Intramuscular Tramadol versus Hyoscine-N-Butylbromide as an intrapartum analgesic during the first stage of labor

Thesis Submitted For Partial Fulfillment of Master Degree in
Obstetrics & Gynecology

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Mohamed Sabry Mahdy
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List of Abbreviations

Abbreviation	Meaning

ADLs ……..: Activities of Daily Livings

BMI …….: Body mass index

CFMF …….: Congenital Fetal Malformation

CNS…….: Central nervous System

CS ……...: Cesarean section

CSE……..: Combined Spinal-Epidural

CYP2D6 …….: Cytochrome P450 2D6

DDI……..: Dose- delivery interval

HBB ……..…… : Hyoscine butylbromide

IM ……: Intramuscular

IQR……...: Inter-quartile range

IUFD ……: Intrauterine Fetal Death

NRM…….: Nucleus Raphe Magnus

NRS …….: Numerical Rating Scale

NSAID……..: Non-Sterioidal Anti-Inflammatory Drug

NVD……..: Normal vaginal delivery

PFS ……...: Pain Face Scale

PG …….: Primigravida

SG……..: Substantia Gelatinosa

T1/2…….……...: Half life

TENS……...:Transcutaneous Electrical Nerve Stimulation

VAS……: Visual Analog Scale

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Protocol of

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Introduction

Pain during childbirth is one of the most excruciating pain experiences that women encountered in their lives (***Eeriksson et al., 2006***). Fear of childbirth has been associated with a longer first and second stage of labor and dissatisfaction with the childbirth experience (***Saisto et al., 2001***). It has also been implicated in women's requests for caesarean sections and a resultant increased rate of caesarean sections (***Eriksson et al., 2006***).

Nulliparous women generally experience more pain during early labor, while multiparous women may experience more pain during the late first stage and the second stage of labor, as a result of rapid fetal descent***(Sheiner et al., 1998)***.

The ideal obstetric analgesic should provide potent analgesic efficacy with minimal maternal and neonatal adverse effects***(Bricker and Lavaender, 2002)***.Epidural analgesia offers the best pain relief for many women in labor, but it requires trained staff***(Bricker and Lavender; 2002).*** But, when this is contraindicated or woman does not wish to have an epidural analgesia, administration of injectable opioids such as tramadol is a simple and less invasive alternative(***Khooshideh and Shahriari, 2009).***

Tramadol is a synthetic analog of codeine and a weak opioid agonist, acting centrally by modifying transmission of pain impulse by altering mono amine reuptake mechanisms***(Khooshideh and Shahriari, 2009).*** It can be administrated orally, rectally, intravenously or intramuscularly, and it is principally metabolized in the liver and 90% of it is excreted in urine (***Lee et al., 1993***). Its main side effects are observed in the central nervous system (dizziness, drowsiness, fatigue, headache, sedation), gastrointestinal system (nausea, vomiting, dryness of mouth, constipation), cardiovascular system (orthostatic dysregulation and tachycardia), and respiratory system (respiratory depression). Central and

respiratory depressant effects of tramadol are due to high doses and may be antagonized by Naloxone. Tramadol crosses the placenta, and its concentration in the umbilical venous serum is approximately 80% of maternal level (***Hussein et al., 1987***). In neonates, there are less incidence of neonatal respiratory depression ***(Khooshideh and Shahriari, 2009)*** and lack of gastrointestinal side-effects ***(Faisal et al., 2006).***

Spasmolytic drugs are frequently employed in India to overcome cervical spasm and thus reduce the duration of labor. One of this spasmolytic is hyoscine-n-butylbromide which has been used to shorten the duration of labor in many hospitals elsewhere in the world***(Samuels et al., 2007).*** It exerts a spasmolytic action on the smooth muscle of the gastrointestinal tract, biliary and genitourinary tracts***(Samuels et al., 2007)***.

Hyoscine-n-butylbromide is a derivative of hyoscine which is extracted from leaves of the Dubosia tree found mainly in Australia. It is known by its spasmolytic action and has been arisen since 1951 (***Tytgat, 2007***). Hyoscine-n-butylbromide acts by inhibiting cholinergic transmission in the abdominal and pelvic parasympathetic ganglion, thus relieving spasm in the smooth muscle of the gastrointestinal, biliary, urinary, and female genital organs, especially the cervicouterine plexus and thus aiding cervical dilation***(Baracho et al., 1984; Hotwani and Ainapure, 2000).***

. Hyoscine-n-butylbromide 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 and heart are less compared to atropine at the therapeutically administrated dose (***Baracho et al., 1984***).

