JOURNAL CLUB

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Original Contribution

Granisetron or ondansentron to prevent hypotension after spinal anesthesia for elective cesarean delivery: A randomized placebo-controlled trial

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BACKGROUND

- Spinal anesthesia is commonly used in cesarean section surgery
- The most important adverse effects (incidence of about 55–100%)
  - Hypotension
  - bradycardia

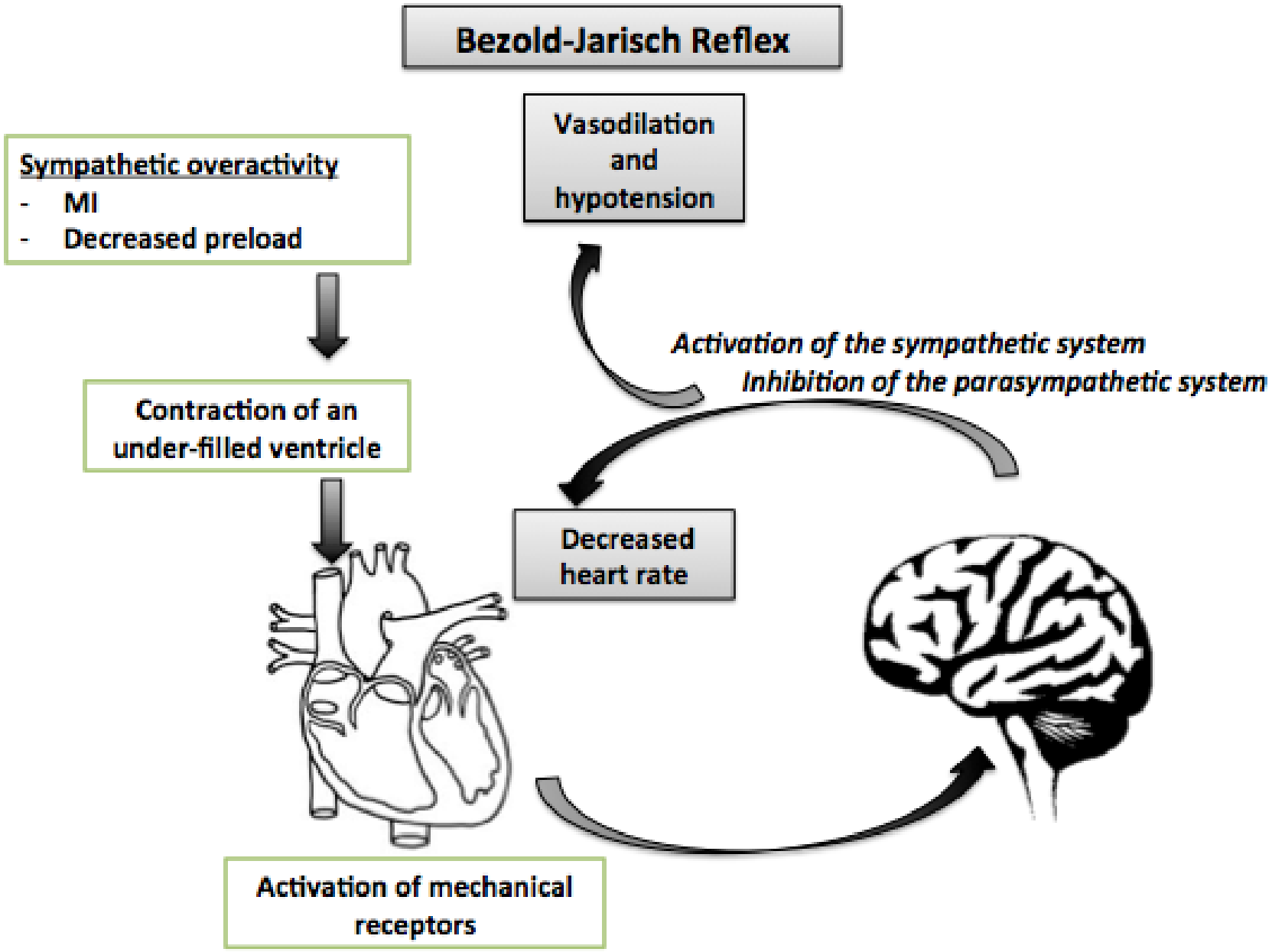
HYPOTENSION

- Maternal
  - Nausea and vomiting
  - Cardiovascular collapse
  - Loss of consciousness
  - Apnea
  - Aspiration of gastric contents
- Neonatal
  - Fetal acidosis
  - Fetal death

