Intrapartum Synthetic Oxytocin Reduce the Expression of Primitive Reflexes Associated with Breastfeeding

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Abstract

Aim: Several synthetic peptide manipulations during the time surrounding birth can alter the specific neurohormonal status in the newborn brain. This study is aimed at assessing whether intrapartum oxytocin administration has any effect on primitive neonatal reflexes and determining whether such an effect is dose-dependent.

Materials and Methods: A cohort prospective study was conducted at a tertiary hospital. Mother–infant dyads who received intrapartum oxytocin ($n=53$) were compared with mother–infant dyads who did not receive intrapartum oxytocin ($n=45$). Primitive neonatal reflexes (endogenous, antigravity, motor, and rhythmic reflexes) were quantified by analyzing videotaped breastfeeding sessions in a biological nurturing position. Two observers blind to the group assignment and the oxytocin dose analyzed the videotapes and assessed the newborn's state of consciousness according to the Brazelton scale.

Results: The release of all rhythmic reflexes ($p=0.01$), the antigravity reflex ($p=0.04$), and total primitive neonatal reflexes ($p=0.02$) in the group exposed to oxytocin was lower than in the group not exposed to oxytocin. No correlations were observed between the dose of oxytocin administered and the percentage of primitive neonatal reflexes released ($r=0.03$; $p=0.82$).

Conclusions: Intrapartum oxytocin administration might inhibit the expression of several primitive neonatal reflexes associated with breastfeeding. This correlation does not seem to be dose-dependent.

Introduction

OXYTOCIN HAS A CRUCIAL ROLE in labor (it induces uterine contractions), as well as in the regulation of social behavior including sexual behavior, maternal bonding, and social memory and recognition.^{1–4} Synthetic oxytocin is the most commonly used drug to induce or augment labor contractions. Intrapartum oxytocin administration involves the continuous infusion of oxytocin, which results in the inhibition of physiological pulsatility.⁵ However, the administration of synthetic oxytocin to induce or increase uterine dynamics is growing. The presence of oxytocin kinases in the placenta and in the brain–blood barrier of the fetus reduces synthetic oxytocin concentrations in the brain of the newborn. However, some synthetic oxytocin concentrations may reach the fetal brain.⁶ In mammals, several peptide manipulations during the time surrounding birth may induce persistent changes in the neuroanatomical and neuroendocrine system of the newborn.⁷

Attachment behaviors can be observed immediately after birth. In the period just after birth, human newborns exhibit behaviors aimed at maintaining proximity to the mother and initiating lactation. Skin-to-skin contact between the newborn and the mother facilitates spontaneous latching due, among other factors, to primitive neonatal reflexes (PNRs).⁸ PNRs include a group of innate reflexes, spontaneous behaviors, and reactions to endogenous and environmental stimuli. PNRs develop during the fetal period and are observed in all healthy full-term newborns. Some PNRs have been extensively studied, such as the PNR that facilitates breastfeeding.⁹ However, the effect of intrapartum hormone manipulation on these reflexes has not been studied until recently.^{5,10}

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This study is registered at ClinicalTrials.gov with clinical trial registration number NCT01891201.

This study is aimed at assessing whether intrapartum oxytocin administration has any effect on PNRs and determining whether such effect is dose-dependent.

Materials and Methods

A cohort prospective study conducted at a tertiary hospital. The exposed group included mother–infant dyads who received intrapartum oxytocin ($n=53$). The not exposed group included mother–infant dyads who did not receive intrapartum oxytocin ($n=45$). Inclusion criteria were a single, healthy, full-term newborn delivered by vaginal labor with an Apgar score at 5 minutes of >7 , the expressed desire of the mother to breastfeed, and her provision of informed consent. Exclusion criteria were a preterm newborn, a fetal chromosomal or any other type of anomaly diagnosed during gestation that modifies the newborn's adaptation to the extrauterine environment, the transfer of the mother to the intensive care unit, the transfer of the newborn to the intensive care unit within 48 hours after birth, the mother's desire of providing formula feeding expressed before labor, language barriers, and undergoing a cesarean section. Mother–newborn dyads were recruited before delivery. All practices were performed in accordance with the Baby-Friendly Hospital Initiative guidelines: immediately after birth, newborns were placed in skin-to-skin contact during 90 minutes continuously; as well, breastfeeding sessions were conducted at demand, and they were not restricted any time.