The maternal side effects of hyoscine-n-butylbromide include dry mouth, facial flushing, dryness of the skin, photophobia, loss of concentration, urinary retention and constipation,and in neonates; it may cause tachycardia***(Davenport et al., 2005)***.

Research hypothesis

Research question: Is there difference between the effect of Tramadol100mg amp.IM and Hyoscine-N-Butylbromide (Buscopan) 20mg amp. IM with respect to:analgesic efficacy in theactive phase of 1st stage and 2nd stage of labor.

Research hypothesis:IM Tramadol is superior to Buscopan (Hyoscine-N-Butylbromide) as a labor analgesic in the active first stage and second stage of vaginal birth.

Primary outcome measure: to assess the efficacy of Tramadol IM and Hyoscine-N-Butylbromide (Buscopan) IM in laboring women by measuring the process of pain relief during the first stage of labor.

Secondary outcome measure: to document safety by assessing the adverse effects recorded during the study either maternal or fetal, also to correlate with the duration of labor i.e. the difference between both groups regarding labor duration and early postpartum maternal satisfaction.

Medical application: if pain in the first & second stages of labor is relieved, this will decrease the dissatisfaction of the mother from vaginal delivery, shorten the first & second stages of labor, decrease in women's requests for caesarean sections and provide the best analgesic drug in labor with great efficacy and minimal side effects.

Subjects and methods

Study design:

A randomized double-blinded controlled clinical trial that will be conducted at the labor ward of Ain Shams University Maternity Hospital after being approved by the ethical committee. The patients and investigator will be blind throughout the study period (neither the patient nor the investigator will know if the drug taken is Hyoscine-n-butylbromide or tramadol).

Sample size justification:

Sample size was calculated using STATA® version 11 program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study ***(Aggarwal et al., 2008)*** showed that the mean percentage change in pain scores from baseline (i.e. pain relief) in the hyoscine N-butyl bromide (HBB, buscopan®) group was 35.6% while for tramadol group pain relief is expected to be 60% from baseline. Calculation according to these values produced a minimal sample size of 70 women for each study group.

Participants:

The study will include 140 primigravidae women from those attending the labor ward of Ain Shams University Maternity Hospital seeking for analgesia during labor and that after obtaining an informed written consent from each woman. Woman will be selected to be included in the study according to the following criteria:

Inclusion criteria:

1. Women aged between 18 and less than 35 years.
2. Primigravidae.
3. Vertex presentation.
4. Uncomplicated singleton, viable.
5. Term pregnancy (37-42 wk gestation).
6. Active labor, cervical dilatation of 3-6 cm.
7. Spontaneous onset of labor at term.
8. No relevant systemic disease e.g. hypertension, DM, SLE.

Exclusion criteria:

1. Clinical evidence of cephalopelvic disproportion.
2. Any medical disorder during pregnancy.
3. Induction of labor.
4. Use of any other kind of analgesia before recruitment to the study.
5. Scared uterus.
6. Women receiving Oxytocin.
7. Previous history of hypersensitivity to either drug.
8. Extremes of age (below 18 years or more than 35 yrs).
9. Cervical dilation of more than 6 cm or less than 3 cm.
10. Multiparity.
11. Malpresentation such as breech, face andoblique lie, and malposition as occipitoposterior position.
12. Multiple gestations.
13. Fetal or maternal distress.
14. Obstetric complications such as pre-eclampsia, antepartum hemorrhage, known fetal abnormality or oligo- or polyhodraminos.

Method of the study:

Included women will be divided randomly on computer-generated codes kept in sequentially numbered opaque envelopes into two groups:

Group A:

It includes 70 women who will receiveHyoscine N-butylbromide (Buscopan amp. ، manufactured by Boehringer Ingelheim Co.) at a dose of 20 mg amp IM.

Group B:

It includes 70 women who will receive Tramadol (Mabron 100 mg amp. ، manufactured by Medochemie LTD) at a dose of 100 mg amp IM.

