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Preoperative Oral Midodrine for Prophylaxis Against Post Spinal Hypotension in Knee Arthroscopic Surgeries: A Randomized Clinical Study

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Abstract

Background: Midodrine has been utilized efficiently for prophylaxis against several hypotensive syndromes like weaning cases off the intravenous vasopressors, orthostatic hypotension and reducing the frequency of hypotension happening throughout dialysis.

Objective: Our aim was to assess the efficiency of oral midodrine as a prophylaxis against hypotension following spinal anesthesia in cases having knee arthroscopy.

Methods: This randomized double blinded controlled study has been carried out on 100 patients aged 21 to 45 years of either gender having elective knee arthroscopy under spinal anesthesia. Cases have been randomized to midodrine group (administered ten milligrams pills of midodrine) or placebo (control) group (administered placebo pills), and pills have been given 75 minutes prior to spinal anesthesia (intrathecal injection of 12.5 milligrams 0.5 percent hyperbaric bupivacaine and 25 milligrams fentanyl). The 1^{ry} result was the prevalence of hypotension, identified as a systolic blood pressure below ninety millimeter Hg or below eighty percent of baseline. 2^{ry} results were hemodynamic features (heart rate (HR) and mean arterial pressure (MAP)) following spinal anesthesia, ephedrine or atropine doses, and the prevalence of complications involving vasovagal attacks, bradycardia, reactive hypertension vomiting, nausea, in addition to shivering.

Results: Baseline hemodynamic features were similar among the 2 groups. In the midodrine group, 25 (50%) cases had hypotension following spinal anesthesia against 43 cases (86%) in the placebo group. The median intraoperative (quartile) overall dose of ephedrine was significantly reduced in midodrine group 12 (0-27) milligrams compared to placebo group 36 (21-45) milligrams, *P*-value: 0.001). The frequency of bradycardia in addition to hypertension were similar among the 2 groups. Moreover, the MAP and HR were similar among the 2 groups. In the two groups, the MAP during surgery reduced in association with the baseline reading, whereas the HR has been generally sustained.

Conclusions: preoperative administration of oral midodrine ten milligrams tablets prior to spinal anesthesia is an efficient technique in the avoidance of post-spinal hypotension in adult cases having elective knee arthroscopic surgeries.

Keywords: Knee arthroscopy; Ephedrine; Hypotension; Midodrine; Spinal anesthesia.

Introduction

Knee arthroscopy was conducted for different underlying pathologies and the majority of cases having this procedure are young **[1].**

Spinal anesthesia was favored by anesthetists in young and elderly cases nevertheless, its prevalent and occasionally dangerous complications might restrict its utilization **[2]** Bradycardia and hypotension are the most common complications reaching up to 1/3 in non-obstetric populations **[3, 4].**

Hypotension during surgery compromises perfusion of vital organs, hence elevating the possibility of renal injury, cardiac ischemia, brain ischemia, and death within thirty days **[5, 6]**.

Current methods utilized to avoid hypotension of spinal anesthesia involve preloading via intravenous fluid, sympathomimetic medications, as well as physical techniques like leg bindings and compression stockings **[7].** Nevertheless, a Cochrane Review determined that no single method alone was efficient in removing hypotension and suggested future study to be performed to examine the combinations of procedures **[8].**

The frequently utilized vasopressor medications in the settings prior to operation include agonists of alpha-adrenoreceptor like phenylephrine, ephedrine, and lately norepinephrine. All these medications are efficient in sustaining blood pressure; nevertheless, they have certain disadvantages; ephedrine is frequently related to tachycardia (because of the activity of beta-agonist) **[9],** norepinephrine and phenylephrine are typically related to reactive bradycardia **[10].**

Midodrine hydrochloride is an agonist of alpha-adrenoreceptor medication utilized for the treatment of different hypotensive conditions. Midodrine is the pro-drug that is metabolized to desglymidodrine, a direct venous and arteriolar vasopressor **[11].** Midodrine is an oral medication, with minimal side effects in central nervous system, and better oral bioavailability **[12, 13].**

It was utilized efficiently for prophylaxis against several hypotensive syndromes like orthostatic hypotension **[14, 15],** weaning cases off the intravenous vasopressors **[16],** in addition to reducing frequency of hypotension happening throughout dialysis and elevating the systolic blood pressure happening following dialysis **[17].**

This study aimed to assess the efficiency of oral midodrine as a prophylaxis against hypotension following spinal anesthesia in cases having knee arthroscopy.