This study was approved by the local ethics committee.

The study of PNRs was performed in an experimental maternal skin-to-skin contact situation during the stay at the Maternity Unit (Fig. 1). Parents chose the best moment to videotape the mother and the newborn at least 1 hour after the last feed, in order to favor PNR expression. The mother was positioned in the biological nurturing position¹¹ (skin-to-skin contact, with the newborn only dressed with a diaper facing, touching and in close apposition with the interbreast zone of the mother at a 30–64° angle). The mother was asked not to induce the newborn to seek or latch, although she was allowed to touch or speak to him or her. One of the researchers (I.O.F., M.A.M.G., or C.G.A.) videotaped the situation for 15 minutes. Parents were provided with a CD with the recordings as a gift.

Next, two observers blind to the group assignment and the oxytocin dose administered analyzed the videotapes and assessed the newborn's state of consciousness at the start of the recording, according to the Brazelton scale,¹² and scored the PNRs using a dichotomous code (achieved/not achieved).

The 15 PNRs evaluated were as follows: (1) endogenous reflexes—hand to mouth, finger flexion and extension, mouth gape, tongue dart, arm/leg cycle, and foot/hand flex; (2) antigravity reflex—gazing; (3) motor reflexes—head turning, bobbing, plantar grasp, and Babinski toe fan; and (4) rhythmic reflexes—suck, jaw jerk, and swallowing.

The intraclass correlation coefficient was obtained for all 15 PNRs. The value of the intraclass correlation coefficient was as follows: (1) endogenous reflexes, 0.73 (0.59–0.83); (2) antigravity reflex, 0.70 (0.54–0.80); (3) motor reflexes, 0.74 (0.61–0.83); (4) rhythmic reflexes, 0.95 (0.93–0.97); and (5) and total PNRs, 0.83 (0.73–0.88).

Demographic data, such as educational level, previous deliveries, civil status, delivery mode (instrumental or not), sex of the newborn, Apgar score, gestational age, and weight of the newborn, among other parameters, were collected. Eutocic delivery was considered if no instrument (such as forceps or vacuum) was used during vaginal delivery.

Oxytocin administration during labor induction was performed as indicated by the obstetrician in accordance with the Cardiff protocol: infusion of 10 units of oxytocin (Syntocinon®; Defiante Farmaceutica, Funchal, Portugal) added to a 500-mL bag of physiologic saline (0.9% NaCl) solution. Administration of 2 mIU was initiated, and the dose was doubled every 15 minutes until at least three contractions were achieved in 10 minutes, up to a maximum of 40 mIU. The final dose of oxytocin administered was recorded by the midwives conducting the delivery. All mothers received oxytocin after the delivery for preventing bleeding in the third stage of the labor.

Epidural analgesia was induced with 0.125% levobupivacaine (Chirocane®; Abbott, Abbott Park, IL) or 0.2% ropivacaine (Naropin® Polybag®; AstraZeneca, London, United Kingdom) in conjunction with fentanyl. As many as 95.6% of the women exposed to oxytocin received epidural analgesia, versus 26.8% of the women in the control group.

FIG. 1. Experimental maternal skin-to-skin contact situation.

Statistical analysis

Accepting an alpha risk of 0.05 and a beta risk of 0.20 in a bilateral contrast, the sample size necessary was 90 subjects (45 in each group) for detecting a difference of ≥ 10 percentage units. The common standard deviation was assumed to be 20. We calculated a lost to follow-up rate of 0.05.

Results are expressed as mean $\pm$ standard deviation or median (interquartile range). Qualitative variables are presented as absolute frequency values and percentage values. The hypothesis of normal distribution was confirmed by the Shapiro–Wilk test. Differences between groups were assessed by Student's *t* test and the nonparametric Mann–Whitney U test. The association between oxytocin and neonatal reflexes was determined through Pearson's correlation coefficient. Qualitative variables were analyzed by the chi-squared test using Yates–Fisher correlation coefficients, when necessary. A multiple regression analysis was performed to study the variables that could modify the expression of PNRs. The intraclass correlation coefficient is a measurement of agreement between observers. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS version 14.0 software (SPSS Inc., Chicago, IL).

