The Effect of Subanaesthetic Dose of Intrathecal Ketamine with Bupivacaine on Blood Pressure after Spinal Anaesthesia

تأثير جرعة تحت التخديرية من الكيتامين داخل القراب (السائل الشوكى) مع البوبيفاكايين على ضغط الدم بعد التخدير الشوكي

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Abstract

Background:

Spinal anaesthesia is commonly used in many surgeries especially caesarean section (CS). It is one of the most common complications of spinal anesthesia, and it is a challenge for anesthesiologists. It refers to low blood pressure after spinal anaesthesia hypotension, which may reach the point of shock that need rapid intervention to decrease peri-operative morbidity and mortality. A lot of techniques have been described to prevent such hypotension, but an effective method is yet to be found. Ketamine is one of the anaesthetic drugs that can be injected intrathecally due to its synergistic effect with the effects of local and analgesic anesthesia and has a sympathetic stimulating effect that can raise blood pressure.

Objectives:

The aim of the study is to evaluate the effect of using a sub-anesthetic dose of ketamine intrathecally on hypotension that follow spinal anaesthesia especially in CS delivery and other surgeries that receive spinal anaesthesia.

Methods:

This double-blinded randomized prospective study was conducted on 40 participation patients who were ASA 1 and 2, all the patients received spinal anesthesia. The patients were then randomly divided into two equal groups (n= 20 in each); ketamine group received a sub- anesthetic dose of ketamine of 0.5 mg/ kg intrathecal with local anaesthetic bupivacaine10 - 15 mg (2-3 ml 0.5%) and control (non ketamine) group received the same dose of local anaesthetics without ketamine. Mean arterial blood pressure (MAP) was recorded at baseline (5 minutes prior to the intrathecal injection), and at 5, 10, 15, 20 and 30 minutes after the injection. Incidences of hypotension and severe hypotension were recorded. The total doses of ephedrine and volume of infused fluid as cohydration were also recorded.

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Results:

Compared to the control group, mild hypotension and severe hypotension were less frequent among the ketamine group. MAP was higher among ketamine group with statistical significance at 5 and 10 minutes. The number of cases who received ephedrine and the total ephedrine doses were significantly lower among the ketamine group. The volume of infused fluid and number of cases who received that volume were also significantly lower among the ketamine group.

Conclusion:

It is concluded that ketamine in a sub-anaesthetic dose intrathecally is an effective agent that can be used for alleviation of post-spinal anesthesia hypotension in patients undergoing spinal anaesthesia especially with CS delivery.

Key words: Spinal anesthesia, hypotension, intrathecal ketamine, ephedrine.

الملخص:

يستخدم التخدير النخاعي بشكل شائع في العديد من العمليات الجراحية وخاصة العمليات القيصرية (CS). يعد أحد أكثر مضاعفات التخدير النخاعي شيوعًا، ويمثل تحديًا لأطباء التخدير، هو انخفاض ضغط الدم بعد التخدير النخاعي، والذى قد يصل لحد الصدمة مما يحتاج إلى تدخل سريع لتقليل المضاعفات المرضية المرضية والوفيات المحيطة بالجراحة. تم وصف الكثير من التقنيات لمنع انخفاض ضغط الدم هذا، ولكن لم يتم العثور على طريقة فعالة بعد. الكيتامين هو أحد أدوية التخدير التي يمكن حقنها داخل القراب بسبب تأثيره التآزري مع تأثيرات التخدير الموضعي والمسكن وله تأثير تحفيزي ودي يمكن أن يرفع ضغط الدم.

الأهداف:

الهدف من هذه الدراسة هو تقييم تأثير استخدام جرعة تحت التخدير من الكيتامين داخل القراب على انخفاض ضغط الدم الذي يتبع التخدير الشوكي خاصة في عمليات الولادة القيصرية والعمليات الجراحية الأخرى التي تتلقى التخدير الشوكي.

الطرق:

تم إجراء هذه الدراسة الاستباقية العشوائية مزدوجة التعمية على 40 مريضًا مشاركًا كانوا ASA 1 و2، وقد تلقى جميع المرضى التخدير الشوكي. ثم تم تقسيم المرضى بشكل عشوائي إلى مجموعتين متساويتين (ن = 20 في كل منهما)؛ تلقت مجموعة الكيتامين جرعة تحت التخدير من الكيتامين 0.5 ملغم / كغم داخل القراب مع مخدر موضعي بوبيفاكايين 15-10 ملغم (3-2 مل 0.5٪) وتلقت مجموعة السيطرة (غير الكيتامين) نفس الجرعة من التخدير الموضعي بدون الكيتامين. تم تسجيل متوسط ضغط الدم الشرياني (MAP) عند خط الأساس (5 دقائق قبل الحقن داخل القراب)، وبعد 5 و10 و15 و20 و30 دقيقة من الحقن. تم تسجيل حالات انخفاض ضغط الدم وانخفاض ضغط الدم الشديد. كما تم تسجيل الجرعات الإجمالية للإيفيدرين وحجم المحاليل الوريدية الكلية المعطاة للمريض.