BACKGROUND

- Serotonin and 5-HT3 receptors play an important role in the occurrence of the BJR after spinal anesthesia
- Triad of the Bezold–Jarisch refex (BJR)
  - Bradycardia
  - Hypotension
  - Apnea

Bezold-Jarisch Reflex



BACKGROUND

- 5-HT3 antagonists may attenuate spinal anesthesia induced hypotension
  - inhibiting peripheral vasodilatation
  - alleviating the BJR
  - increasing venous return to the heart

BACKGROUND

- The hypothesized of this study
  - High doses of ondansetron or granisetron may be more effective in reducing the incidence of spinal anesthesia-induced hypotension in the obstetric population compared to placebo

BACKGROUND

- The primary outcome
  - A comparison of the ephedrine requirements among groups
- Secondary outcomes
  - A difference among groups in terms of blood pressure and heart rate values
  - The incidence of intraoperative nausea or vomiting
  - Motor and sensory block characteristics

METHODS

- Trial Design
  - A prospective randomized placebo-controlled double-blind study
  - Registered at ClinicalTrials.gov
  - Approved by the Ethical Committee of Ataturk University, Medical Faculty, Erzurum, Turkey
  - Informed consent from all participants

METHODS

- Inclusion criteria
  - Aged 18–45 years
  - ASA I or II
  - Elective cesarean section with combined spinal-epidural anesthesia (CSEA)

METHODS

- Exclusion criteria
  - Diabetes
  - Pregnancy-induced hypertension
  - Chronic hypertension
  - Fetal anomaly
  - History of allergy to study drugs
  - Psychiatric diseases
  - Coagulation abnormalities
  - Multiple pregnancies
  - Patients receiving SSRIs

METHODS

- Three groups (n = 40 for each group) were formed by randomization using a computer-generated table of random numbers
- Patients and investigators who were assessing the patients were blinded to the group allocation

METHODS

- NPO 8 hrs
- Peripheral IV access : 16/18 gauge cannula
- Preload Ringer's lactate solution 500 ml
- Patients' age, weight, height, ASA physical status, baseline values of NIBP, HR were recorded

METHODS

- An investigator prepared the studied drugs for an anesthetist
  - diluted with 10 ml normal saline
- The anesthetist injected the drugs 5 min before the CSEA procedure and performed intraoperative data collection
  - Group I received IV 8 mg ondansetron
  - Group II received IV 3 mg granisetron
  - Group III received IV 10 ml normal saline

METHODS

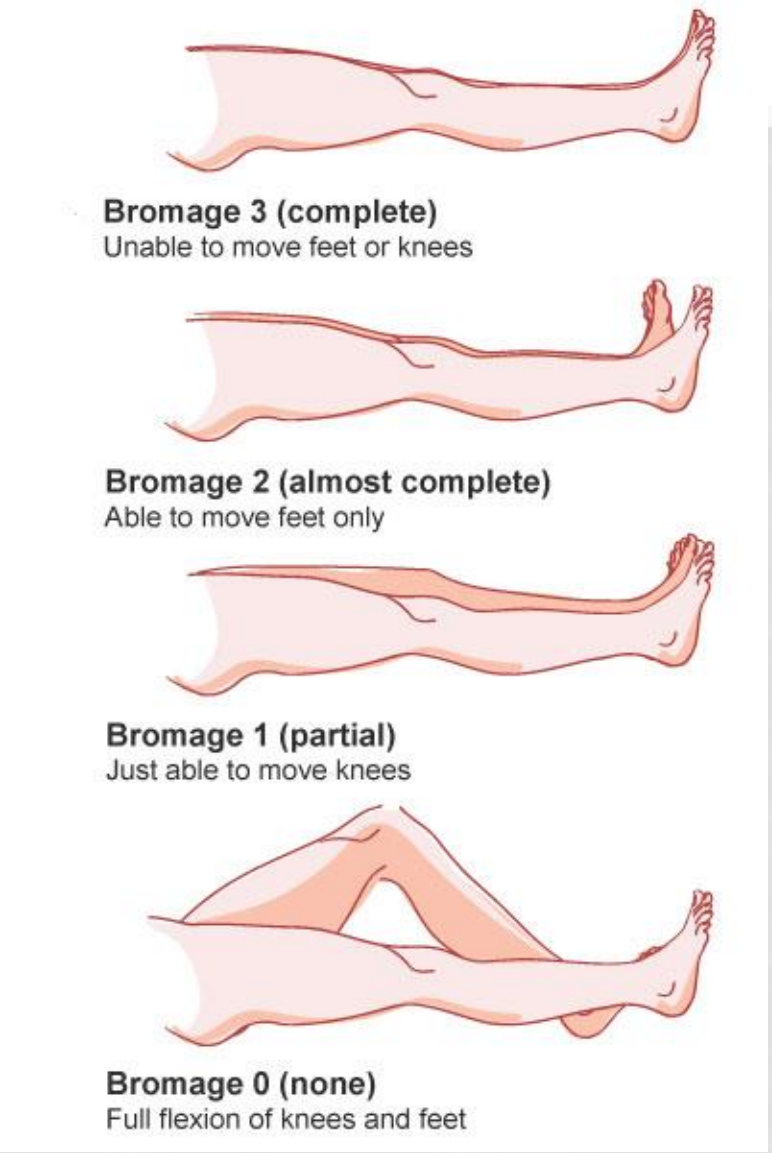
- CSEA in the sitting position was performed in all patients
  - Local anesthetic infltration (2% lidocaine)
  - 18-gauge Tuohy needle
  - Midline L2–3 or L3–4 intervertebral spaces using the loss-of-resistance technique with saline
  - 27- gauge pencil-point needle was inserted 0.5% isobaric bupivacaine 1.8 ml and 15 µg fentanyl
  - The epidural catheter was advanced 3–5 cm into the epidural space
- Patients were placed in the supine position
- The operating table was tilted 20◦ to the left

