179

NUMBER 5

### INTRODUCTION

180

Hyoscine N-butyl bromide (HBB, Buscopan<sup>™</sup>) is a derivative of hyoscine, which is extracted from the leaves of the Dubosia tree found mainly in Australia. It is known for its antispasmodic action and has been around since 1951.<sup>[1]</sup> HBB acts by inhibiting cholinergic transmission in the abdominal and pelvic parasympathetic ganglia, thus relieving spasm in the smooth muscles of gastrointestinal, biliary, urinary tract and female genital organs, especially the cervico-uterine plexus and thus aiding cervical dilatation.<sup>[2,3]</sup> Uterine contractions are not affected,<sup>[3]</sup> rather due to better co-ordination between uterine contractions and cervical dilatation, the latter is increased.<sup>[3]</sup> Since vagotonic states lead to increased tension at the lower uterine segment and cervix, parasympatholytics are useful in arrested or delayed cervical dilatation. In addition, the pain relieving effects of parasympatholytics made HBB the drug that was tried for labor acceleration and analgesia<sup>[4]</sup>

HBB, unlike atropine, does not cross the blood-brain barrier therefore no central action is seen, thus the frequency and severity of side effects on the sweat and salivary glands, eyes, heart may be less compared to atropine at the therapeutically administered doses.<sup>[2,3]</sup> Its onset of action after intravenous dosing is 10 minutes, peak effect is seen at 20-60 minutes, and action lasts for two hours, with an elimination half life of 4.8 hours.<sup>[5]</sup>

Many studies<sup>[3,4,6-9]</sup> have been carried out to evaluate the effects of HBB in the active management of labor, but no studies have evaluated its role as a labor analgesic. Most of

these studies have been with the intramuscular route,<sup>[3,4,6]</sup> a few isolated studies using the intravenous<sup>[7,9]</sup> and suppository routes<sup>[8]</sup> but none with a dose of 40 mg as a single dose.

The present study was undertaken to observe the effects of intravenous HBB on labor as a labor analgesic and as a labor accelerant.

## MATERIALS AND METHODS

This prospective study was carried out on 104 pregnant women between 37-40 weeks of gestation, admitted to the labor room between April 2005-June 2005, to evaluate the efficacy and safety of 40 mg of HBB intravenously in the first stage of labor. The study was approved by the institutional ethics committee. Since there are no prior studies evaluating HBB as a labor analgesic, sample sizes for the study and control groups were calculated based on an expected pain relief of at least 30 % in the test group as significant versus no pain relief in the control group. Using power of the study as 95% and alpha value of 0.05, we determined that 41 women would be required in each arm of the study. Primigravidae with a single live fetus in cephalic presentation between 37-40 weeks period of gestation with spontaneous onset of labor, in active phase of labor with intact membranes were included in the study. Active phase was defined by cervical dilatation of >3 cm with uterine contraction at intervals of 3-4 minutes lasting at least 40 seconds. Women with high risk factors like pre-eclampsia, antepartum hemorrhage, previous uterine scar, and any contraindications to vaginal delivery were excluded from the study.

Women were randomized into test (group I)

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# **ORIGINAL CONTRIBUTIONS**

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# ROLE OF HYOSCINE N-BUTYL BROMIDE (HBB, BUSCOPAN®) AS LABOR ANALGESIC

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## ABSTRACT

BACKGROUND: Hyoscine N-butyl bromide (HBB) acts by inhibiting cholinergic transmission in the abdomino-pelvic parasympathetic ganglia, thus relieving spasm in the smooth muscles of gastrointestinal, biliary, urinary tract and female genital organs, especially the cervico-uterine plexus and aiding cervical dilatation. AIM: The study was undertaken to observe the effects of 40 mg intravenous HBB as a labor analgesic and labor accelerant. SETTINGS AND DESIGN: This prospective randomized control trial was carried out on 104 primigravidae with single live fetus in cephalic presentation, with spontaneous onset of labor, between 37-40 weeks of gestation. MATERIALS AND METHODS: Women were consecutively randomized into study (group I) and control (group II) groups, each with 52 patients after excluding high risk factors like preeclampsia, antepartum hemorrhage, previous uterine scar, and any contraindications to vaginal delivery. Group I received 40 mg HBB as a slow intravenous injection in the active phase of labor while Group II received 2mL normal saline. Pain scores were assessed at baseline and two hours later. Secondary outcome measures compared were progress of labor based on injection delivery interval, mode of delivery and neonatal condition at birth. STATISTICAL ANALYSIS: Statistical significance was assessed by using Student's t-test and Chi-square test. P-value < 0.05 was taken as significant. RESULTS: Pain relief of 35.6% was noted on visual analog score with the use of HBB. Mean duration of labor was 3 hours 46 minutes in Group I compared to 8 hours 16 minutes in Group II (P value: <0.001). Mode of delivery and neonatal outcome were comparable. No adverse maternal effects were noted. CONCLUSIONS: Intravenous Hyoscine N-Butyl Bromide causes pain relief of up to 36% and shortens the duration of active phase without any untoward short term fetal or maternal effects.