PATIENTS AND METHODS

This randomized controlled double blinded placebo research has been performed at Al-Azhar University Hospitals (Assiut) between March 2023 to September 2023, after Al-Azhar University Research Ethics Committee approval. Consent has been attained from the case prior to the enrolment after detailed explanation of the surgical, anesthetic and analgesic techniques and their possible risks.

Patients who included in the study were consecutive American Society of Anesthesiologists (ASA) class I- II of both genders, aged 21 to 45 years undergoing elective arthroscopic knee surgeries under spinal anesthesia.

Exclusion criteria were cases with uncontrolled hypertension or comorbidities (cardiac, renal and hepatic). Patients were also excluded if they have contraindications to spinal anesthesia, history of allergy to midodrine or if they taking vasoconstrictors.

Eligible cases have been randomly allocated via an independent researcher to the placebo (control) group as well as midodrine group utilizing computer-generated codes based on the permuted block randomization technique with block size of four, and the separation of group were concealed in sequentially numbered, sealed opaque envelopes which have been opened only following attaining

the consent. The cases and the anesthesiologists who were responsible for gathering the information in the operating room have been blinded to the separation of group.

Patients were randomly allocated to the following:

Midodrine (number = 50): A Midodrine tablet of ten milligrams was administered 75 minutes prior to spinal anesthesia

Placebo (n =50): A Placebo tablet (Metoclopramide tablets) was administered 75 minutes before spinal anesthesia.

Preoperative preparation:

In the last hospital visit before surgery, patients were directed to fast for six hours after solid light meals and two hours after clear fluids. All cases have been examined in the ward prior to attending the theater through the anesthesiologist supervising the tablets giving. Standard follows-up (pulse oximetry, noninvasive blood pressure, five-lead electrocardiogram) have been utilized and intravenous access has been attained. The baseline blood pressure and heart rate have been determined in the preparation room 75 minutes prior to spinal anesthesia (average of three readings were attained in the supine position with variability below ten percent in MAP).

Seventy-five minutes prior to the spinal anesthesia, cases underwent the examined medication based on the randomization. Cases in the midodrine group underwent oral midodrine pill (Gutron ten milligrams, Blumed Labial Farma, India). Cases in the control group underwent oral placebo (metoclopramide ten milligrams). Metoclopramide tablet (Meclopram ten milligrams, Alexandria Co for pharmaceutical, Egypt) has been selected as a placebo due to it's identical appearance as midodrine tablet with no cardiovascular impacts. Cases have been monitored for heart rate and blood pressure at fifteen-min periods following giving of the examined medication.

Anesthesia management:

10 milliliters per kilogram of lactated Ringer's solution has been administered to all cases prior to induction of spinal anesthesia. Spinal anesthesia has been conducted in the sitting position through hyperbaric bupivacaine 12.5 milligrams (2.5 milliliters of 0.5 percent hyperbaric bupivacaine) and 25 micrograms fentanyl (0.5 milliliters) in L3–4 or L4–5 space utilizing a 25-gauge River spinal needle subsequently the case has been repositioned to supine.

The greatest sensory level of the spinal block has been examined through the pinprick technique every five minutes for twenty minutes and has been documented following twenty minutes. When spinal anesthesia failed, the case has been removed from the research and has been treated based on the discretion of the attending anesthetist. Following the initiation of spinal anesthesia, two milliliters per kilogram per hour of Ringer's lactate has been given.

Hemodynamic including MAP and HR were documented at two, four, six, eight, ten minutes, and then every five minutes till the termination of arthroscope following spinal anesthesia. Furthermore, these variables have been documented following tourniquet deflation at the termination of the procedure.

Hypotension (systolic blood pressure below ninety millimeter Hg or below eighty percent of baseline) has been managed with an intravenous bolus of 6 milligrams ephedrine (Ephedrine sulphate USP 43, Misr company for pharmaceutical, Egypt), administered again if hypotension continued, and elevating infusion rate of lactated Ringer's solution acetate. Severe hypotension (systolic blood pressure below eighty millimeter Hg) has been managed with an intravenous bolus of 12 milligrams ephedrine and a hundred milliliters bolus of lactated Ringer's solution acetate. Bradycardia (heart rate below fifty beats per minute) has been managed with intravenous atropine

0.5 milligrams (Atropine sulphate USP 43, Misr company for pharmaceutical, Egypt), administered again as necessary.