METHODS

- Sensory block level was evaluated via pinprick test (level of the T6 dermatome)
- Failed spinal anesthesia
  - Add 2% lidocaine 5 ml via the epidural catheter
  - Excluded from the study
- General anesthesia protocol was planned in case of three unsuccessful attempts to reach the intrathecal space

METHODS

- Motor block level was evaluated with the modifed Bromage scale



METHODS

- IV ephedrine (6 mg) : treat hypotension
  - ↓30% in SBP compared to preoperative values
- IV atropine (1 mg) : treat bradycardia
  - HR < 45 BPM
- IV metoclopramide (10 mg) : treat N/V

METHODS

- MAP and HR : record every 2 min for 20 min then every 5 min until the end of the operation
- Operation time
- Anesthetic complications
  - pruritus and nausea or vomiting
- Number of patients requiring epidural medication, ephedrine, and atropine
- Neonatal Apgar scores at 1 and 5 min
- Neonatal umbilical artery blood gas

METHODS

- Evaluated in the recovery room for 120 min by an independent observer who was blinded to the group assignment
  - Visual analogue scale : pain scores at rest
    - VAS > 3 : 0.1% bupivacaine 10 ml via the epidural catheter
  - Anesthesia-related side effects (N/V , headache)
  - Sensory block time (spinal injection to the recovery of T10 dermatome)

SAMPLE SIZE

- A sample size of 120 patients (40 in each group)
- Power of 90% , P value < 0.05

STATISTICAL ANALYSIS

- SPSS version 20 were used for analyses
- Demographic data : Bonferroni post-hoc test
- Compare groups : Chisquare test
- Statistical significance was defined as $P < .05$