Key words: Buscopan, hyoscine, labor analgesic, spasmolytic.

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Correspondence: Dr. Pakhee Aggarwal C-I/11, Ansari Nagar, A.I.I.M.S. Campus (E), New Delhi - 110 029, India. E-mail: pakh\_ag@yahoo.com and control (group II) groups, each with 52 patients, by consecutive randomization, i.e. alternate women were allocated to test and control groups. The allocation was known only to the principal investigator who prepared the syringes. Neither the patients nor the nurses administering the solution were aware of its contents. Informed consent was taken at the time of entry into the labor ward if a woman fit the inclusion criteria. Patients in both groups were asked to indicate on a visual analog scale the amount of pain they felt at the point of recruitment into the study. The visual analog scale consisted of a straight line 100 mm in length, with one end indicating 'no pain', and the opposite end indicating 'worst possible pain' with markings from 0-10, the smallest difference being 0.5. Patients indicated the pain they felt at that particular time, using a pen/pencil to mark the number. At subsequent assessment, they marked on the scale again, the amount of pain felt, i.e patients were told "put a mark on the line at the point that best describes the amount of pain you are having right now". Test group patients received 40 mg HBB (2ml solution) as a slow intravenous injection (over 1-2 minutes) in the active phase of labor at 3-5 cm dilatation. Control group patients received 2 mL normal saline. General physical examination, obstetric examination and routine investigations were carried out in all patients by a resident/registrar in Obstetrics and Gynaecology. Partogram was maintained throughout labor. Conduct of labor in both groups was as per the labor ward protocols of the department. Cesarean delivery was carried out for usual obstetric indications. like fetal distress. Fetal monitoring was done by intermittent auscultation every half hour.

Patients were reassessed after two hours

for pain relief using the visual analog scale, and percentage change in pain from baseline was recorded. Percentage pain relief was the difference in pain score just before treatment and pain score two hours later. As the effect of the drug lasts for two hours, and may last up to its elimination half-life (4.8 hours) occurrence of pain after 4 hours was not taken into account. However the need for further analgesia was not felt as majority delivered within this time. The secondary outcome measures compared were progress of labor based on injection delivery interval, mode of delivery and neonatal condition at birth. Statistical significance was assessed by using Student's t-test and Chi-square test, and P-value < 0.05 was taken as significant. Data was analysed using Statistical Package for Social Sciences ver 10.0 (SPSS, Illinois, USA).

## RESULTS

The age of patients in both groups ranged between 18-32 years with a median of 24 years in the test group and 23.8 years in the control group. The median gestational age was 38 weeks with 6 days in test group and 38 weeks in the control group. The two groups were comparable in cervical findings at time of presentation and recruitment into the study, i.e. all patients were 3-5 cm dilated with good uterine contractions.

Patients in the test group reported pain relief between 25-75%, while control group patients reported no pain relief, or relief or <25% at two hours [Table 1]. The mean percentage change in pain scores from baseline (i.e. pain relief) in the test group was 35.6% while it was 12.5% in the control group. This was statistically significant (*P* value <0.001).

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Table 1: Pain relief (percentage decrease in pain score from baseline)

Percentage Pain Relief	Group I (n=52) Number (%)	Group I (n=52) Number (%)
<25	12 (23.1)	52 (100)
>25-50	32 (61.5)	-
>50-75	8 (15.4)	-
>75	-	-

Since the exact time of full dilatation of the cervix is difficult to determine, delivery was taken as the end point and injection-delivery interval was compared in the two groups. The injection delivery interval was between 2-4 hours in the majority of patients in the test group (mean duration 3 hours 46 minutes), while maximum patients in the control group delivered between 8-10 hours (mean duration 8 hours 16 minutes) [Table 2]. Thus, labor was shortened by 4 hours 30 minutes in test group as compared to controls. Fifty women (96%) in test group had duration of labor less than 8 hours, as compared to 18 women (34%) in the control group, and this result was statistically significant (P value < 0.001).

Two patients in the test group and five in the control group went for cesarean section, which were for fetal distress (*P*-value 0.24, non-significant).

