎት ወይም የሚያመጣበዎት ተጓዳኝ ችግር እንደሌለ አረጋግጥለወታለሁ፡፡ የርእሰዎ የግል ምስጢር የተጠበቀ መሆኑን እና ምንም አይነት የግል ኢነፎርሜሽን የማናስተላልፍ መሆኑን ከወዲሁ ላሳውቀወት እወዳለሁ፡፡ በጥናቱ ለመሳተፍ ፈቃደኛ ከሆኑ የግል ፊርማዎትን ወይም አሻራዎትን ያስቀምጡ፡፡ ለተሳትፎዎ እናመሰግናለን፡፡

ፊርማ _____

II. Structured checklist:

1.	**Pt. code**_____ Age (years)_____ Sex _____Weight (Kg) _____ BMI _____ ASA ☐ I ☐ II Height (meters) _____					
2.	**Monitoring**	Pulse oximeter ☐ Capnography ☐ ECG ☐ P.N. stimulator ☐ NIBP ☐ Temperature ☐ Urine output ☐ Other _____				
3.	**Type of procedure**_____ Duration of surgery (min)_____					
4.	**Spinal block**	Drug name_____ Conc. (%) _____ Volume (ml)____ gauge of needle _____ Level of autonomic block (Rt) _____ (Lt) ____ Surgical Position _____ Adjuvants 1. Neostigmine _____ 2. Opioid _____ 3. Other _____				
5.	**Name of Fluid** _____ preload (ml) _____ Total fluid in 1st hr (ml) _____ **Prophylactic Atropine (mg) _____** Other drug _____					
6.	**Intraoperative V/S**	**HR**			**MAP**	Remark
	Baseline					
	5 min					
	10 min					
	15 min					
	20 min					
	30 min					
	40 min					
	50 min					
	60 min					
7.	**Any Intra/post-operative events**	**yes**	**No**	**Treated with**		**Dose of drug used**

	Bradycardia				
	Tachycardia				
	Hypotension				
	Hypertension				
	Other adverse effects _____, _____				
8.	**Data collector's name _____ Signature_____** **Date_____**				