The occurrence of vasovagal attacks throughout spinal needle insertion, post-spinal hypotension, reactive hypertension, bradycardia, severe hypotension, shivering, vomiting and nausea, needs of atropine as well as ephedrine during operation, and overall volume of fluids infused has been documented.

The 1^{ry} endpoint in the present study is the prevention of prevalence of hypotension identified as systolic blood pressure below ninety millimeter Hg or below eighty percent of baseline, following spinal anesthesia. Secondary endpoint includes measurement of serial alterations in HR and MAP following spinal anesthesia for detection of (duration to beginning of the 1st hypotension, the number of bradycardic episodes per case, and the proportion of cases without hypotension) needs of atropine, ephedrine, and infused fluids; and the incidence of complications such as reactive hypertension in addition to bradycardia, nausea and vomiting, shivering, as well as vasovagal attacks.

Sample size calculation:

This research base on a research performed by **Alseoudy et al. [18]** Epi Info STATCALC has been utilized to estimate the size of the sample through based on the following assumptions: - ninety-five percent 2-sided confidence level, with a power of eighty percent & α error of five percent. The final maximum size of the sample determined from the Epi- Info output was 82. Consequently, the size of the sample has been elevated to hundred individuals to account for any dropout cases throughout monitor.

$(Z\ a/2 + ZB \div p1 - p2)^2\ (p1q1+p2q2)$ **Takazawa & Morita [19]**

n = size of the sample

Z a/2 (The critical value which divides the central ninety –five percent of the Z distribution) =1.96

ZB (The critical value which divides the central twenty percent of the Z distribution) =0.84

p1 = (14.7%) patients who became hypotensive in midodrine group.

p2 = (38.1%) patients who became hypotensive in placebo group.

q = 1-p

Statistical analysis:

Information analysis has been conducted utilizing SPSS software, version 26 for Microsoft Windows (IBM Crop., NY, United States of America). Categorical information is expressed as percentages as well as numbers and has been analyzed utilizing the Chi-square test. The normality of the constant information has been examined utilizing the Kolmogorov Smirnov test. Information has normal distribution are expressed as Mean ± SD and has been examined utilizing the unpaired Student t-test. Skewed information are expressed as medians (quartiles) and has been examined utilizing the Mann Whitney U test. For repeated determined information (HR and MAP), difference analysis for repeated measure has been utilized to assess medication (between-groups factor) and duration (repeated measures) impact. The Bonferroni test has been utilized to adjust for numerous comparisons. A P value below 0.05 has been deemed significant.

RESULTS

117 cases have been examined for eligibility, 9 cases have been excluded for not meeting the inclusion criteria and 8 cases refused to participate in the study. 100 cases have been involved (50 cases in each group) and have been randomized to the groups of the research. All cases have been examined (50 in the midodrine group and 50 in the placebo group) (Fig. 1).