Results

In total, 98 mother–newborn dyads were initially included in the study, of which 53 were included in the group exposed to oxytocin and 45 were assigned to the not exposed group. Eight patients (15%) of the exposed group were excluded for the following reasons: four patients were excluded for technical reasons, two for missing data, and two for refusal to continuing after having provided initial consent. Four patients (8.8%) were excluded from the not exposed group: one was excluded for technical problems, and three were excluded for medical reasons (broken collarbone, gastric lavage, and admission to phototherapy, respectively).

The final sample included 86 mother–infant dyads, of which 45 were exposed to oxytocin and 41 were not exposed. Epidemiologic characteristics are shown in Table 1. The women exposed to oxytocin were more likely to be primiparous, receive epidural analgesia, and record earlier and require the use of instrumental aid during labor, compared with the not exposed group. The median dose of oxytocin was 1,400 units (range, 340–4,460 mU).

PNRs

The release of all the rhythmic reflexes, the gravity reflex, and total PNRs in the group exposed to oxytocin was lower compared with that in the not exposed group (Table 2).

No differences were found in the state of consciousness of the newborn on initiation of the experimental situation of biological nurturing. No differences were found in the percentage of endogenous reflexes released or in the percentage of motor reflexes.

A multiple regression analysis was performed to study if the different epidemiological characteristics between groups (multiparous, eutocic delivery, epidural analgesia, time at videotaping, and group) could modify the expression of PNRs. No significant differences in any of the analyzed variables were observed except in the treatment group ($p = 0.04$) (Table 3).

TABLE 1. EPIDEMIOLOGIC CHARACTERISTICS

	Oxytocin group	Control group	p
Mother's education			0.79
Primary	2.3%	2.5%	
Secondary	31.8%	35%	
University	65.9%	62.5%	
Multiparous	40%	73.2%	0.004
Eutocic delivery	77.8%	100%	0.01
Epidural analgesia	100%	26.8%	<0.001
Newborn's sex (male)	46.7%	48.8%	0.81
Gestational age (weeks)	39.7 $\pm$ 1.1	39.2 $\pm$ 1.2	0.17
Newborn's weight (g)	3,324 $\pm$ 375	3,240 $\pm$ 476	1
Apgar score at 5 minutes	10 (10–10)	10 (10–10)	1
Not requiring resuscitation	77.8%	85.4%	0.57
Time after birth (hours)	23.4 $\pm$ 11.2	30.8 $\pm$ 8.2	0.001

Data are expressed as percentages, in mean $\pm$ standard deviation or median values (interquartile range), as indicated.

Correlation with the dose of oxytocin administered

No correlations were observed between the dose of oxytocin administered and the percentage of PNRs released ($r = 0.03$; $p = 0.82$).

Discussion

The results obtained in this study suggest that intrapartum oxytocin administration may influence the expression of primitive reflexes favoring breastfeeding initiation. Specifically, the administration of oxytocin was observed to have higher impact on antigravity and rhythmic reflexes, with the latter being associated with effective breastfeeding. However, these results should be carefully considered.

The results observed are consistent with those of a previous study conducted by our group¹⁰; indeed, a slightly higher correlation has been observed in our study. Also, Bell et al.⁵ in

TABLE 2. STATE OF CONSCIOUSNESS AND PERCENTAGE OF PRIMITIVE NEONATAL REFLEX EXPRESSION IN THE OXYTOCIN AND CONTROL GROUPS

	Oxytocin group	Control group	p
Brazelton scale ^a			0.16
1–3	36.6%	17.1%	
4–5	41.5%	58.5%	
6	22%	24.4%	
PNR			
Endogenous reflexes (%)	67.2 $\pm$ 31.3	79.7 $\pm$ 24.1	0.08
Motor reflexes (%)	66.6 $\pm$ 36.1	82.3 $\pm$ 26.9	0.06
Rhythmic reflexes achieved	17.8%	43.9%	0.01
Antigravity reflexes achieved	73.3%	90.2%	0.04
Total PNR (%)	58.4 $\pm$ 28.9	74.1 $\pm$ 25.4	0.02

Results are expressed as mean $\pm$ standard deviation values.

