Original Article

Effect of co-administration of different doses of phenylephrine with oxytocin on the prevention of oxytocin-induced hypotension in caesarean section under spinal anaesthesia: A randomised comparative study

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ABSTRACT

Introduction: Co-administration of phenylephrine prevents oxytocin-induced hypotension during caesarean section under spinal anaesthesia (SA), but higher doses cause reflex bradycardia. This study compares the effects of co-administration of two different doses of phenylephrine on oxytocin-induced hypotension during caesarean section under SA. **Methods:** In this prospective, double-blind study, 90 parturients belonging to the American Society of Anesthesiologists' physical status 1 or 2, undergoing caesarean section under SA were randomised into Group A: oxytocin 3U and phenylephrine 50 μg, Group B: oxytocin 3U and phenylephrine 75 μg, Group C: oxytocin 3U and normal saline, administered intravenously over 5 min after baby extraction. The incidence of hypotension (the primary outcome), rescue vasopressor requirement and side effects were recorded. Statistical analyses were with analysis of variance, Kruskal-Wallis, chi-square and Fisher's exact tests. **Results:** Demographic parameters such as age, height, weight, level of sensory block at 20 min and duration of surgery were comparable in all the groups. The incidence of hypotension (Group A – 90%, Group B – 10%, Group C – 98%, $P = 0.001$), magnitude of fall in mean arterial pressure (Group A-15.03 ± 6.12 mm of Hg, Group B – 6.63 ± 4.49 mm of Hg and Group C-13.03 ± 3.39 mm of Hg, $P < 0.001$) and rescue vasopressor requirement (Group A-45 ± 15.25 mg, Group B-5 ± 15.25, Group C-91.66 ± 26.53, $P < 0.001$) were significantly lower in Group B compared to A and C. **Conclusion:** Co-administration of phenylephrine 75 μg with oxytocin 3U reduces the incidence of oxytocin-induced hypotension compared to phenylephrine 50 μg with oxytocin 3U during caesarean section under spinal anaesthesia.

Key words: Caesarean section, hypotension, oxytocin, phenylephrine, subarachnoid block

INTRODUCTION

Postpartum haemorrhage (PPH) is one of the leading causes of maternal mortality with uterine atony being the cause in about 50% cases.[1] It can be reduced by proper use of uterotonic agents. Among the various uterotonics, oxytocin is most commonly used. Prophylactic routine use of oxytocin has been shown to reduce the incidence of PPH by up to 40%.[2] However, oxytocin causes hypotension and reflex tachycardia as an adverse effect due to action on oxytocin receptors found in the heart and large vessels.[3] To treat this hypotension, various vasopressors such as ephedrine, mephentermine and phenylephrine can be

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used. Among this phenylephrine is shown to have a quicker control of blood pressure (BP) during spinal anaesthesia-induced hypotension.[4]

Phenylephrine, a short-acting alpha agonist, can be administered by bolus as well as by infusion,[5] in titrated doses to treat oxytocin-induced hypotension. It has been observed that co-administration of phenylephrine obtunds oxytocin-induced decrease in systemic vascular resistance (SVR) and increase in heart rate and cardiac output.[6] However, phenylephrine at higher doses is known to cause reflex bradycardia with decreased cardiac output.[7]

Studies recommending a minimum effective dose of phenylephrine required for co-administration with oxytocin to obtund cardiovascular effects of oxytocin are sparse.

Hence, the present study was undertaken to compare the two different doses of phenylephrine required to prevent adverse haemodynamic changes due to oxytocin infusion in parturients undergoing caesarean section under spinal anaesthesia.

The primary objective of the study was to compare the effects of co-administration of oxytocin with phenylephrine 50 or 75 μg on the incidence of oxytocin-induced hypotension during caesarean section under spinal anaesthesia. Rescue vasopressor requirement, magnitude of haemodynamic changes and the incidence of side effects were the secondary objectives. We hypothesised that a higher dose of phenylephrine would result in lower incidence of hypotension.

METHODS

This prospective double-blind study was carried out after obtaining Ethical Committee approval. The study was conducted from March to June 2016.

Parturients posted for elective and emergency lower segment caesarean section (LSCS) and all parturients with uncomplicated singleton pregnancy were included in the study.

