

**SIGNIFICANT COMBINATION OF PREFERENTIAL COX-2 INHIBITOR AND  
NON-ANTICHOLINERGIC SPASMOLYTIC USED IN LABOR  
AUGMENTATION**

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**Summary**

As a serious circumstance, prolonged labor contributes to increased perinatal loss and infant mortality and morbidity apart from causing psychological trauma to the mother. In recent decade, Spasmolytics and spasm-analgesics combinations are frequently administered to facilitate dilatation of the cervix during delivery and to shorten first stage of labor as an attempt to speed up the process of labor. Among those, the anticholinergic spasmolytics have undesirable anticholinergic side-effects, which may leads to various pharmacological problems. Hence, Non-anticholinergic Spasmolytics are preferable choice during pregnancy now a day. The current review gives past development and the basis for selection of a significant combination of Aceclofenac, a COX-2 inhibitor and Drotaverine HCl, an antispasmodic agent with non-anticholinergic action as a suitable choice to augment the labor over the other combinations.

**Keywords:** NSAIDs, Anticholinergic, Spasmolytics, COX-2, Drotaverine, Labor

**Introduction**

Labor is a natural physiological process characterized by progressive increase in frequency, intensity and duration of uterine contractions, effacement and dilatation of cervix with descent of the foetus through the birth canal. Prolongation in labor may result into increased perinatal loss and infant mortality and morbidity apart from causing psychological trauma to the mother. Active management of labor is being practiced into clinical practice by obstetrician all over the world; its aim is to reduce the duration of labor. Programmed labor protocol is analgesia, active management of labor and monitoring events of labor using a partogram<sup>1</sup>.

Labor Augmentation is a procedure which attempts to speed up the process of labor. The problems and hazards of prolonged labor, both for the mother and foetus have been recognized for many years. The mother is exposed to high risk of infection, ketosis and obstructed labor while the foetus faces the danger of infection, asphyxia and excessive cranial moulding<sup>2</sup>.

Smooth muscle relaxants are well accepted in progression of labor. Apart from uterine contraction, cervical dilatation is an important factor; which determines the duration of labor. It is the resistant off all driving forces of uterine contraction against passive tissue resistance. Smooth muscle relaxants inhibit impulses in the form of spasm that impairs the effective cervical dilatation. Various agents have been used to combat cervical muscle spasm<sup>3</sup>.

Hence the need of the hour is a pharmacological agent that would help in dilatation and effacement of cervix and there by shorten the duration of first stage of labor, not interfere with myometrial activity and with second & third stage of labor, not cause any side effects, No untoward effect on the foetus. Spasmolytics and spasm-analgesics mixtures are administered to facilitate dilatation of the cervix during delivery and to shorten first stage of labor<sup>2</sup>.

The current review presents the developments & progresses in labor augmentation past decade and focused on the selection of a suitable and significant spasm-analgesic combination to induce the labor augmentation.

### **Role of spasmolytics in labor augmentation**

Spasmolytics are the drugs that relax the smooth muscle of the gut, used to treat indigestion not associated with peptic ulcers, irritable bowel syndrome, and of diverticular disease. Contraction in smooth muscle, mediated by interactions between actin filaments and cross-bridges on adjacent myosin filaments, is triggered by the rise in cytoplasmic calcium and consequent phosphorylation of the 20 kDa light chains of myosin. The cross-bridges are the motors that utilize ATP as an energy source for the generation of force and work. The increase in Ca<sup>2+</sup> has many consequences like Activation of protein kinase such as Protein kinase A, Protein kinase C $\gamma$  (PKC $\gamma$ ), Calcium-calmodulin activated kinase II (CAMK-II), Mice lacking PKC $\gamma$  or CAMK-II show reduce hyperalgesia in nerve inflammatory pain, Activation of nitric oxide synthase (NOS), Activation of cyclooxygenase 2 (Cox-2), Increase intracellular Na<sup>+</sup> activates tyrosine kinase. The antispasmodic agents are classified into two main categories on the basis of mechanism of action i.e.; Anticholinergic (anti-muscarinic) spasmolytics and Non-anticholinergic spasmolytics<sup>4</sup>.