^aBrazelton scores are as follows: 1, deep sleeping; 2, active sleeping; 3, sleepiness; 4, alert when awake; 5, unrestlessly alert; and 6, crying. PNR, primitive neonatal reflexes.

TABLE 3. MULTIPLE REGRESSION ANALYSIS TO STUDY THE VARIABLES THAT COULD MODIFY THE EXPRESSION OF PRIMITIVE NEONATAL REFLEXES

	β	95% CI	p
Multiparous	-4.02	(-17.3, 9.2)	0.54
Eutocic delivery	16.8	(-1.3, 35.1)	0.07
Epidural analgesia	-6.1	(-21.9, 9.6)	0.44
Time of videotaping	0.4	(-0.1, 1)	0.18
Group	-12.7	(-25, -0.5)	0.04

Results are expressed as β coefficients and 95% confidence intervals (CIs).

a study with 47 healthy full-term infants (36 exposed and 11 not exposed to intrapartum synthetic oxytocin) described fewer prefeeding cues in infants exposed versus not exposed to intrapartum oxytocin. Oxytocin administration during labor has some impact on both onset and duration of breastfeeding, as reported by García Fortea et al.¹³ In a retrospective cohort study they found an increased risk of bottle feeding and also an increased risk of breastfeeding withdrawal at 3 months in those exposed to intrapartum oxytocin.

The negative association found between intrapartum oxytocin administration and PNRs suggests that oxytocin can cross the placental barrier and the fetal brain-blood barrier, thus causing an effect that can still be observed in the newborn during the first days of life. It has also been observed that this effect is not dose-dependent, most likely because of the mean lifetime of oxytocin.¹⁴ However, the continuous infusion of oxytocin inhibits the physiologic pulsatile release of oxytocin. This may induce changes in the neuroendocrine environment of the fetal nervous system, with potential effects on the neural development of the newborn that can be determined in an objective manner, at least in the short term.¹⁵

There are several oxytocin receptors areas in the central nervous system, including the nucleus accumbens, the amygdala, the hippocampus, or the spinal cord, among others.¹⁶ The increased density of oxytocin receptors in these areas is associated with a greater bonding and social behavior.¹⁷ Oxytocin administered at low doses favors memory, social learning, and maternal behaviors.¹⁸ However, when administered at high doses, oxytocin may interfere in social memory. In fact, some authors have suggested a relationship between the current tendency to increase oxytocin doses and the increase in the incidence of autism¹⁹ and attention deficit hyperactivity disorder.²⁰ The triggering mechanism seems to be associated with a desensitization of the oxytocin receptor system.²¹ Gimpl and Fahrenholz²² observed that after stimulating the oxytocin receptor with agonists for 5–10 minutes, oxytocin was internalized within the cell and was not restored to the membrane surface. Excessive administration of oxytocin has also been observed to reduce oxytocin receptor mRNA synthesis and, consequently, oxytocin receptor availability.²³ Thus, intrapartum oxytocin administration may reduce the expression of PNRs as a result of its effects on several areas of the central nervous system of the newborn. In consequence, administering oxytocin during labor may reduce the expression of the oxytocin receptor or cause its desensitization.

The Epigenetic Impact of Childbirth hypothesis suggests that intrapartum oxytocin manipulation may lead to fetal epigenomic remodeling anomalies leading to abnormal gene

expression that could cause in a range of noncommunicative diseases and biobehavioral problems in the neonate and adulthood unknown up to date.²⁴

Studies in rodents have shown how perinatal manipulations with either synthetic oxytocin or an oxytocin antagonist have long-term behavioral consequences such as inhibited parental behavior or altered capacity to form pair bonds in adulthood.^{25,26}

The oxytocinergic system is also related with the regulation of aspects such as food intake and satiety.^{27,28} Studies performed on rats have revealed that the intracerebroventricular administration of oxytocin inhibits food and water intake, thus suggesting that oxytocin is involved in the regulation of feeding.²⁹ This might lead us to think that the inhibitory effects of oxytocin administered during labor on PNRs—especially on the rhythmic reflexes of sucking, jaw jerk, and swallowing, which involve the correct transfer of food—are similar to the anorectic effects of administering intracerebroventricular oxytocin to animals.