النتائج:

بالمقارنة مع المجموعة الضابطة، كان انخفاض ضغط الدم الخفيف وانخفاض ضغط الدم الشديد أقل تواترا بين مجموعة الكيتامين. كان MAP أعلى بين مجموعة الكيتامين مع دلالة إحصائية عند 5 و 10 دقائق. وكان عدد الحالات التي تلقت الإيفيدرين وإجمالي جرعات الإيفيدرين أقل بكثير بين مجموعة الكيتامين. كما كان حجم المحاليل الوريدية المحقونة وعدد الحالات التي تلقت هذا الحجم أقل بشكل ملحوظ بين مجموعة الكيتامين.

الخلاصة:

خلصت الدراسة إلى أن الكيتامين في جرعة تحت التخديرية داخل القراب هو عامل فعال يمكن استخدامه للتخفيف من انخفاض ضغط الدم بعد التخدير النخاعي في المرضى الذين يخضعون للتخدير النخاعي وخاصة مع حالات العمليات القيصرية.

الكلمات المفتاحية: التخدير الشوكي، انخفاض ضغط الدم، الكيتامين داخل القراب، الايفيدرين

Introduction

Spinal anesthesia started since 1898 in Germany by August Bier (**Olawin and Das**, **2022**) and it has many advantages over general anesthesia such as reduction of stress responses, less harmful effect on lungs and breathing system, good pain relief, reduced risk for heart complicacations, reduced amount of blood loss, low cost, decreased morbidity and mortality rates in high risk patients and shortened the overall hospital stay by allowing immediate ambulation after surgery (**Kathirvel et al**, **2000**). Spinal anaesthesia is commonly used in many surgeries specially caesarean section (**Reynold et al**., **2005**).

Hypotension is the most common complication of spinal anesthesia, which represents a challenge for anaesthesiologists. It tends to cause even a shock that needs rapid intervention to decrease perioperative morbidity and mortality (**Dalton et al**., **2011**). Hypotension was reported to occur due to blockade of preganglionic sympathetic fibers which in turn causes reduction in cardiac output and mean arterial pressure (MAP) and thus decrease in perfusion to vital organs (**Hanss et al**., 2006).

A lot of techniques have been described to overcome such hypotension. These techniques include infusion of iv fluid, lower limb compression, sympathomimetic drugs as ephedrine, the use **of phenylephrine** and ondanestrone (**Chooi et al**, **2017**, **Ferré et al**, **2020**).

Ketamine is a non- competitive antagonist at the N-Methyl-D-Aspartate (NMDA) receptor (**Monteggia and Zarate**, **2015**), stimulating the cardiovascular system with high blood pressure, heart rate and cardiac output. These changes are not related to the dose of ketamine (**Donicke et al**., **1992**). The mechanism by which ketamine stimulates the cardiovascular system seems to be central rather than peripheral (**Issei et al**., **2021**). Ketamine attenuates the baroreceptor effect by blocking the NMDA receptors in the nucleus tractus solitarius. This effects results in a centrally mediated sympathetic response (**Ogawa et al**., 1 9 9 3) .

Ketamine is a structural analogue of phenyl cyclidine that has been used as anesthetic in veterinary medicine (**Butterworth**, **2022**). Ketamine is used intrathecally to produce synergistic anaesthetic effect with bupivacaine (local anesthetic) and to induce potent analgesic properties. When ketamine is injected with bupivacaine intrathecally in small dose, it can produce central stimulation of sympathetic nervous system and inhibition of norepinephrine reuptake after release at nerve terminal (**Kathirvel**, **etal 2000**). Ketamine's indirect stimulatory effect may be beneficial to patients with acute shock (**Butterworth et al**., **2022**).

Our study is aimed to evaluate the effect of using a sub-anesthetic dose of ketamine intrathecally on hypotension that follow spinal anaesthesia and whether it is possible to alleviate the hypotensive effect of spinal anaesthesia without using more fluid infusion and vasopressors.

n=**methods** =384

This prospective randomized double blinded prospective study was conducted in Kara General Hospital in Marib city, between October, 2023 and January 2024. The patients were of physical status ASA 1 and 2 (American society of anesthesiologists) normal and mild medical diseased patients, aged between 18 and 55 years. Exclusion criteria included contraindication to spinal anesthesia.