The neonatal outcome was comparable in both the groups. Only one neonate in the test group

#### Table 2: Injection-delivery interval

Time (in hours)	Group I (n=52) Number %	Group II (n=52) Number %
2-4	44 (84.6)	5 (9.6)
>4-6	2 (3.8)	7 (13.4)
>6-8	4 (7.6)	6 (11.5)
>8-10	-	25 (48.0)
>10-12	-	2 (3.8)
>12	2 (3.8)	7 (13.4)

had an APGAR of <7 at 1 minute, but fared well subsequently. The APGAR scores were >7 in all babies at 5 minutes. There were no neonatal unit admissions. Median APGAR scores at 5 minutes were 9 in both groups.

No adverse maternal complications like dizziness, significant tachycardia (pulse rate >100bpm), blurred vision, dryness of mouth, or significant changes in blood pressure (>30mm systolic, or >15mm diastolic) were noted.

## DISCUSSION

Hyoscine N-butyl bromide has been in usage for more than half a century in varying doses (20mg, 30mg, 40mg) and varying routes (intramuscular, intravenous, rectal, oral). Corsen *et al*,<sup>[10]</sup> studied the various uses and modes of action of HBB in obstetrics and gynecology, and found that most prompt action occurred with intravenous and suppository routes, optimal time of administration was at 2.5-3 cm cervical dilatation and no significant side effects were observed with up to 30 mg dose.

The role of HBB as an analgesic has not been evaluated despite the fact that the same pathways which mediate cervical dilation mediate pain.<sup>[4]</sup> In the present study, a pain relief of up to 75% was reported in some patients, although the mean pain relief was around 36%. This may indicate two things: one, mediators other than parasympathomimetics may be involved in the pain pathways from the pelvic structures in general and cervical dilatation in particular, and two, part of the pain relief afforded by HBB may be due to shortening the duration of labor and thus

181

making it less tiring. Mean pain relief of 12.5% in the control group can be explained by the placebo effect, however majority of patients in this group reported no pain relief. Nevertheless, difference in pain scores with and without HBB is statistically significant.

That HBB can be used as a cervical spasmolytic has been evaluated in many studies,<sup>[3,4,6-9]</sup> and the results corroborated with our study. Bhattacharya et al,<sup>[4]</sup> studied the effect of 20 mg HBB intramuscularly on 100 primigravidas and found that mean labor time was shortened by 3 hours 40 minutes and 81% delivered within 8 hours. Samal et al,<sup>[6]</sup> in a similar study showed a shortening of labor by 2 hours 42 minutes with 88% women delivering within 8 hours. Neonatal outcomes were similar in the two groups. Tewari et al,[7] were the first to use a dose of 40 mg intravenously, but in two divided doses 20 minutes apart, and found labor to be shortened by 5 hours 12 minutes compared to controls. A recent study from Jamaica also showed shortening of the first stage of labor by 32%, without any adverse effects on the mother or neonate, with 20 mg intravenous dose.<sup>[9]</sup>

The advantages of intravenous route in a controlled manner (slow i/v over 1-2 minutes) are its rapid onset of action and bypass of hepatic metabolism. The rectal route is also popular<sup>[8]</sup> for this reason.

Although the numbers are small, and the period of neonatal assessment short, HBB did not statistically increase the rate of operative delivery and neonatal APGAR scores were comparable between the two groups, in our study and as well as others suggesting that HBB may be safe for use. The limitations of this study are that assessing a subjective component like pain is not always accurate, as many factors confound its assessment, including personal pain threshold, preexisting psychological problems, socio-demographics and the kind of support provided during labor. The first of these cannot be controlled for in any study. Also since the sample size is small and period of study short, many outcomes like fetal heart rate abnormalities, long term neurodevelopmental outcomes, maternal side effects may not have surfaced, which may be better evaluated in larger well designed double blind control studies.

To conclude, our study has shown that intravenous Hyoscine N-Butyl Bromide smoothens the passage of labor by affording pain relief of up to 36% and also shortening the duration of active phase without any untoward short term fetal or maternal effects.

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184

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#### Presentations:

- Paper on 'Use of Buscopan for Labor Analgesia' at the 27th Annual Conference of AOGD, organized by AOGD, Delhi, at New Delhi on 6th November 2005.
- Poster on 'Labor Analgesia Use of Buscopan ?' at CME and 15th Annual Conference of National Association of Reproductive and Child Health in India (NARCHI), organized by Sir Ganga Ram Hospital, New Delhi, on 5th February 2006. Awarded 3<sup>rd</sup> prize.