Parturients with an increased risk of atony or excessive bleeding (known placenta praevia, multiple gestation, abnormal presentations, prolonged labour, more than 2 previous LSCS, PPH), cardiovascular instability, pre-eclampsia, essential hypertension, gestational diabetes, those with systemic illnesses such as severe anaemia, bleeding diathesis and cardiovascular disease, parturients with height <150 cm were excluded from the study. We also excluded those parturients who had a fall in BP >20% of basal mean arterial pressure (MAP) following spinal anaesthesia but before oxytocin infusion.

A total of 104 parturients were randomised into three Groups using numbers generated from randomisation table[8] and allocation concealment was made by envelope method. The envelope was opened by the principal investigator just before the administration of subarachnoid block (SAB) to the patient. Group A patients received oxytocin 3U and phenylephrine 50 μg diluted to 10cc with normal saline as an infusion over 5 min, Group B patients received oxytocin 3U and phenylephrine 75 μg diluted to 10cc infusion over 5 min and Group C patients received oxytocin 3U and normal saline diluted to 10cc infusion over 5 min.

The operation theatre technician who was not involved in the care of the parturient prepared the drug solution based on the instructions from the principal investigator. The parturient and the anaesthesiologist involved in the anaesthetic management of the parturient were unaware of the contents of the solution administered.

Pre-anaesthetic evaluation of all the parturients was done and an informed written consent was taken. In the operation theatre, electrocardiogram, non-invasive BP and pulse oximeter were connected and basal parameters recorded. Intravenous (IV) access with 18G cannula was established. Parturients were pre-medicated with ranitidine 50 mg IV and metoclopramide 10 mg IV half an hour before the administration of SAB and pre-loaded with 500 mL Ringer lactate just before the administration of SAB.

The SAB was performed at L_3-L_4/L_4-L_5 interspace using 25G Quincke Babcock needle in the left lateral decubitus position and bupivacaine hyperbaric (0.5%) 9 mg with fentanyl 12.5 μg was administered. Immediately after the SAB, the patient was repositioned supine with 15° wedge below the right buttock to achieve left uterine tilt. Oxygen was administered through simple face mask at 4 L/min.[9] IV fluid infusion was continued at a rate of 200 mL/10 min throughout the surgery. Heart rate (HR), systolic BP (SBP), diastolic BP (DBP), MAP and peripheral oxygen saturation was monitored every 2 min till baby extraction and up to 10 min after

administration of the test drug solution, then every 5 min till the end of surgery.

After baby extraction, test drug solutions (10 mL) were administered based on group allocation over a period of 5 min using a syringe infusion pump (Sino medical systems, China) through a separate IV line. Following this oxytocin infusion at 10U/h was continued up to 4 h. The level of sensory blockade was assessed using cold swab test at 20 min. The APGAR score was recorded for all the neonates at 1 and 5 min.

Uterine tone was assessed by obstetricians at the end of uterine closure and noted as either 'adequate' or 'inadequate'. If uterus was not adequately contracted methylergometrine 0.2 mg intramuscular (IM) or prostaglandin F2α 250 μg IM was given and noted.

Hypotension was defined as a fall in MAP >20% from baseline and treated with 100 mL IV fluid bolus and rescue dose of phenylephrine 50 μg IV over 2 min. Phenylephrine IV was repeated every 2 min till the MAP increased to within 20% of baseline. A maximum of 4 doses of phenylephrine were administered after which rescue vasopressor was changed to ephedrine 6 mg IV. The requirement of rescue vasopressors was noted. Bradycardia was defined as heart rate <60 beats/min (bpm) and treated with atropine 0.6 mg IV. Adverse effects such as desaturation, nausea, vomiting, headache, bronchospasm, flushing and dysrhythmias if any, during intraoperative period were noted and treated accordingly. The patient was monitored in the postoperative care unit for 6 h.

The initial power analysis assumed that 70% of patients require a vasopressor, based on previous studies.[6] To detect a minimum of 50% reduction in the incidence of hypotension between the groups, a minimum of 30 parturients would be required in each group, to attain a power of 80% at alpha error of 0.05, assuming normal distribution of values in all the groups and using Chi-square test for comparison of proportions.