A total of 40 male and female patients were divided into two groups, patients undergoing different surgeries using spinal anesthesia, and female patients surgeries were mainly cesarean section, whether elective or emergent.

In ketamine group (K group), ketamine was given in a dose of 0.5 mg/ kg intrathecally (**Sohnen et al**., **2021**) with bupivacaine 10-15 mg (2-3 ml 0.5%). In non-ketamine group (N group), bupivacaine (the same dose) was given without Ketamine.

An iv infusion of ringer lactate solution (5- 10 ml/kg) prior to subarachnoid block was started in the operating room in all patients. Standard anesthe-

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sia monitoring was applied. Spinal anesthesia was performed with a gauge 25 Quinke needle.

Mean arterial pressure (MAP) was recorded, 5 minutes prior to the intrathecal injection and then at 5 min,10 min, 15min, 20 min and 30 minutes after spinal anesthesia. Incidence of hypotension, with MAP (mean arterial pressure) ≤ 65 mmHg, and severe hypotension, with MAP ≤ 55 mmHg, were recorded. Ephedrine 5-10 mg (**Butterworth et al., 2022**) **was** administered, repeated when needed. The number of cases who received ephedrine and total dose of ephedrine were recorded in addition to the total volume of infused fluid as cohydration and the number of cases who received ephedrine.

Sample Size

It was assumed that MAP below 65 mmHg would be clinically significant among two groups with two sided comparisons. Based on this assumption, a sample size for each group was calculated to be 18 at an alpha error of 0.05 and a beta error of 0.1 (power of 90%). Twenty patients were enrolled in each group to accommodate for possible dropouts.

Statistical Methods

The collected data were presented as mean value ± standard deviation and analyzed using SPSS 26 statistical program. Comparison of studied groups was carried out using t-test and Chi-square test. P values <0.05 were considered statistically significant and highly significant if < 0.01.

Results The mean arterial pressure:

In ketamine group, MAP was ≤ 65 mmHg in 4 (20%), 3 (15%), 7 (35%, of which 2 were with MAP ≤ 55 representing 10% of total) and 0 patients after 5, 10, 15 and 20 minutes of anaesthesia respectively. Correspondingly, in non-ketamine group MAP was ≤ 65 mmHg in 10 (50%, of which 6 were with MAP < 55 representing 30% of total), 15 (75%, of which 6 were with MAP < 55 representing 30% of total), 10 (50%, of which 4 were with MAP ≤ 55 repre-

senting 20% of total) and 7 (35%, of which 1 was with MAP < 55 representing 5% of total) patients after 5, 10, 15 and 20 minutes of anaesthesia respectively. These results reflect less incidence of hypotension in ketamine group in which MAP showed higher levels than non-ketamine group. The difference between 2 groups was highly statistically significant after 5, 10 minutes of anaesthesia (P=0.001, 0.002 respectively) statistically insignificant 15 and 20 minutes of anaesthesia (P=0.067, 0.1 respectively).

Table (1): Number and % of cases with MAP ≤ 65 mmHg:

Group		After anes- (thesia (5 min	After an- esthesia (10 (min	After an- esthesia (15 (min	After anesthesia ((20 min
Ketamine group	No. of cases	4	3	with 2) 7 (MAP ≤ 55	0
	%	20%	15%	35%	0
Non ketamine group	No. of cases	with 6) 10 (MAP < 55	with 6) 15 (MAP < 55	with 4) 10 (MAP ≤ 55	with 1) 7 MAP ≤ (55
	%	50%	75%	50%	35%

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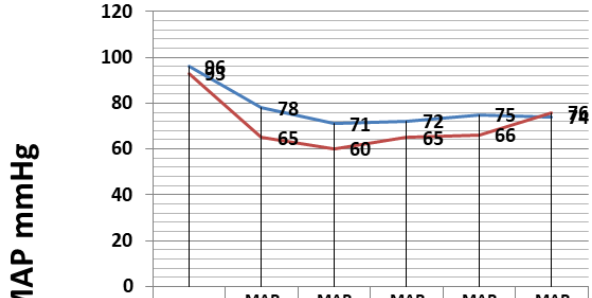
Table (2): Difference between the mean of MAP in ketamine and non-ketamine groups:

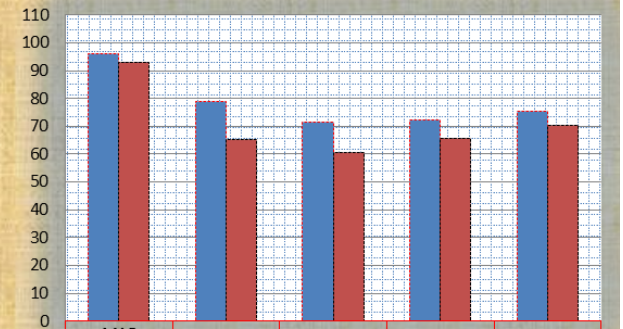
Ketamine		N	Mean	Std. Deviation	Std. Different	Confidence Interval 95% Lower	Confidence Interval 95% Upper	t-test	P. vaue
MAP before anesthesia	Ketamine (k) group	20	96.10	7.433	3	93.00	99.25	1.28	0.21
	Non ketamine (non k) group	20	93.05	7.584		89.62	96.71		
MAP After anesthesia (5 (min	Ketamine (k) group	20	78.85	10.639	13	74.19	83.29	3.44	0.001
	Non ketamine (non k) group	20	65.35	13.971		59.50	71.66		
MAP After anesthesia (10 (min	Ketamine (k) group	20	71.65	6.055	11	69.00	74.11	4.46	0.002
	Non ketamine (non k) group	20	60.35	9.571		56.22	64.52		
MAP After anesthesia (15 (min	Ketamine (k) group	20	72.10	11.516	6	67.39	76.92	1.88	0.067
	Non ketamine (non k) group	20	65.60	10.210		60.74	69.94		
MAP After anesthesia (20 (min	Ketamine (k) group	20	75.30	6.705	5	72.71	78.25	1.31	0.1
	Non ketamine (non k) group	20	70.25	15.824		64.58	77.10		

Fig. (1): Difference between MAP in ketamine and non ketamine groups



	MAP before anesthesia	MAP after anesthesia (5minutes)	MAP after anesthesia (10minutes)	MAP after anesthesia (15minutes)	MAP after anesthesia (20minutes)	MAP after anesthesia (30minutes)
MAP with ketamine	96	78	71	72	75	74
MAP without ketamine	93	65	60	65	66	76

Fig. (2): Difference between MAP in ketamine and non ketamine groups



	MAP before anaesthesia	MAP after (5 min)	MAP after (10 min)	MAP after (15 min)	MAP after (20 min)
Ketamine	96.1	78.85	71.65	72.1	75.3
Non Ketamine	93.05	65.35	60.35	65.6	70.25

A) Ephedrine use:

In ketamine group, the number of cases who received ephedrine was less than that who didn't receive ephedrine. 4 patients (20%) needed ephedrine (in a dose of ≤ 10 mg) and **16** patients (80%) did not need ephedrine. Whereas, in non-ketamine group, the number of cases who received ephedrine was more than that of the cases who did not receive ephedrine. 16 patients (80%) needed ephedrine (**7 of them representing** 43.8% needed ephedrine in a dose of ≤ 10 mg and 9 representing 56.2% needed ephedrine in a dose of >10 mg) and 4 patients (20%) did not need ephedrine. The difference between 2 groups was highly statistically significant (P= 0.0001) for the number and statistically significant (P=0.043) for the dose. The results are shown in tables and Figs.3 & 4.

Table (3): Number of patients who received ephedrine in ketamine and non-ketamine groups:

Ketamine * Ephedrine Crosstabulation		Ephedrine				Total		X2	P. vaue
		Yes		No					
		N	%	N	%	N	%		
	Ketamine group	4	20%	16	80%	20	100%	14.4	0.0001
	Non ketamine group	16	80%	4	20%	20	100%		

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Figure (3): Number of patients who received ephedrine in ketamine and non–ketamine groups:

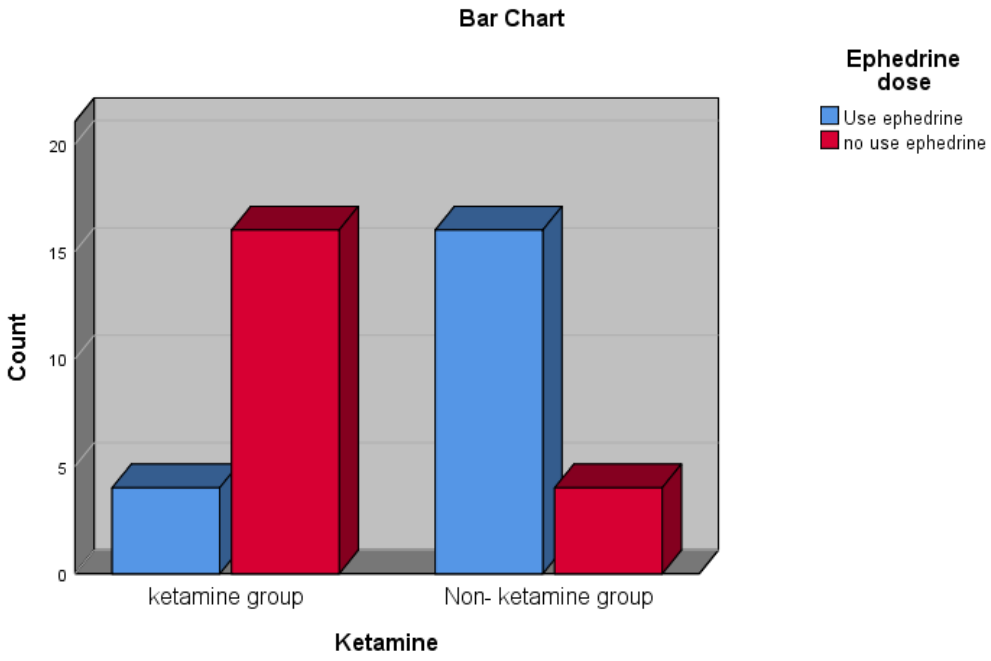

Table (4): Difference between ketamine and non-ketamine groups in dose of ephedrine and number of cases who received such doses:

	EPHEDRINE DOSE			Total	X2	P.value
	mg 10 ≥		mg 10<			
Use ketamine	N	4	0	4	4.091	0.043
	%	100.0%	0.00%	100.00%		
No use ketamine	N	7	9	16		
	%	43.8%	56.2%	100.00%		

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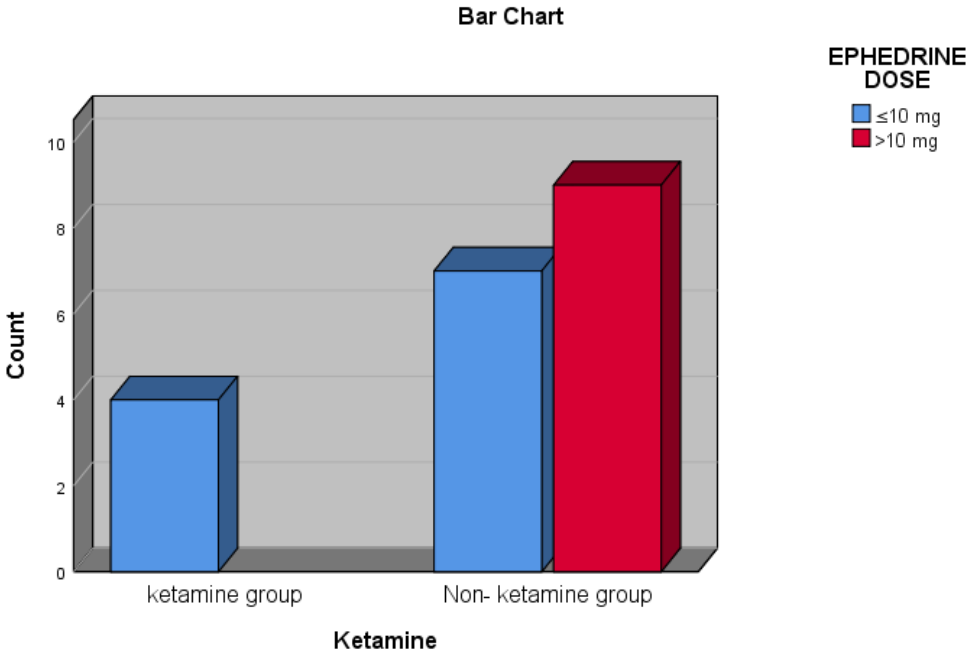
Figure (4): **Dose of ephedrine used in Ketamine and non–ketamine groups**:

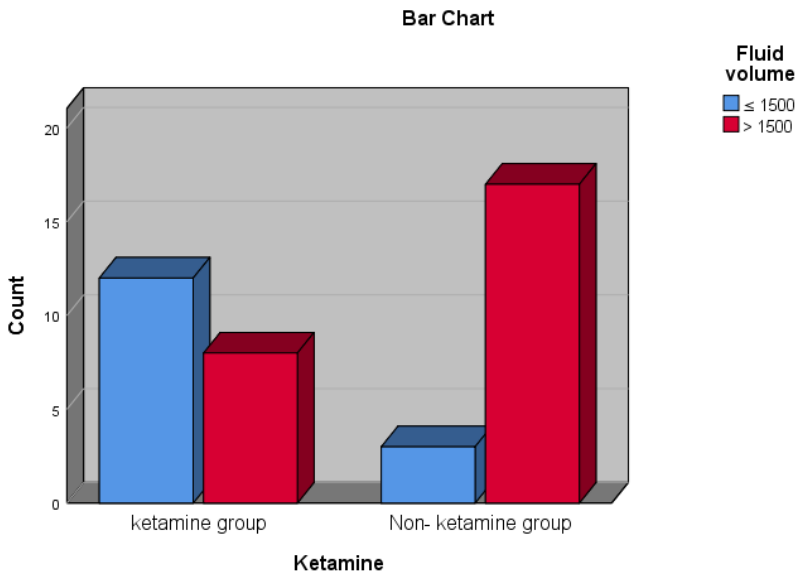


C) Fluid infusion volume: The average total volume of fluid infused in (K group) was lesser than that of (N group). In ketamine group 12 patients (60%) needed <1500 ml fluid and 8 patients (40%) needed 1500 – 2500 ml fluid. In non-ketamine group 3 patients (15%) needed <1500 ml fluid and 17 patients (85%) needed 1500 – 2500 ml fluid. and as shown in table and Fig. 5

Table (5): Difference between Ketamine and non-ketamine groups in the volume of :infused fluid and number of cases who received that volume in both groups

Ketamine * Fluid volume Crosstabulation						
		Fluid dose		Total	X2	P. value
		1500>	2500 - 1500			
Ketamine (k) group	N	12	8	20		0.003
	%	60.0%	40.0%	100.0%	8.64	
Non ketamine (non k) group	N	3	17	20		
	%	15.0%	85.0%	100.0%		

Figure (5): Difference between Ketamine and non–ketamine groups in the volume of infused fluid and number of cases who received that volume in both groups.



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Discussion

Spinal anaesthesia is commonly used in many surgeries and was reported to be the preferred anaesthetic technique for most cases of caesarean section, approximately 80–90% of elective cesarean sections, as it avoids the risks of pulmonary aspiration, and it allows the mother to be awake and interact immediately with her baby (**Burns and Cowan**, **2000 and Reynold et al**., **2005**). So, in this study, most of female cases (75% in both groups) were caesarean sections, while 25% were other different surgeries for males and females.

The most common complication that can limit the widespread use of spinal anaesthesia is hypotension that occurs immediately after it (**Dalton**, **2011**). It was reported that hypotension occurs with MAP < 65 mmHg, while severe hypotension (shock) is considered when MAP decreases below 55 mmHg (**Vincent et al**., **2018**). Severe hypotension for long period can produce poor tissue perfusion to vital organs increasing the incidence of morbidity and mortality (**Dalton 2011**). Hypotension in delivery leads to decrease in uterine blood flow affecting the neonatal outcome (**Lee et al**, **2002**). A lot of techniques have been described by many researchers for eliminating spinal anaesthesia induced hypotension but an effective method is yet to be described.

Ketamine, unlike other intravenous anaesthetics, has sympathetic nervous system stimulation (**White and Elig**, **2013**). In human studies, ketamine has showed the ability to increase maternal blood pressure and uterine blood flow thus improving uterine perfusion (**Tang etal**, **2017**). Ketamine can be administered through iv, im, intrathecal or epidural routes (Morgan and Mikhail, 2022). It was reported that ketamine's lipophilicity allows for rapid diffusion into the venous system namely the azygos vein (**Sohnen et al**., **2021**).

Previous studies were done on ketamine intrathecally as regard to analgesic and anaesthetic effects (**Kathirvell et al**., **2000**). Also other studies including iv ketamine were done regarding the hypertensive effect for prevention of hypotension after spinal anaesthesia (**Salah and Alansary**, **2019**). The current study differs in that it searches for the effect of intrathecal ketamine on spinal anaesthesia induced hypotension. Also. It searches for its effect on the volume

of infused fluid and dose of ephedrine needed to overcome hypotension.