RESULTS

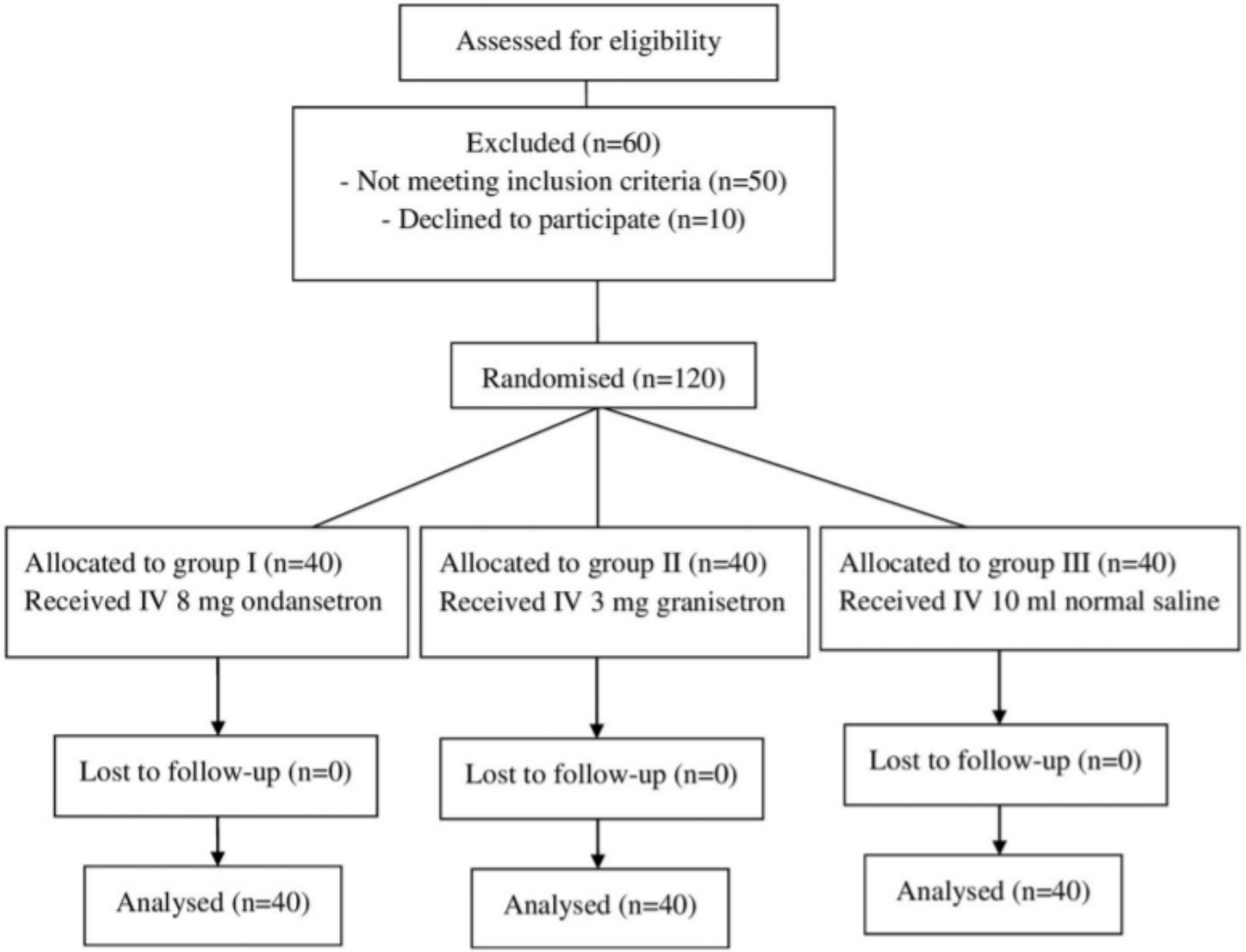


Fig. 1. Flow chart of study participants.

RESULTS

Table 1
Demographic characteristics of the patients.

	Group I ($n = 40$)	Group II (n = 40)	Group III (n = 40)	P value
Age (years)	32.00 ± 5.22	30.00 ± 3.97	31.52 ± 5.67	0.180
Height (cm)	158.80 ± 4.56	158.60 ± 3.98	158.07 ± 3.12	0.697
Weight (kg)	80.07 ± 6.24	78.22 ± 4.93	79.22 ± 6.99	0.403
ASA I/II (n)	25/15	23/17	26/14	0.902
Operation time (min)	32.72 ± 2.45	33.35 ± 2.35	33.42 ± 2.29	0.353
Mean blood pressure (mmHg)	94.35 ± 5.89	93.87 ± 11.98	92.07 ± 13.39	0.618
Baseline heart rate (bpm)	95.10 ± 5.83	94.97 ± 5.73	95.00 ± 6.10	0.995
Baseline SPO_2 value	94.35 ± 5.89	93.87 ± 11.98	92.07 ± 13.39	0.618

Group I: Received IV 8 mg ondansetron, Group II: Received IV 3 mg granisetron, and Group III: Received IV 10 ml normal saline.
Data were expressed as mean ± SD or n. By ANOVA test, $p < 0.05$, statistically significant.