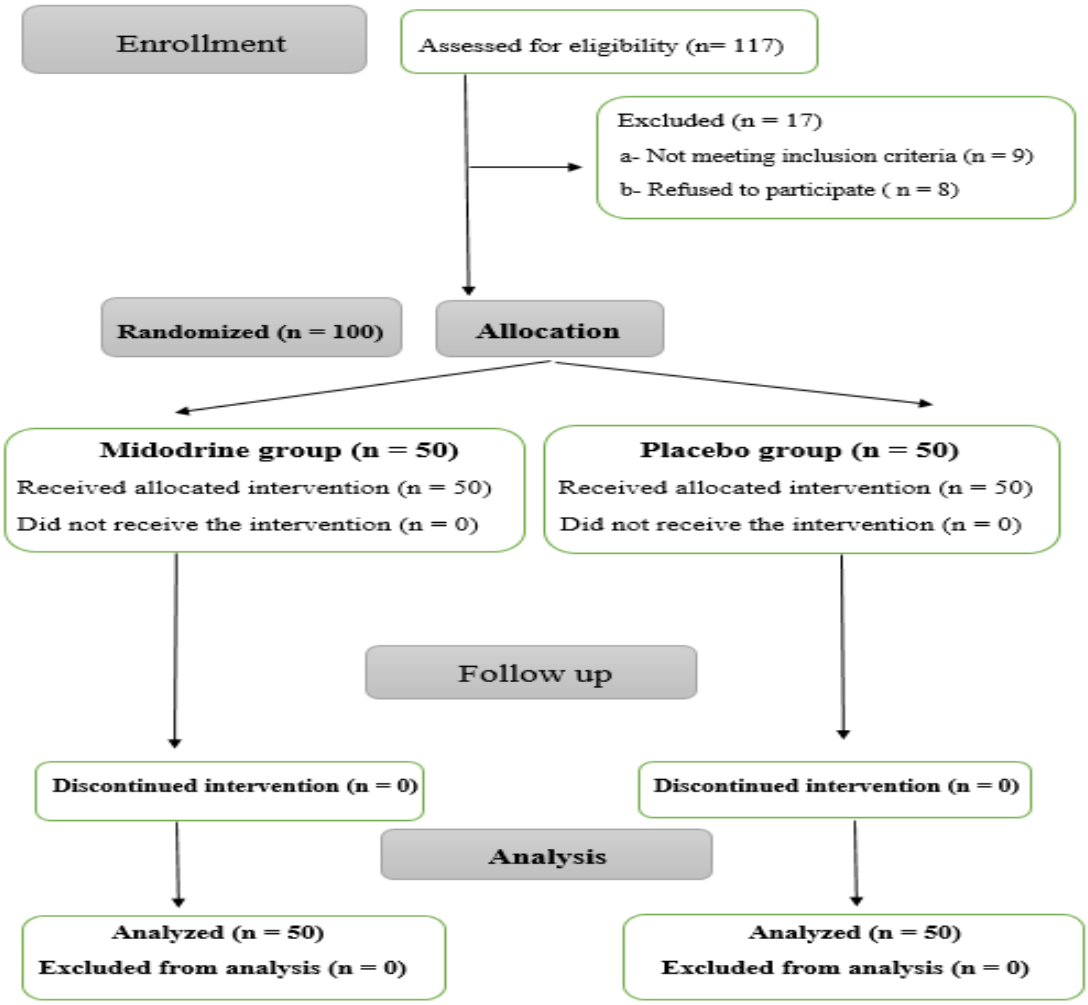

Fig. (1): Consort flow chart.

Patients' characteristics was insignificantly various among the two studied groups (Table 1). Also, baseline hemodynamic characteristics were similar among the 2 groups (Table 2).

Table (1): Patients' characteristics among two groups.

		Placebo (control) group (number= 50)	Midodrine group (number= 50)	p-value
Age (years)		35 (29 – 42)	34 (27 – 43)	0.431
Gender	**male**	34 (68%)	32 (64%)	0.352
	female	16 (32%)	18 (36%)	0.281
Weight (Kg)		77 ± 17	78 ± 16	0.651
Hight (Cm)		155 ± 14	157 ± 13	0.239

Information expressed as frequency (%), median (quartiles) and mean ±standard deviation.

Table (2): Baseline hemodynamic characteristics among two groups.

	Placebo(control) group (number= 50)	Midodrine group (number= 50)	p-value
Baseline HR (bpm)	80 ± 13	82 ± 12	0.295
Baseline MAP (mmHg)	87 ± 11	90 ± 10	0.319

* MAP, mean arterial pressure, HR, heart rate

In the midodrine group, 25 (50%) cases had hypotension following spinal anesthesia against 43 cases (86%) in the placebo group. The median intraoperative (quartile) overall dose of ephedrine was significantly reduced in midodrine group 12 (0-27) milligrams compared to placebo group (36 (21-45) milligrams, *P*-value: 0.001). The frequency of bradycardia in addition to hypertension were similar among the 2 groups. (Table 3). Furthermore, the HR and MAP were similar among the 2 groups. (Figures 2 and 3)

In the two groups, the MAP during surgery reduced in association with to the baseline reading, whereas the HR has been normally sustained (Figures 2 and 3).

Table (3): Results throughout surgery among two groups.

	Placebo (control) group (number= 50)	**Midodrine group (number= 50)**	**p-value**
Incidence of hypotension	43 (86%)	25 (50%)	0.001
Incidence of hypertension	4 (8%)	6 (12%)	0.600
Incidence of bradycardia	2 (4%)	9 (18%)	0.109
Ephedrine consumption (mg)	36 (21 – 45)	12 (0 – 27)	0.001

Information expressed as frequency (%) and median (quartiles).