Statistical analysis was done using IBM SPSS (statistics package for socialistic sciences) version 20 software. Haemodynamic values recorded just before extraction of the baby was considered as baseline value for assessing the effect of oxytocin on haemodynamic parameters. Shapiro Wilk test was done to assess for the normality of the distribution of continuous variables. For values showing normal distribution, Analysis of variance (ANOVA) was used to find the significance between three groups of parturients for continuous variables and paired *t*-test was used for intragroup comparison. *Post hoc* analysis with Bonferroni correction was applied for intergroup comparison of continuous variables. Kruskal–Wallis test was done for intergroup comparison when values showed skewed distribution. Chi-square/ Fisher's exact test was used to find the significance of study parameters on categorical scale. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 104 parturients were enrolled and randomly allocated into three groups (Group A $n = 35$, Group B $n = 35$ and Group C $n = 34$) [Figure 1]. However, 14 parturients (Group A $n = 5$, Group B $n = 5$, Group C $n = 4$) did not receive intervention as they developed hypotension after SAB but before oxytocin infusion and hence were not included for the analysis. A total of 30 parturients in each group were then included for the final analysis.

Demographic parameters such as age, height, weight, level of sensory block at 20 min and duration of surgery were comparable in all the three groups as shown in Table 1. The average time of extraction of the baby was comparable in all the three groups.

The incidence of hypotension was more in Groups A and C compared to Group B. The number of episodes of hypotension was significantly higher in Group C compared to Groups A and B, Group B had the least episodes of hypotension. The rescue vasopressor requirement was significantly lower in Group B compared to A and C. Intergroup comparison using Mann–Whitney U-test showed statistically significant difference between Groups A and C ($P < 0.001$) [Table 2].

Log transformation was done for basal MAP before oxytocin infusion, lowest MAP after oxytocin infusion, the magnitude of change in MAP and the time for maximum fall in MAP after oxytocin infusion to assess for normality of distribution as these parameters showed skewed distribution on initial analysis. Final analysis was done for these parameters after log transformation.

The basal MAP just before infusion of test drug and oxytocin mixture was comparable in all the three

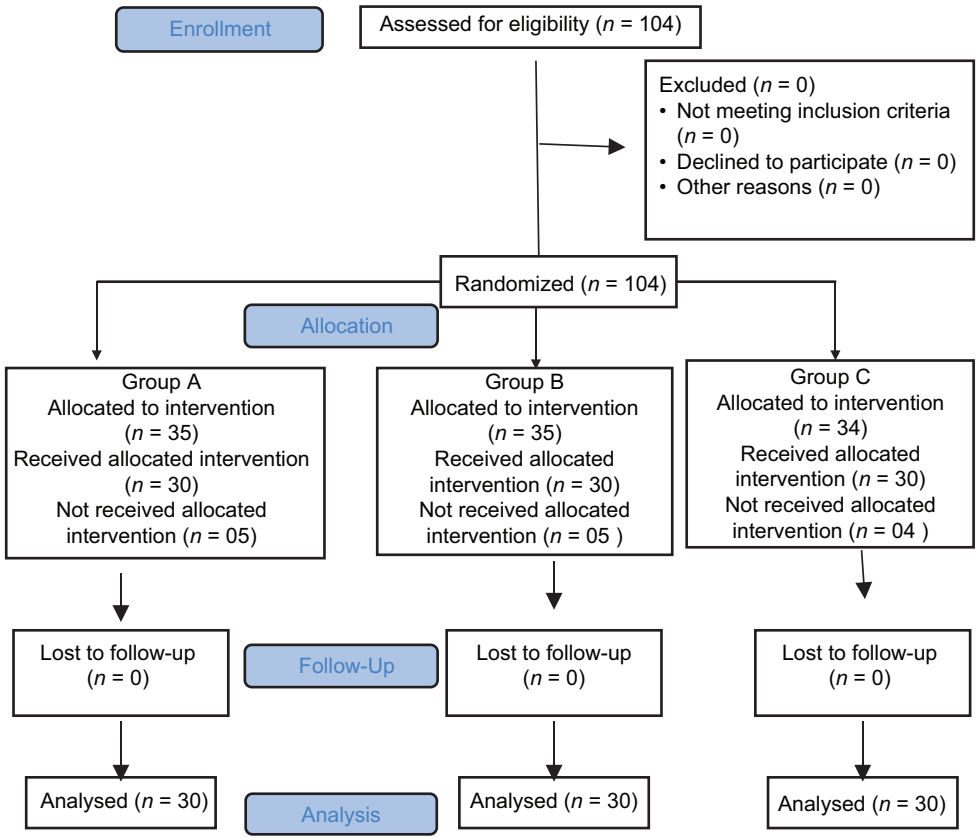

Figure 1: CONSORT flow diagram

Table 1: Demographic parameters (*n*=30)