RESULTS

The ephedrine requirement in Group III was significantly higher than in Groups I (P = 0.033) and II (P < 0.001)

The ephedrine requirement in Group II was lower than in Group I (not statistically significant (P = 0.055))

T10 (min) med (min-max)	(75–300)	(120–230)	(100–230)	
Ephedrine requirement n, (%)	20, (50.0)[β]	12, (30.0)*	29, (72.5)	0.001[φ]
Atropine requirement n, (%)	4, (10)	2, (5)	2, (5)	0.602[φ]
Intraoperative nausea-vomiting n, (%)	4, (10)*	8, (20)[µ]	19, (47.5)	<0.001[φ]
Shivering n, (%)	5, (12.5)	7, (17.5)	4, (10)	0.550[φ]
VAS scores at 30 min.	2 (1–3)	2 (1–3)	2 (1–3)	0.137
VAS scores at 1 h	2 (1–3)	2 (1–3)	2 (1–3)	0.376
VAS scores at 2 h	2 (1–3)	2 (1–3)	3 (1–3)	0.176

Group I: Received IV 8 mg ondansetron, Group II: Received IV 3 mg granisetron, and Group III: Received IV 10 ml normal saline. Data were expressed as med (min-max) or n, %. [ε]ANOVA test, [φ]Chi-squared test; $p < 0.05$, statistically significant. *$P < 0.001$, [µ]$P = 0.009$, [β]$P = 0.033$; compared with Group III.

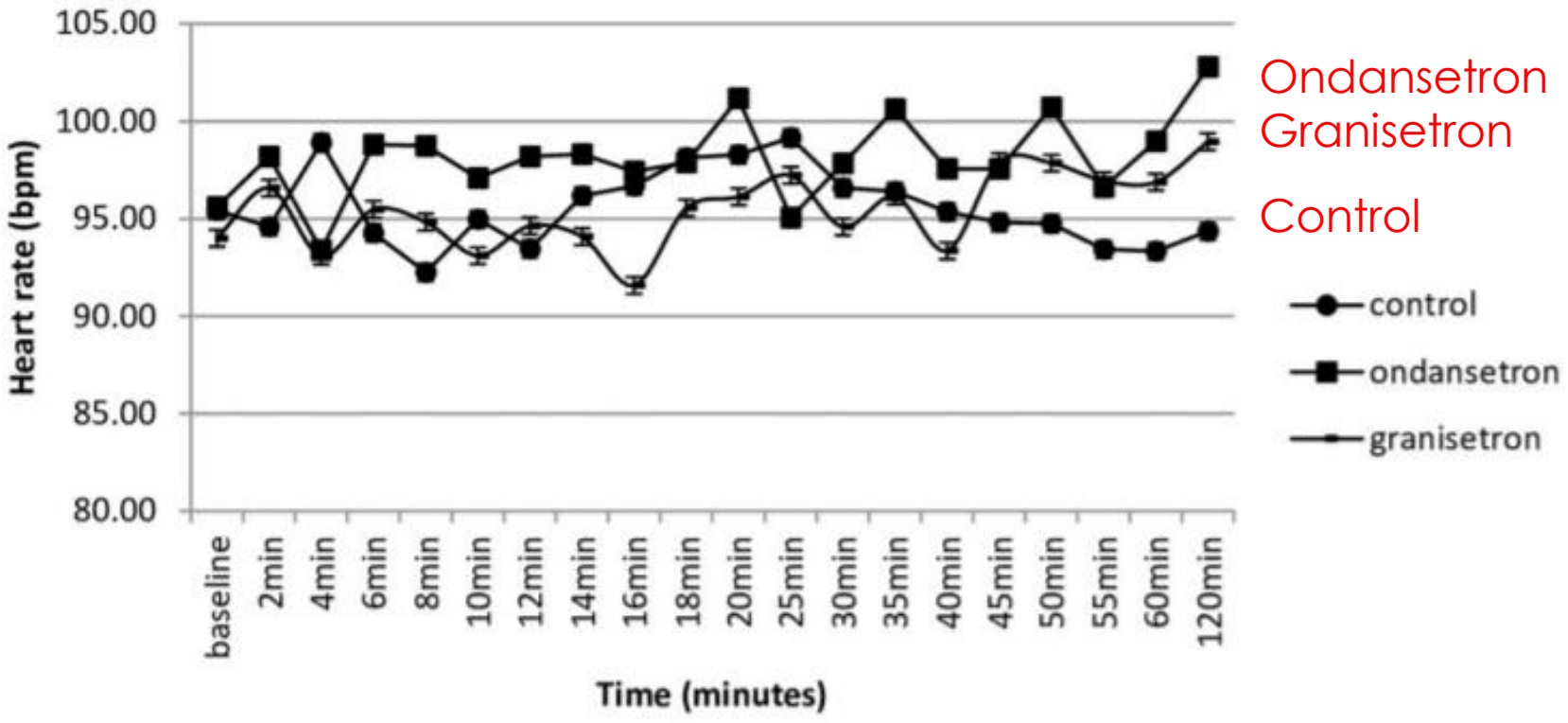
Table 3
Comparison of MAP (mmHg) values among groups at different times after spinal injection.