The mechanism of action of intrathecal ketamine is incompletely understood. It was reported that it increases the release and inhibits reuptake of catecholamine in circulation thus helps preserve vascular resistance and arterial blood pressure (**Hemmingsen and Nielsen**, **1991**). Another study hypothesized that spinal ketamine first binds to NMDA receptors then inhibits NMDA, monoaminergic and opiate receptors (**Kathirvell et al**., **2000**). An experimental study was done by **Morimoto et al**. (**2021**) to confirm that an increase in blood pressure induced by ketamine is mediated through the central nervous system. They detected an increase in blood pressure after ketamine injection into the basolateral and central nuclei of the amygdala, endopiriform nucleus and piriform cortex.

A previous experimental study reveals that ketamine with benzethonium chloride preservative did not cause neurotoxicity (**Brock–utne et al**., **1982**). So, ketamine with benzethonium chloride preservative was used in this study. Different doses of ketamine were used in different studies. **Abd El–Rahman et al**. (**2018**) studied the analgesic effect of ketamine in a dose 0.1 mg /kg. Dose of ketamine above 0.75 mg /kg can produce neurotoxicity in the form of hallucination, nystagmus (**Sohnen et al**., **2021**). So, the dose recommended in this study was 0.5 mg /kg up to maximally 40 mg.

This study proves that ketamine intrathecally in subanaesthetic dose (0.5 mg/ kg) with bupivacaine 2–3 ml 0.5% (hyperbaric) can alleviate the hypotensive effect of spinal anaesthesia significantly. Less incidence of mild and severe hypotension was observed in ketamine group compared to non–ketamine group. Few cases (20%) of ketamine group, with average MAP $\leq$ 65 mmHg, needed vasopressor (ephedrine) in small doses $\leq$ 10mg, while most of cases (80%) did not need, as the average MAP was > 65 mmHg. Also, the average total volume of fluid which was necessary to overcome hypotension was lower than that of non–ketamine group. So, the doses of ephedrine and average total volume of fluid infusion indicated the effectiveness of ketamine in prevention or decrease spinal hypotension.

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Sessler et al, (**2019**) mentioned that intraoperative mean arterial pressures below 60–70 mm Hg is associated with myocardial injury, acute kidney injury, and death. **Wehrwein et al**. (**2013**) reported that a higher MAP > 65 can improve survival and decrease end organ damage. Other studies are needed with a much larger group of patients to consider safely issue.

Conclusion

We concluded that ketamine intrathecally in a dose of 25mg is an effective agent to be used in preventing or decreasing the incidence and severity of post-spinal hypotension in patients undergoing surgeries indicating spinal anaesthesia. So, fluid infusion becomes less and ephedrine is rarely used to elevate blood pressure.

References

1) Olawin AM and M Das J. spinal anaesthesia{Updated 2022,Jun 27}. In: statpear is {Internet}. Treasure Is 1and (FL): Statpear1s Publishing; 2024 Jun-. Available from: htt: //wwwncbi. n1m. nih. Gov/books/NBK537299.

2) Kathirvel S, Sadhasivam S, Saxena A, Kannan TR, Ganjoo P. (2000): Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. Anaesthesia. Sep; 55(9):899-904. doi: 10.1046/j.1365- 2044.2000.01472.x. PMID: 10947756.

3) Reynolds F, Seed PT. Anaesthesia for Caesarean section and neonatal acid-base status: a meta-analysis. Anaesthesia. 2005 Jul; 60(7):636-53. doi: 10.1111/j.1365-2044.2005.04223.x. PMID: 15960713.

4) Dalton J E, Kurz A, Turan A, Mascha E J., Sessler D I., M.D., eif Saager L (2011): Development and Validation of a Risk Quantification Index for 30-Day Postoperative Mortality and Morbidity in Non cardiac Surgical Patients. Anesthesiology; 114:1336 – 44.

5) Hanss R, Bein B, Weseloh H, Bauer M, Cavus E, Steinfath M, Scholz J, Tonner P H. (2006) : Heart Rate Variability Predicts Severe Hypotension after Spinal Anesthesia. *Anesthesiology*; 104:537–545. doi: https://doi.org/10.1097/00000542-200603000-00022

6) Chooi C, Cox JJ, Lumb RS, Middleton P, Chemali M, EmmettRS, Simmons SW, Cyna AM (2017): Techniques for preventinghypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev. 4; 8(8): CD00251. doi: 10.1002/14651858.pu. Update in: Cochrane Database Syst Rev. 2020 Jul 1; 7: CD00251. PMID:28976555; PMCID: PMC6483677

7) Ferré F, Martin C, Bosch L, Kurrek M, Lairez O, Minville V. Control of Spinal Anesthesia-Induced Hypotension in Adults. Local Reg Anesth. 2020 Jun 3; 13:39-46. doi: 10.2147/LRA.S240753. PMID: 32581577; PMCID: PMC7276328

8) Monteggia LM, Zarate C Jr. (2015): Antidepressant actions of ketamine: From molecular mechanisms to clinical practice. Curr Opin Neurobiol; 30: 139-43.