Parameter	Group A	Group B	Group C	*P*
Age (years), [median (IQR)]	24 (23-26)	23.5 (22-25)	23 (22-24)	
Height (cm), (Mean±SD)	155.53±5.08	155.84±4.52	156.42±4.10	
Weight (kg), (Mean±SD)	64.47±13.87	67.03±6.57	67.69±4.75	
Sensory block [median (IQR)]	T6 (T6-T8)	T6 (T6-T8)	T6 (T6-T8)	
Duration of surgery (min), (mean±SD)	52.3±5.42	53±5.02	52.08±4.89	
Extraction time of baby from induction (min), [mean±SD (95% CI)]	10.56±2.06 (9.79-11.33)	10.66±2.21 (9.83-11.49)	11.10±2.27 (10.24-11.95)	0.606
Extraction time of baby from skin incision (min), [mean±SD (95% CI)]	6.90±1.82 (6.21-7.58)	7.10±1.88 (6.39-7.8)	7.26±1.89 (6.56-7.97)	0.749

SD – Standard deviation; CI – Confidence interval; IQR – Interquartile range

groups. There was a decrease in MAP in all the three groups after oxytocin infusion which was statistically significant ($P < 0.001$). The magnitude of fall in MAP after oxytocin infusion was maximum in Group A and C when compared to Group B, although *post hoc* analysis showed no statistical difference between Group A and C. The time at which lowest MAP recorded after oxytocin infusion was between 6 and 9 min and was comparable in all the three groups. The amount of intraoperative IV fluid administered was maximum in Group C compared to Groups A and B which was statistically significant. However, *post hoc* analysis showed no statistical difference between Group A and B [Table 2]. Heart rate was comparable in all the three groups, and there was no incidence of bradycardia [Figure 2]. Comparison of SBP between three groups using one way ANOVA test showed statistically significant difference at 12^{th}–20^{th} min ($P < 0.001$). *Post hoc* analysis with Bonferroni correction showed statistically significant difference between Groups B and C from 12^{th} to 40^{th} min and statistically significant difference between Groups A and B from 16^{th} to 45^{th} min. However, there was no significant difference between Group A and C. Comparison of DBP between three groups showed a statistically significant difference at 14^{th}–30^{th} min ($P < 0.001$). There was statistically significant difference between Groups B and C at 14^{th}–40^{th} min.

Table 2: Incidence and magnitude of hypotension, vasopressor and IV fluid requirement

Outcomes and Haemodynamics	Group A	Group B	Group C	*P*
Incidence of hypotension (%)	27 (90)	3 (10)	28 (93.3)	<0.001*
Number of episodes of hypotension				
0	3	27	2	<0.001*
1	27	3	1	
2	0	0	27	
Dose of rescue vasopressor given (μg)				
Mean±SD (95% CI)	45±15.25 (39.3-50.69)	5±15.25 (−0.69-10.69)	91.66±26.53 (81.75-101.57)	
Median (IQR)	50 (50-50)	0	100 (100-100)	<0.001**
Baseline MAP before oxytocin infusion, [median (IQR)]	80.5 (76.5-84)	80.5 (74-85.75)	77 (75-80)	0.200***
Lowest MAP after oxytocin infusion, [median (IQR)]	66 (62-68.75)	74 (68.25-77)	64 (63-66)#	<0.001**
Time at which lowest MAP was recorded after oxytocin infusion (min), [median (IQR)]	9 (6-11)	6 (2.25-9)	8 (5.25-14)	0.052**