### **Limitations of antimuscarinic spasmolytics**

The anticholinergic spasmolytics have undesirable anticholinergic side-effects, which may leads to various pharmacological problems. Hence, Non-anticholinergic Spasmolytics are preferred during pregnancy. Atropine when injected into humans during pregnancy, atropine has been reported to increase the heartbeat of the fetus. Dicyclomine has been associated with a few cases of human birth defects. Hyoscyamine when injected into humans during pregnancy, has been reported to increase the heartbeat of the fetus.

Although these drugs may pass into the breast milk, they have not been reported to cause problems in nursing babies. However, the flow of breast milk may be reduced in some patients. The use of dicyclomine in nursing mothers has been reported to cause breathing problems in infants. There have been several studies on different Antispasmodic agents that shorten stage of labor. Among these agents are Hyoscine-N- butyl bromide, Drotaverine hydrochloride, Phloroglucinol and Valethamate bromide.

Hyoscine-N-butyl bromide, (quarternary ammonium compound) is a muscarinic antagonist and hence acts as a cervical spasmolytic agent Hyoscine-N- butyl bromide and its metabolites have been observed at the sites of action. After intravenous administration the substance is rapidly disturbed into the tissues. The main metabolites found in urine bind poorly to the muscarinic receptor. Hyoscine-N-butyl bromide dose not pass the blood brain barrier and plasma-protein binding is low<sup>5</sup>.

Valethamate bromide is an ester with a quaternary N atom, time tested extensively used drug by virtue of its anticholinergic parasympatholytic and musculotropic action, which relieves spasm of smooth muscles of cervix. Valethamate is associated with higher incidence of adverse effect due to its anticholinergic properties<sup>6</sup>.

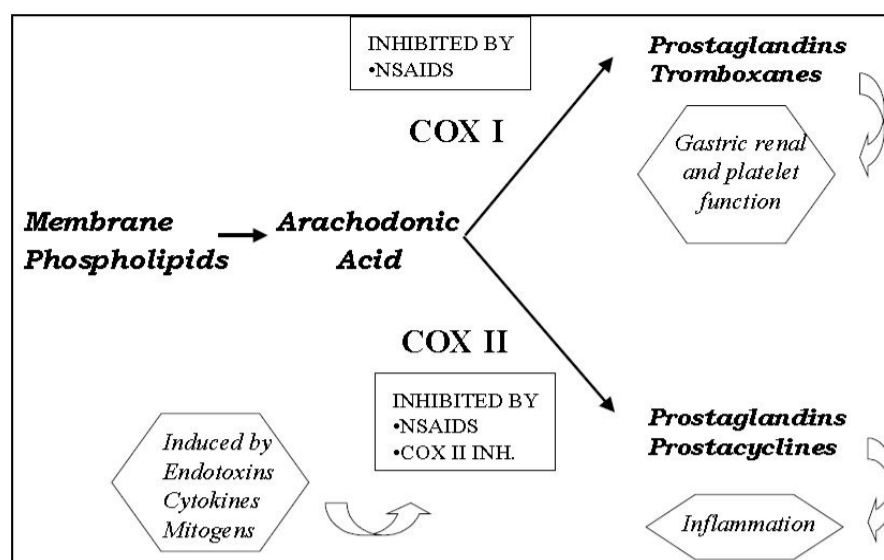
Drotaverine is an iso-quinoline derivative. It is safe and very effective in shortening the duration of labor. It acts by increasing the intracellular concentration of substrate camp, which produces cervical dilatation. The smooth muscle cone of the uterine cervix which remains normally contracted during pregnancy till early labor, starts relaxing near term when cervix is taken up. Once contraction sets in, this cone is situated above the equator of the fetal head. This pulling up process requires adequate relaxation of the smooth muscle cells of muscle cone. Dilatation of the smooth muscle cone helps the rest of the ground substance of the cervix to respond to uterine contractions<sup>7</sup>.