Time (minutes)	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	P value
Baseline	94.35 ± 5.89[α]	93.87 ± 11.98[α]	92.07 ± 13.39[α]	0.618
2	88.25 ± 12.83	83.75 ± 12.39	86.22 ± 13.67	0.303
4	82.55 ± 13.83	79.65 ± 16.30	84.35 ± 18.24	0.428
6	80.17 ± 13.77	83.67 ± 17.53	79.45 ± 16.40	0.452
8	82.57 ± 14.77	86.02 ± 11.70	78.65 ± 12.83	0.083
10	79.75 ± 12.96	84.55 ± 10.57[#]	77.50 ± 13.55	0.038
12	80.50 ± 12.08	82.02 ± 11.32	77.30 ± 14.24	0.236
14	81.60 ± 12.37	79.67 ± 11.82	79.07 ± 13.14	0.640
16	82.55 ± 9.67	77.50 ± 13.12	77.97 ± 12.38	0.113
18	82.27 ± 8.32[λ]	76.62 ± 14.15[μ]	76.72 ± 11.18	0.045
20	77.37 ± 10.08	79.27 ± 11.23	78.27 ± 11.11	0.735
25	76.85 ± 8.82	81.55 ± 12.71	79.62 ± 10.77	0.157
30	77.95 ± 8.61	79.85 ± 15.29	78.35 ± 11.03	0.756
35	80.62 ± 8.96	83.07 ± 8.91	80.05 ± 12.17	0.369
40	81.00 ± 10.65	83.75 ± 7.39	79.10 ± 11.32	0.114
45	78.97 ± 16.00	83.72 ± 7.86	79.50 ± 9.94	0.147
50	83.70 ± 79.05	85.12 ± 7.19	80.87 ± 10.99	0.453
55	82.65 ± 9.91	85.85 ± 7.33	82.57 ± 8.24	0.153
60	82.47 ± 10.01	87.65 ± 7.55[*]	84.05 ± 9.23	0.034
120	85.40 ± 8.93	87.42 ± 7.86	85.02 ± 9.05	0.412

Group I: Received IV 8 mg ondansetron, Group II: Received IV 3 mg granisetron, and Group III: Received IV 10 ml normal saline. MAP: Mean Arterial Pressure. Data were expressed as mean ± SD. By ANOVA test, $p < 0.05$, statistically significant.

[*] $P = 0.011$, [μ]P = 0.030, compared with Group I; [#]$P = 0.013$, [λ]P = 0.033, compared with Group III. [α]P < 0.001, compared with MAP values at all time points during surgery and postoperatively in each group.

RESULTS



Ondansetron
Granisetron

Control

Fig. 2. The comparison of heart rate values in the three groups.

THE SECONDARY OUTCOME

- A difference among groups in terms of blood pressure and heart rate values
  - No significant differences among the groups in terms of HR values
- The incidence of intraoperative nausea or vomiting
  - Significantly lower in Groups I and II than in Group III
- Motor and sensory block characteristics
  - The time needed to reach T6 dermatome sensory level was similar among groups
  - 15 minutes after spinal injection, all patients had a modifed Bromage scale of 3
  - No significant differences in terms of the time of sensory block regression to T10

DISCUSSION

- Prophylactic IV administration of 3 mg granisetron or 8 mg ondansetron before spinal anesthesia results in a significantly lower ephedrine requirement compared to prophylactic IV administration of saline
- Significantly higher frequency of nausea or vomiting in the control group than in the therapeutic groups

DISCUSSION

- Rashad and Farmawy
  - IV 4 mg ondansetron before a subarachnoid block leads to significantly lower vasopressor use compared with IV 1 mg granisetron
- Behdad et al.
  - IV 3 mg granisetron immediately before spinal anesthesia had no effect on spinal anesthesia-induced hypotension and bradycardia compared with a placebo in elective C/S