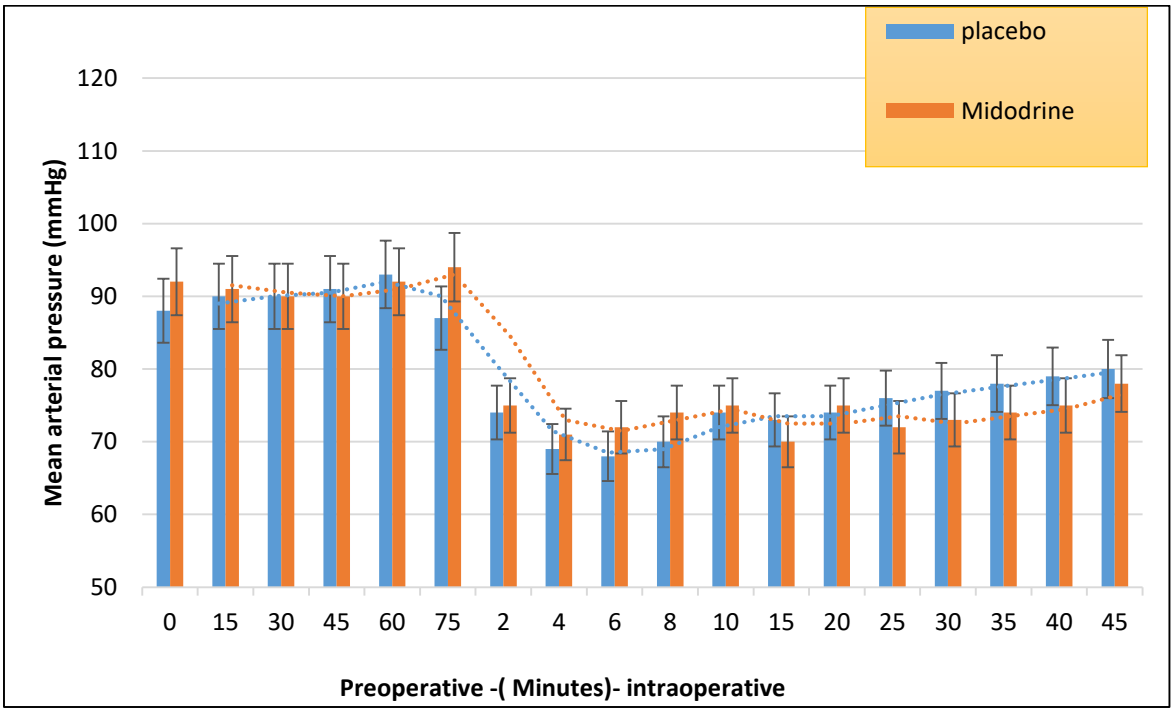

Fig. (2): MAP (preoperative – intraoperative) among two studied groups.