Phloroglucinol is one of spasmolytics, primarily used for gastrointestinal tract colic. The drug was extensively used during 1970s and early 1980s for augmentation of labor. There has been a resurgence of interest in the subject. 18% incidence of Post-Partum Haemorrhage was reported due to uterine atony with the use Drotaverine hydrochloride. This incidence is statistically significant and limits the use of Drotaverine in labor. Although the number of patients with these complications were not large enough but still it is suggested that phloroglucinol can be used in patients with above mentioned complications with no toxic effects and a good outcome. Phloroglucinol shortens the duration of labor, is non toxic to both mother and foetus and does not cause uterine atony. It also has an analgesic action. As Spasmolytic, phloroglucinol have a definite role in obstetrics<sup>2</sup>.

#### **Role of NSAIDs in labor augmentation**

The world market for NSAIDs, including the selective inhibitors of (COX)-2, now exceeds 8 billion Euros per year. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed categories of drugs worldwide in the treatment of pain and inflammation in many conditions<sup>8</sup>. While the primary use of NSAIDs is pain and inflammation, there is increasing use of these drugs for other indications too<sup>9</sup>.

NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps. Aspirin is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk. NSAIDs also are included in many cold and allergy preparations. Two drugs in this category, ibuprofen and naproxen, also reduce fever<sup>8</sup>.



**Figure 1: Mechanism of Action of NSAIDs in Labor Augmentation**

Mechanism of action of NSAIDs in labor augmentation is shown in figure 1. NSAIDs work by suppressing the production of fatty acids called prostaglandins that cause inflammation and pain. They do this by blocking the action of an enzyme, cyclo-oxygenase (COX). This enzyme is responsible for converting precursor acids into prostaglandins.

In the periphery NSAIDs work by decreasing the sensitivity of the nociceptor (sensory neurons that are found in any area of the body that can sense pain either externally or internally) to painful stimuli induced by heat, trauma, or inflammation. In the central nervous system, they are thought to function as anti-hyper analgesics and block the increased transmission of repetitive incoming signals to higher centers. In effect, they modulate perception of pain caused by repetitive stimulation from the periphery<sup>8</sup>.

NSAIDs vary in their potency, duration of action, and the way in which they are eliminated from the body. Another important difference is their ability to cause ulcers and promote bleeding. The more an NSAID blocks Cox-1, the greater is its tendency to cause ulcers and promote bleeding.[2] COX-2 agents have been shown to reduce (by as much as 50%) the incidence of serious gastrointestinal adverse events, as compared to conventional NSAIDs. However, selective COX-2 inhibitors still exhibit significant renal toxicity, interfere with the healing of gastrointestinal ulcers, and may exert significant pro-thrombotic and hypertensive effects<sup>9</sup>.

The hypothesis of COX iso-enzyme selectivity has led to a proposed classification for COX inhibitors. The majority of classified NSAIDs are COX non-selective inhibitors, which when administered over the long term, e.g., in cases of rheumatoid arthritis, cause duodenal ulcers in 20% of cases and gastric hemorrhage in 1-4% of cases/year. Preliminary clinical studies have shown that COX-2 selective inhibitors (celecoxib, rofecoxib) are as efficient as standard NSAIDs and have fewer adverse digestive side effects. Among the different classes of COX-2 inhibitors, preferential COX-2 inhibitors i.e.; Aceclofenac, meloxicam, nimesulide etc. have fewer gastric side effects than standard NSAIDs but which are not risk-free at high doses<sup>10</sup>.

**Limitations of Non-selective COX inhibitor NSAIDs in respect of labor**

Adverse effects of the Non-selective cox inhibitor NSAIDs are usually dose related, although many dose unrelated effects like idiosyncratic effects also appear. These include urticarial rashes, angioedema and bronchospasm<sup>11</sup>. Non selective are effective in the temporary treatment of moderate pain but have the potential for long-term side effects i.e.; cause stomach disorders, Long-term use may cause kidney disorders, even accelerate the course of joint degeneration may induce high blood pressure, ulceration and bleeding in the stomach, tiny pinpoint perforations in the surface of the small intestine (can induce “leaky gut syndrome”)<sup>12</sup>.