Rashad MM, Farmawy MS. Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing cesarean section. Egypt J Anaesth 2013;29: 369–74.
Behdad S, Saberi V, Saberi H. Investigating the effect of granisetron on the prevention of hypotension after spinal anesthesia in cesarean section. JBCM 2016; 5:22–5

DISCUSSION

- A meta-analysis by Heesen et al.
  - Suggested prophylactic administration of 5-HT3 antagonists is effective in reducing the incidence of hypotension and bradycardia in the obstetric population
  - This meta-analysis did not reveal the specific doses of these drugs to prevent spinal anesthesia-induced hypotension in the obstetric population

Heesen M, Klimek M, Hoeks SE, Rossaint R. Prevention of spinal anesthesiainduced hypotension during cesarean delivery by 5-hydroxytryptamine-3 receptor antagonists: a systematic review and meta-analysis and meta-regression. Anesth Analg 2016;123:977–88.

DISCUSSION

- Eldaba and Amr , Chatterjee et al.
  - Granisetron 1 mg administered before a subarachnoid block may attenuate hypotension
- Naithani et al. , Khalifa
  - Ondansetron 4 mg is more effective than 1 mg granisetron in reducing hypotension

Eldaba AA, Amr YM. Intravenous granisetron attenuates hypotension during spinal anesthesia in cesarean delivery: a double-blind, prospective randomized controlled study. J Anaesthesiol Clin Pharmacol 2015;31:329–32.
Naithani B, Khan MP, Singh V, Hemlata Dube M, Mishra NK. Comparision of granisetron and ondansetron for attenuation of subarachnoid block induced hypotension in parturients undergoing elective caesarean section: a randomized double-blind placebo-controlled study. Int J Adv Res 2018;9:15655–61.

DISCUSSION

- Previous study suggest that high doses of granisetron or ondansetron may be more effective than their lower doses in eliminating the BJR

- In the present study both granisetron and ondansetron were well tolerated in all patients, and no maternal or neonatal side effects were observed

- Granisetron is c
  receptor antag
- Granisetron mo
  hemodynamic

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Comparison of MAP (mmHg) values among groups at different times after spinal injection.

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DISCUSSION

- Sensory block time of spinal anesthesia
  - Neither drug affected the sensory block time or the time of fixation for the sensory level
  - Choudhary et al. : no significant differences in the time needed to achieve maximum sensory level and sensory block (granisetron and palonosetron)
  - Naithani et al. : granisetron prior to intrathecal bupivacaine provides faster sensory regression compared to IV ondansetron

Choudhary J, Mahajan R, Mahajan A, Gulati S, Mehta A, Nazir R. Comparison of IV granisetron and IV palonosetron on hemodynamics and sensory and motor block after spinal anesthesia with hyperbaric bupivacaine in patients undergoing abdominal hysterectomy. J Anaesthesiol Clin Pharmacol 2019;35:176–81.
Naithani B, Khan MP, Singh V, Hemlata Dube M, Mishra NK. Comparision of granisetron and ondansetron for attenuation of subarachnoid block induced hypotension in parturients undergoing elective caesarean section: a randomized double-blind placebo-controlled study. Int J Adv Res 2018;9:15655–61.

LIMITATION

- Small patient population
- The standardization of the dose of subarachnoid isobaric bupivacaine
  - 9 mg 0.5% isobaric bupivacaine and 15 μg fentanyl
- Further studies are needed to investigate the effects of 5-HT3 antagonists on spinal anesthesia-induced hypotension in patients undergoing cesarean with different intrathecal medications and adjuvants

CONCLUSION

- Prophylactic IV administration of high doses of granisetron (3 mg) or ondansetron (8 mg) before spinal anesthesia results in a significantly lower ephedrine requirement compared to the placebo without any side effects on the mother and neonate

CRITICAL APPRAISAL : RCT

- Does this study address a clear question?

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

CRITICAL APPRAISAL : RCT

- Are the results of this single trial valid?

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?	✓		
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

CRITICAL APPRAISAL : RCT

- Are the results of this single trial valid?

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes ✓	Can't tell	No
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

CRITICAL APPRAISAL : RCT

- What were the results?

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	?
10. How precise were the results? Were the results presented with confidence intervals?	YES

CRITICAL APPRAISAL : RCT

- Can I apply these valid, important results to my patients?

11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?	**Yes** ✓	**Can't tell**	**No** ✓
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?	✓ ✓		