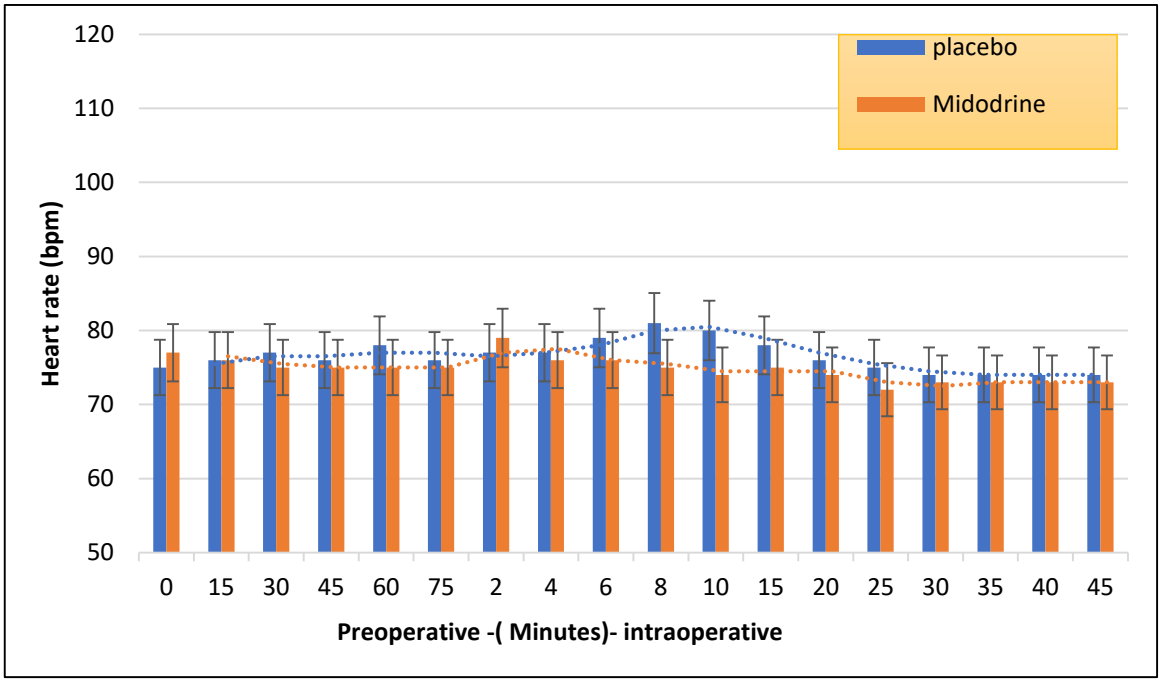

Fig. (3): Heart rate (preoperative – intraoperative) among two studied groups.

DISCUSSION

In this study we evaluated the preoperative oral administration of midodrine in patients subjected for knee arthroscopic surgeries under spinal anesthesia and we found that the oral midodrine 10 mg improved the intraoperative hemodynamics, the incidence of hypotension and decreasing ephedrine consumption indicating superior preservation of mean blood pressure in comparison with control placebo.

Midodrine is an agonist of oral α1-adrenoreceptor. In the process of metabolism, midodrine is converted into desglymidodrine. Desglymidodrine is a chemical that causes direct vasoconstriction of the venous and arterial blood vessels, which in turn results in an elevation in the systemic vascular resistance **[20].**

Numerous researches in various populations support the positive cardiovascular impacts of midodrine. Midodrine is primarily utilized for the management of chronic orthostatic hypotension **[12],** midodrine exhibited controversial outcomes in certain groups of cases like critically diseased cases with circulatory shock and operative cases following operation **[21].**

The utilization of midodrine for the avoidance of hypotension following spinal anesthesia wasn't sufficiently assessed. One randomized controlled trial demonstrated that the medication might diminish the frequency of post-spinal hypotension in different population **[18].**

Spinal anesthesia is a common option for knee operation and is frequently related to many complications as hypotension but less than general anesthesia **[22].** It has been observed that fluid loading alone will not remove spinal hypotension. Many factors control that as the amount and type of intravenous fluid should consider the impacts of sympathetic blockade, the volume status of the case prior to the spinal anesthesia in addition to any fluid losses during operation and following operation **[23].** Consequently, there is greater interest in the utilization of vasopressors, preferably prophylactic, to reduce hypotension severity as well as frequency **[24].**

We utilized midodrine 10 mg tablets administered 75 minutes prior to spinal anesthesia. The typical dose of the medication in earlier researches varied among 2.5- and 10 milligrams per dose **[12, 13, 17, 18].** The peak impact of midodrine varies among 1-2 hours after oral administration **[15].** The impacts of other doses and duration of medication giving need additional research.

Based on our study and its outcomes, we propose that the use of oral midodrine 10 mg tablets preoperatively would maintain stable blood pressure in adult patients undergoing knee arthroscopy undergoing spinal anesthesia. We selected the incidence of hypotension instead of the ephedrine consumption (vasopressor) as 1^{ry} result as the former rapidly reflects both the severity and incidence of post-spinal hypotension.

Advantages of our research included the randomized controlled design, sufficient size of the sample and a new group of surgery (knee arthroscopy). There are some limitations in the research like being conducted in single center, the utilization of 1 dose of the medication (10 mg), and excluding cases with significant cardiovascular pathologies. These restrictions necessitate future proper researches.

At the end, the utilization of oral midodrine 10 mg preoperatively reduced post-spinal hypotension and ephedrine (vasopressors) requirements and incidence of for knee arthroscopic surgeries.

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by [Medhat H Allam, Mohamed M Abo Elenin and Mohamed B. Mohamed Khedrawy]. All surgeries done by [Ahmed S. Ismail KHashaba]. Postoperative follow up done by [Mohamed B. Mohamed Khedrawy and Mohamed A Abu Hatab] Data analysis and interpretation were done by [Mahmoud A Abdel Salam, and Mohamed A Abu Hatab]. The first draft of the manuscript was written by [Medhat H Allam and Mohamed M Abo Elenin] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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