**Preferential COX-2 inhibitors**

Although cyclooxygenase-2 selective inhibitors (coxibs) represent a new class of analgesic and anti-inflammatory drugs that exhibits preference for inhibition of cyclooxygenase-2, its cardiovascular safety is controversial, since trial showed increased incidence of cardiovascular events in patients receiving coxibs. There is a need of a drug, which has high efficacy like traditional NSAIDs, shows high GI tolerability like selective cox-2 inhibitors but have no adverse cardiovascular effects<sup>13</sup>.

Nimesulide, a preferential COX-2 inhibitor is a non-carboxylic acid non-steroidal anti-inflammatory drug (NSAID) that has been effectively used for the treatment of a variety of inflammatory and painful conditions, including osteoarthritis in European and Asian countries for more than 15 years<sup>14</sup>. Pharmaco-epidemiological studies suggest that nimesulide is an effective NSAID with relatively favorable profile of safety for the treatment of osteoarthritis and non-rheumatoid musculo-skeletal conditions<sup>15</sup>. But the uses of medicinal products containing nimesulide are contraindicated in third trimester of pregnancy<sup>16</sup>.

Among the Preferential COX-2 inhibitors, Aceclofenac has been shown to have potent analgesic and anti-inflammatory activities, similar to indomethacin and diclofenac and due to its preferential cox-2 blockade, it has better safety than conventional NSAIDs with respect to adverse effects on gastrointestinal and cardiovascular system<sup>17</sup>.

**Available combinations of nsaid and antispasmodic agents**

There are number of combinations of NSAID and Antispasmodic agents available in market or under research. The characteristics of given combinations are given in Table 1<sup>18</sup>.

Table 1: Developed Combinations of NSAID and Antispasmodic agents

Sr. No.	MARKETED PRODUCTS	COMBINATION OF DRUGS	NAME OF COMPANY	EFFECT OF DRUG
1	Tuela	Mefenamic acid + Drotaverine HCl	Cipla	Mefenamic acid- can't be used in last three months of pregnancy. Drotaverine HCl- antispasmodic agent with non-anticholinergic action.
2	Ospas Tablets	Nimesulide + Drotaverine HCl	Auspi medicaments	Nimesulide- preferential COX-2 inhibitor, contraindicated in pregnancy. Drotaverine HCl- antispasmodic agent with non-anticholinergic action.
3	Petro tablets	Paracetamol + Drotaverine HCl	Acapi products	Paracetamol- poor anti-inflammatory action. Drotaverine HCl- antispasmodic agent with non-anticholinergic action.
4	Not available	Piroxicam + Phloroglucinol	(under research)	Piroxicam- long acting NSAID with anti-inflammatory action (reversible COX inhibitor). Phloroglucinol- combination with NSAID is not deleterious but does not improve pain relief.
5	Paracetamol & Dicyclomine HCl Tablets	Paracetamol + Dicyclomine	Eurolife Healthcare Pvt. Ltd.	Paracetamol- has poor anti-inflammatory action. Dicyclomine- has Anti-cholinergic side-effects.
6	Drolgan	Aceclofenac + Drotaverine HCl	IPCA labs	Aceclofenac- preferential COX-2 inhibitor. Drotaverine HCl- antispasmodic agent with non-anticholinergic action.

### CONCLUSION

The resultant lethal complications, contributed by prolongation in labor, can be augmented by various spasmolytics and spasm-analgesics combinations. In order to select the effective and significant combination for above said, the present review contributes and concludes that the combination of Aceclofenac, a preferential COX-2 inhibitor and Drotaverine HCl, the only antispasmodic agent with no anti-cholinergic side-effects, can be efficiently used to augment the labor and may be considered as a suitable one among the others.

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