Theoretically, there are two barriers impeding the flow of oxytocin into the brain of the newborn: the placental barrier and the brain-blood barrier. On the one hand, the placental barrier contains oxytocinases involved in the degradation of oxytocin.³⁰ However, studies have demonstrated that despite the existence of these enzymes, small quantities of oxytocin reach the fetal bloodstream.⁶ On the other hand, the brain-blood barrier considerably inhibits the passage of peptides such as oxytocin. However, during the fetal stage, this barrier is not entirely mature, and a range of factors may increase its permeability^{31,32} (stress, infections, etc.), thus allowing the flow of oxytocin into the brain of the newborn.

There are several limitations to this study. First, the epidemiologic characteristics of both groups are not homogeneous because the control group included more multiparous women. As multiparous women have previous experience in breastfeeding and caring for a newborn, when they are positioned in the biological nurturing position, they may make reflex movements favoring PNR expression. Similarly, the group of patients exposed to oxytocin was more likely to receive epidural analgesia. The administration of epidural analgesia reduces the release of endogenous oxytocin,³³ which might influence PNR expression. However, both factors were not observed in this study to have any influence on PNR expression. The videotaping occurred earlier in the oxytocin-exposed group, and it may reflect a different state of awakeness, but there were no differences on the Brazelton scale or on PNRs. Traditionally, the main difference in the state of consciousness is between the first 6 hours (usually a state of alert) after delivery and beyond. Time of recording was done when both newborn groups were more than 6 hours old. Our hospital works according to the Baby-Friendly Hospital Initiative guidelines, so it is possible that the effects on breastfeeding may be undervalued. According to the power calculation 45 mother–newborn dyads were required in each group, but the nonexposed group had 41 dyads. This may influence the results.

Conclusions

Intrapartum oxytocin administration may inhibit the expression of several PNRs associated with breastfeeding. However, this correlation does not seem to be dose-dependent.

Further studies are necessary to confirm the results obtained in this study and to investigate the potential effects of oxytocin on breastfeeding or on the behavior of the newborn.

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Disclosure Statement

No competing financial interests exist.