9) Doenicke A, Angster R, Mayer M, Adams HA, Grillenberger G, Nebauer AE. (1992): [The action of S- (+)-ketamine on serum catecholamine and cortisol. A comparison with ketamine racemate]. Anaesthesist; 41(10): 597-603.Issei et al., 2021
10) Ogawa A, Uemura M, Kataoka Y, OI K, Inokuchi T. (1993): Effects of ketamine on cardiovascular responses mediated by N-methyl-D-aspartate receptor in the rat nucleus tractus solitarius. Anesthesiology; 78(1): 163-7.
11) Butterworth J F, Mackey D C and Wasnick J D (2022): Morgan & Mikhail's Clinical Anaesthesiology, volume 1, 7 th edition, Mc group Hill education New York.
12) Sohnen S, Dowling O, Shore-Lesserson L. Single dose perioperative intrathecal ketamine as an adjuvant to intrathecal bupivacaine: A systematic review and meta-analysis of adult human randomized controlled trials. J Clin Anesth. 2021 Oct;73:110331. doi: 10.1016/j.jclinane.2021.110331. Epub 2021 May 5. PMID: 33962333.
13) Burns SM, Cowan CM. Spinal anaesthesia for caesarean section: current clinical practice. Hosp Med. 2000 Dec; 61(12):855-8. doi: 10.12968/hosp.2000.61.12.1485. Erratum in: Hosp Med. 2001 Feb; 62(2):113. PMID: 11211587.
14) Vincent JL, Nielsen ND, Shapiro NI, Gerbasi ME, Grossman A, Doroff R, Zeng F, Young PJ, Russell JA. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. Ann Intensive Care. 2018 Nov 8;8(1):107. doi: 10.1186/s13613-018-0448-9. PMID: 30411243; PMCID: PMC6223403.

15) Lee A, Warwick NganKee. (2002): Prophylactic ephedrine prevents hypotension during spinal anaesthesia for caesarean delivery, but does not improve neonatal outcome-A quantitative systematic review. Can J Anaesth; 49(6): 588- 99.
16) White PF, Elig MR. (2013): Intravenous anaesthetics. Clinical Anaesthesia 6th ed.; 478-500. Tang Y, Liu R, Zhao P (2017): Ketamine: An update for obstetric anesthesia. Transl Perioper Pain Med; 4(4): 1-12.
17) Tang Y, Liu R, Zhao P (2017): Ketamine: An update for obstetric anesthesia. Transl Perioper Pain Med; 4(4): 1-12.

18) Salah D. and Alansary A M (2019): Impact of Sub-Anesthetic Dose of Ketamine on Post Spinal Hypotension in Cesarean Delivery. The open anesthesia journal. Vol. 13: 86- 92. ID: TOATJ-13-86. DOI: 10.2174/2589645801913010086

19) Hemmingsen C, Nielsen JE. (1991): Intravenous ketamine for prevention of severe hypotension during spinal anaesthesia. Acta Anaesthesiol Scand; 35(8): 755-7.

20) Morimoto I, Koyama Y, Murakawa M. Increase in Blood Pressure by Local Injection of Ketamine into the Amygdala in Rats. Biol Pharm Bull. 2021 Apr 1; 44(4):544-549. doi: 10.1248/bpb.b20-00881. Epub 2021 Feb 11. PMID: 33583871

21) Brock-utne J G, Mankowitz E, Kallichurum S, Downing J W (1982): Effects of intrathecal saline and ketamine with and without preservative on the spinal nerve roots of monkeys. SA Medical Journal. 360-361.

22) Abd El-Rahman AM, Mohamed AA, Mohamed SA, Mostafa MAM. Effect of Intrathecally Administered Ketamine, Morphine, and Their Combination Added to Bupivacaine in Patients Undergoing Major Abdominal Cancer Surgery a Randomized, Double-Blind Study. Pain Med. 2018 Mar 1; 19(3):561-568. doi: 10.1093/pm/pnx105. PMID: 28520955.

23) Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, Miller TE; Miller TE, Mythen MG, Grocott MP, Edwards MR (2019): Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth. May; 122(5):563-574. doi: 10.1016/j.bja.2019.01.013. Epub 2019 Feb 27. PMID: 30916004.

24) Wehrwein EA and Joyner MJ (2013): Handbook of clinical neurology.