All the recruited women will undergo:

1. Written consent.
2. Complete history:
    a. Personal history: name, age, residence, occupation and special habits.

    b. Present history: current medications and to exclude history of chronic medical disorders (such ascardiac disease, hypertension, diabetes mellitus, chest, mental disorders and epilepsy….etc).

    c. Past history: previous history of blood transfusion, previous operations and drug allergy (to exclude allergy to either Hyoscine N-butylbromide or tramadol).

    d. Family history: history of chronic medical disorders such ascardiac disease, hypertension, diabetes mellitus and Familial hereditary diseases.

e. Obstetrical history: in details such as last menstrual period, expected date of delivery etc. (to excludeany contraindication for vaginal delivery).

3. Examination of the patients including :
   a) General examination: including general appearance and vital signs (pulse, blood pressure, temperature).
   b) Systemic examination: including head, upper limb, lower limb, chest and heart.
   c) Obstetric abdominal examination including fetal lie, fetal presentation, head station, estimated fetal weight, fetal heart rate, and uterine contraction, amount of liquor and to exclude multiple pregnancies.
   d) Vaginal examination including cervical dilation, effacement and position, state of fetal membranes,presenting part, position of fetal head, color of liquor and pelvic adequacy.

4. Partographic representation of labor and duration of first & second stages to determine the secondary outcome of the study which is the duration of 1st stage and 2nd stage of labor.

5. **Visual analogue scale:** to assess feeling of pain.
   1. VAS, is one of the most commonly used pain assessment instruments, and is regarded as the gold standard in research and clinical practice ***(Yarnitsky et al., 1996; Myles and Urquhart, 2005 and Siddik et al, 2008).***

2. It is a horizontal line, 100 mm in length, anchored by word descriptors at each end where the patient marks on the line the point that she feels represent her perception of her current state.

No pain01020 30405060708090100worst pain

Fig (1): Visual analogue scale (VAS) scores for pain.

3. VAS will be done at 30 min, 1 hour , 2 hours and 3i hours of the drug administration.

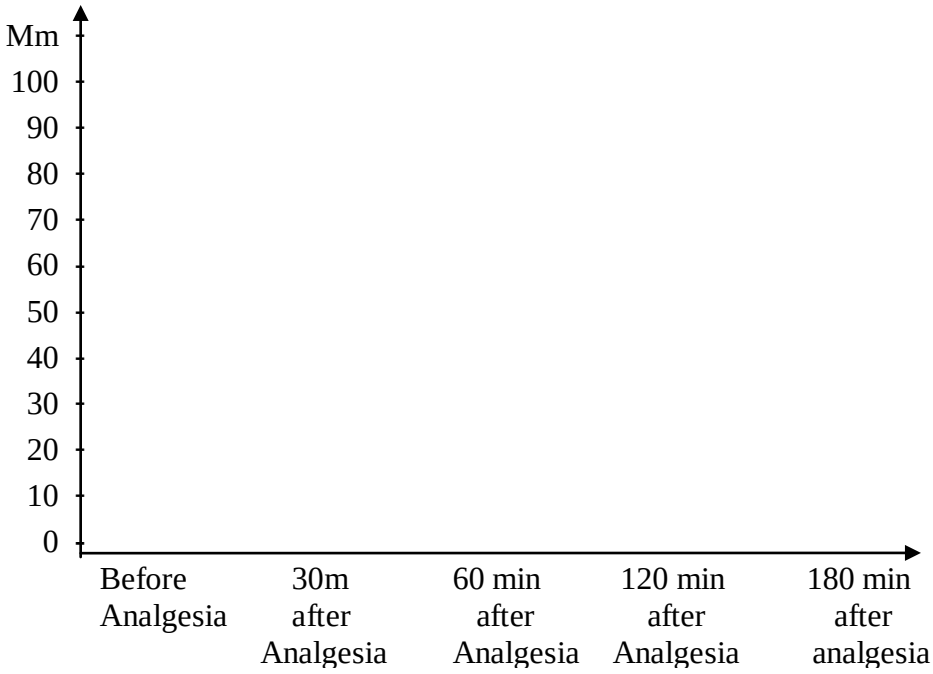

Fig. (2) VAS Chart.

Participants reported pain intensity on a 100-mmVAS, bounded by “no pain” and “the worst pain”,immediately before receiving the study drug and at 30 minutes,1 hour, 2 hours and 3 hoursafter drug administration and immediately after release of contraction and not during it. Painassessment