References

- Carter CS. Developmental consequences of oxytocin. *Physiol Behav* 2003;79:383–397.
- Insel TR, Young LJ. The neurobiology of attachment. *Nat Rev Neurosci* 2001;2:129–136.
- Baumgartner T, Heinrichs M, Vonlanthen A, et al. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron* 2008;58:639–650.
- Olza-Fernández I, Marín Gabriel MA, Gil-Sánchez A, et al. Neuroendocrinology of childbirth and mother-child attachment: The basis of an etiopathogenic model of perinatal neurobiological disorders. *Front Neuroendocrinol* 2014;35:459–472.
- Bell AF, White-Traut R, Rankin K. Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth. *Early Hum Dev* 2012;89:137–143.
- Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. *J Matern Fetal Med* 1996;5:245–255.
- Bales KL, Lewis-Reese AD, Pfeifer LA, et al. Early experience affects the traits of monogamy in a sexually dimorphic manner. *Dev Psychobiol* 2007;49:335–342.
- Widstrom AM, Ransjö-Arvidson AB, Matthiesen AS, et al. Gastric suction in healthy newborn infants. *Acta Paediatr Scand* 1987;76:566–572.
- Bu'Lock F, Woolridge MW, Baum JD. Development of co-ordination of sucking, swallowing and breathing: Ultrasound study of term and preterm infants. *Dev Med Infant Neurol* 1990;32:669–678.
- Olza Fernández I, Marín Gabriel MA, Malalana Martínez A, et al. Newborn feeding behaviour depressed by intrapartum oxytocin: A pilot study. *Acta Paediatr* 2012;101:749–754.
- Colson SD, Meek JH, Hawdon JM. Optimal positions for the release of primitive neonatal reflexes stimulating breastfeeding. *Early Hum Dev* 2008;84:441–449.
- Brazelton TB, Nugent JK. *Neonatal Behavioral Assessment Scale*, 3rd ed. MacKeith Press, London, 1995.
- García Fortea P, González Mesa E, Blasco M, et al. Oxytocin administered during labor and breast-feeding: A retrospective cohort study. *J Matern Fetal Neonatal Med* 2014;27:1598–1603.
- Rowland M, Tozer TN. Why clinical pharmacokinetics? In: *Clinical Pharmacokinetics: Concepts and Applications*, 3rd ed. Lippincott Williams and Wilkins, Philadelphia, 1995, pp. 1–10.
- Rydén G, Sjöholm I. Half-life of oxytocin in blood of pregnant and non-pregnant women. *Acta Obstet Gynecol Scand* 1969;48(Suppl 3):139+.
- Feldman R. Oxytocin and social affiliation in humans. *Horm Behav* 2012;61:380–391.
- Francis DD, Champagne FC, Meaney MJ. Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. *J Neuroendocrinol* 2000;12:1145–1148.
- Klenerova V, Krejci I, Sida P, et al. Oxytocin and carbocytocin effects on spontaneous behavior of male rats: Modulation by oxytocin receptor antagonists. *Neuro Endocrinol Lett* 2009;30:335–342.
- Hollander E, Cartwright C, Wong C, et al. A dimensional approach to the autism spectrum. *CNS Spectrums* 1998;3:22–39.
- Kurth L, Haussmann R. Perinatal pitocin as an early ADHD biomarker: Neurodevelopmental risk? *J Atten Disord* 2011;15:423–431.
- Robinson C, Schumann R, Zhang P, et al. Oxytocin-induced desensitization of the oxytocin receptor. *Am J Obstet Gynecol* 2003;188:497–502.
- Gimpl G, Fahrenholz F. The oxytocin receptor system: Structure, function and regulation. *Physiol Rev* 2001;81:642–643.
- Phaneuf S, Asboth G, Carrasco M, et al. The desensitization of oxytocin receptors in human myometrial cells is accompanied by downregulation of oxytocin receptor messenger RNA. *J Endocrinol* 1997;154:7–18.
- Dahlen HG, Kennedy HP, Anderson CM, et al. The EPIIC hypothesis: Intrapartum effects on the neonatal epigenome and consequent health outcomes. *Med Hypotheses* 2013;80:656–662.
- Bales KL, Pfeifer LA, Carter CS. Sex differences and developmental effects of manipulations of oxytocin on alloparenting and anxiety in prairie voles. *Dev Psychobiol* 2004;44:123–131.
- Bales KL, van Westerhuyzen JA, Lewis-Reese AD, et al. Oxytocin has dose-dependent developmental effects on pair-bonding and alloparental care in female prairie voles. *Horm Behav* 2007;52:274–279.
- Olszewski PK, Klockars A, Olszewska AM, et al. Molecular, immunohistochemical, and pharmacological evidence of oxytocin's role as inhibitor of carbohydrate but not fat intake. *Endocrinology* 2010;151:4736–4744.
- Olszewski PK, Klockars A, Schioth HB, et al. Oxytocin as feeding inhibitor: Maintaining homeostasis in consummatory behaviour. *Pharmacol Biochem Behav* 2010;97:47–54.
- Arletti R, Benelli A, Bertolini A. Oxytocin inhibits food and fluid intake in rats. *Physiol Behav* 1990;48:825–830.
- Patient C, Davison J, Charlton L, et al. The effect of labour and maternal oxytocin infusion on fetal plasma oxytocin concentration. *Br J Obstet Gynaecol* 1999;106:1311–1313.
- Agnagnostakis D, Messaritakis J, Damianos D, et al. Blood-brain barrier permeability in healthy infected and stressed neonates. *J Pediatr* 1992;121:291–294.
- Noseworthy M, Bray T. Effect of oxidative stress on brain damage detected by MRI and in vivo ³¹P-NMR. *Free Radic Biol Med* 1998;24:942–951.
- Rahm VA, Hallgren A, Hogberg H, et al. Plasma oxytocin levels in women during labor with or without epidural analgesia: A prospective study. *Acta Obstet Gynecol Scand* 2002;81:1033–1039.

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