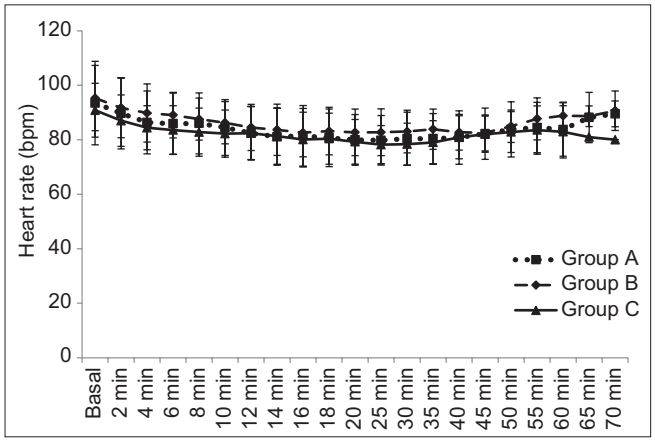

Figure 2: Trends in heart rate

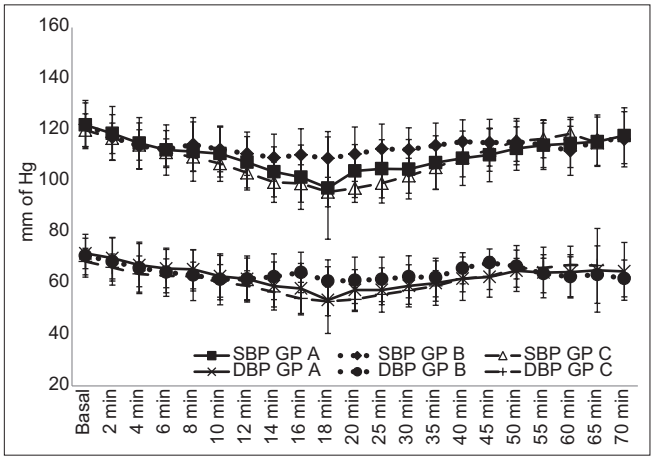

Figure 3: Comparison of trends of systolic blood pressure and diastolic blood pressure between the three groups

However, there was no significant difference between Groups A-C and Groups A-B [Figure 3].

Comparison of MAP between three groups showed a statistically significant difference at 12th–35th min ($P < 0.001$). There was statistically significant difference between Groups A and B at 16th–30th min and statistically significant difference between Group B and C at 12th–55th min. However, there was no significant difference between Groups A and C [Figure 4].

Median (range) APGAR score at 1 min in Group A was 8 (7–9), in Group B was 8 (7–9) and in Group C was 8 (7–9). APGAR score at 5 min in Group A was 9 (7–9) in Group B was 9 (8–9) and in Group C was 9 (8–9) ($P = 0.19$).

Uterine tone was adequate in all the 3 groups.

The incidence of nausea and vomiting was highest in Group C (40%) compared to Group A (16.7%) and Group B (3.3%). We did not observe any other side effect in all the three groups.

DISCUSSION

In the present study, it was observed that co-administration of 75 μg phenylephrine with oxytocin reduced the incidence and the number of episodes of oxytocin-induced hypotension whereas 50 μg of phenylephrine did not reduce the incidence of hypotension but reduced the number of episodes of hypotension and rescue vasopressor requirement compared to control.

Endogenous oxytocin is a 9–amino acid polypeptide produced in the posterior pituitary. The exogenous form of the drug (Pitocin, Syntocinon) is a synthetic preparation.[10] The uterotonic effect of oxytocin is important in reducing blood loss from the site of placental attachment and decreasing the risk of postpartum haemorrhage, thus making it the primary choice among uterotonics.[11]

Oxytocin causes hypotension and reflex tachycardia as an adverse effect because oxytocin receptors are

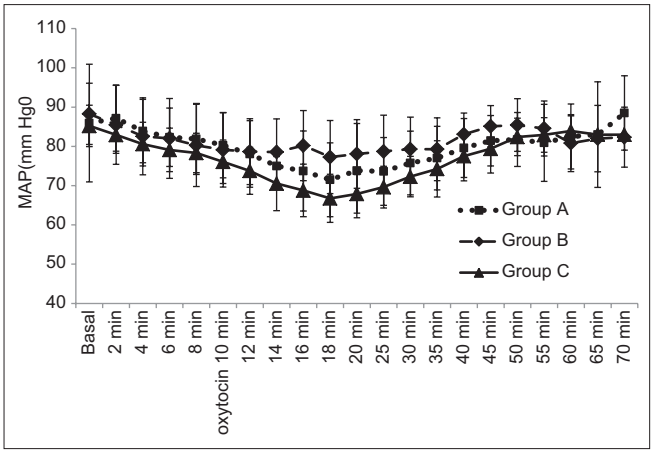

Figure 4: Trends in mean arterial pressure in all the three groups

also found in the heart and large vessels. The principal effect of oxytocin seems to be on SVR, and hence a drug which directly increases SVR would counteract the effect of oxytocin.[3] Some studies have shown that slower injection of oxytocin can effectively minimise the cardiovascular side-effects of a bolus dose without compromising the therapeutic benefits.[12]

There is no uniformity in the dose of oxytocin that is given for adequate uterine contraction. The routine use of 5U oxytocin during elective caesarean delivery can no longer be recommended, as adequate uterine tone can occur with lower doses of oxytocin (0.5–3 units).[11] Some have compared haemodynamic effects of oxytocin 3 U IV bolus over 15 s and 3 U infusion over 5 min on women undergoing caesarean section and concluded that 3 U infusion is superior to 3 U IV bolus.[13] In our study, we have used 3U oxytocin over 5 min and found that uterine contraction was adequate in all the cases and no additional doses of uterotonic agent were needed.

Few authors have noted that phenylephrine (100 μg) had quicker control of BP compared to mephentermine (6 mg) and ephedrine (6 mg) groups.[4] There are studies which have observed that the minimum vasopressor dose for preventing post-spinal hypotension in caesarean section was 532 μg for phenylephrine and 43 mg for ephedrine. Hence, they concluded that phenylephrine is more potent than ephedrine by a factor of 80 for equivalent maternal BP control.[14]

Studies have compared the efficacy of different doses of phenylephrine i.e. 100 μg, 125 μg and 150 μg to treat post-spinal hypotension in elective caesarean section and concluded that there was no significant difference in all the 3 groups.[15]

IV phenylephrine 50 μg administered immediately before 3 U oxytocin during elective caesarean section did not prevent maternal hypotension and tachycardia,[16] whereas co-administration of phenylephrine 80 μg with oxytocin 2.5 U obtunded oxytocin-induced decreases in SVR and increases in heart rate and cardiac output.[6]

However, there are no studies suggesting the optimal dose for co-administration with oxytocin, hence the present study was undertaken to compare co-administration of two lower doses in an effort to minimise phenylephrine-induced side effects. We found that the co-administration of phenylephrine 75 μg with oxytocin 3U had better efficacy compared to phenylephrine 50 μg with oxytocin 3U and was associated with the minimal adverse effect.

We considered the haemodynamic recordings just before baby extraction as the baseline to avoid confounding by SAB-induced hypotension, and they were found to be comparable. We also excluded parturients developing hypotension before oxytocin administration so that effect of phenylephrine on oxytocin-induced hypotension could be studied, presuming that hypotension caused after oxytocin administration would be due to the effect of oxytocin.

Phenylephrine causes a significant reduction in heart rate after the bolus dose.[17] There was no incidence of bradycardia in the present study which may be attributed to the administration of phenylephrine as infusion rather than bolus. There is evidence that phenylephrine delivered as an infusion is the most effective method for preventing maternal hypotension and intraoperative nausea or vomiting.[18]

Estimation of intraoperative blood loss was not done and hence the effect of phenylephrine co-administration on blood loss could not be studied. We have not done pulse waveform analysis (perfusion index) and cardiac output monitoring for our cases which can be a limitation. Cardiac output monitoring is used as a marker of oxygen delivery to tissues. It is used in guiding treatment for fluid resuscitation, and the use of vasoactive and inotropic drugs and hence may require further studies.[19]

CONCLUSION

Co-administration of phenylephrine 75 μg with oxytocin after baby extraction reduces the incidence

of oxytocin-induced hypotension and rescue vasopressor requirement compared to co-administered phenylephrine 50 μg during caesarean section under spinal anaesthesia.

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Conflicts of interest

There are no conflicts of interest.

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