# Efficacy of Intravenous Tenoxicam as an Analgesic during the First Stage of Labor: A Randomized Controlled Trial

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**ABSTRACT**
**Background:** childbirth is one of the most painful events of a woman's life. The experience of labor pain is a complex, multidimensional response to sensory stimuli generated during parturition and its intensity can vary greatly. Unlike other acute and chronic pain experiences, labor pain is not associated with pathology, but with the most basic and fundamental of life's experiences
**Aim of the work**: this work aimed to study the efficacy of intravenous tenoxicam for labor analgesia.
**Patient and methods:** this was two-arm, randomized controlled trial. The first arm (**Group T**) represented subjects who received tenoxicam. The second arm (**Group R**) represented subjects who received routine analgesic pethidine and it is given at a dose of 50 mg diluted over 10 ml of normal saline. The parturient woman was given 3-4 cm of diluted pethidine whenever she has intolerable pain.
**Results:** this study included 260 subjects that were allocated into two arms: tenoxicam arm (n=118) and pethidine arm (n=142) as the control group. Tenoxicam group included 118 subjects and the pethidine group included 142 subjects. Maternal age was 23.74 ± 3.76 in tenoxicam group vs 23.99 ± 3.5 in pethidine group. Gestational age was 39.04 ± 1.42 in tenoxicam group vs 38.93 ± 1.5 in pethidine group. Birth weight was 3.43 ± 0.26 in tenoxicam arm vs 3.41 ± 0.26 in pethidine arm, average fetal heart rate was 140.1 ± 17.12 in tenoxicam arm vs 138.1 ± 16.39 pethidine arm, cervical dilatation was 4.19 ± 0.77 in tenoxicam arm vs 4.25 ± 0.7 and interval to delivery was 5.89 ± 1.29 in tenoxicam arm vs 6.2 ± 1.62 in pethidine arm.
**Conclusion:** tenoxicam (40 mg iv), a long acting NSAID that induces analgesia by inhibiting peripheral prostaglandin synthesis, reduced postpartum uterine contraction pain without apparent maternal or neonatal adverse effects. Furthermore, tenoxicam exhibits superior analgesic properties over the routinely used pethidine as labor analgesic. Further studies should evaluate analgesic effects vs side effects of iv tenoxicam as a function of dosage or as part of combination therapy with different opioid analgesics.
**Keywords:** tenoxicam, labor analgesia.

## INTRODUCTION

The sensation of pain is undeniably subjective. Personality, recollections of painful events, emotional state, age, culture, context and other factors influence an individual's responses to, and description of, pain [1-2]. Pain during the early first stage of labor arises from dilation of the lower uterine segment and cervix. Pain during the late first stage and second stage of labor arises from descent of the fetus in the birth canal, resulting in distension and tearing of tissues in the vagina and perineum [3].

Most women in labor require pain relief. Pain management strategies include non-pharmacological interventions that aim to help women cope with pain in labor and pharmacological interventions that aim to relieve the pain of labor [4]. Non-opioid analgesics can effectively relieve mild to moderate pain and for moderate to severe pain, they can be used in combination with other drugs to enhance pain relief. Most non-opioids are quite safe when used for temporary acute pain; problems may arise when they

are taken over a long period of time (for chronic pain), then they could damage the lining of the gastro-intestinal tract or the kidneys or more rarely other organs [4].

**Non-opioid analgesic agents are divided into two groups:**

**The first group** included substances which have anti-inflammatory effects in addition to their analgesic and antipyretic activities and are called non-steroidal anti-inflammatory drugs **(NSAIDs)**. The members of this group, with the exception of almost all selective inhibitors of cyclooxygenase 2 (COX-2), are acids. Acidic NSAIDs, which include salicylates, derivatives of acetic acid ,propionic acid and oxicams among others, comprise molecules containing a lipophilic and a hydrophilic region and are more than 99 % bound to plasma proteins [5].

**The second group** of non-opioid analgesics, which are not classified as NSAIDs, consists of substances that lack anti-inflammatory properties, such

as phenazones, metamizole (dipyrone) and paracetamol. Their molecules are neutral or weakly basic, have no hydrophilic polarity and are much less strongly bound to plasma proteins than NSAIDs [5]. The role of COX-1 and COX-2 in spontaneous human myometrial contractility was studied through the use of highly selective inhibitors of both isoforms, to investigate whether NSAIDs achieve uterine quiescence through COX inhibition. Findings suggested that spontaneous myometrial contractions are not dependent on myometrial COX activity or prostaglandin production. Little evidence was found that selective blockade of COX-1 or COX-2 had effects on the spontaneous contractility of human myometrium in vitro, even though it is clear that both isoforms are present in the tissue [6].

Tenoxicam is a thienothiazine derivative of the oxicam class of NSAIDs. It is a potent analgesic, anti-inflammatory and antipyretic agent. It is a non-specific inhibitor of COX, with a long elimination half-life, about 70 h, which allows single daily dosing [5].

A study indicated that tenoxicam has a lower gastrotoxic potential than some other NSAIDs, including aspirin and diclofenac. Tenoxicam is a potent reversible inhibitor of the secondary (collagen-induced) phase of platelet aggregation but does not appear to affect fibrinolytic potential. Renal function is not normally altered during treatment with tenoxicam, although a minor decrease in creatinine clearance may occur in patients with pre-existing renal impairment, an effect generally seen with most other NSAIDs [7].

A slight increase of bleeding time was seen one hour after intravenous administration. However, this increase is clinically insignificant since bleeding times after tenoxicam were below the normal upper limit of 10 min in all patients, with no clinical evidence of hematological impairment following a single intravenous administration of tenoxicam 20 mg [4].

Total concentration of tenoxicam in human breast milk is low; a total concentration of 0.04 mg/L was reported when the drug was found in plasma at the therapeutic concentrations. As the quantity of the drug excreted in breast milk is small, single or occasional use of the drug would be expected to be well tolerated [8].

**Aim of the work**: this study aimed to evaluate the efficacy of intravenous tenoxicam for labor analgesia.

# PATIENT AND METHODS
## Study Design
Two-arm, randomized controlled trial was done to study the efficacy of intravenous tenoxicam as an intrapartum analgesic:

The first arm (**Group T**) represents subjects who will receive tenoxicam

The second arm (**Group R**) represents subjects receiving routine analgesic which is pethidine given at a dose of 50 mg diluted over 10 ml of normal saline. the parturient woman will be given 3-4 cm of diluted pethidine whenever she has intolerable pain.

## Study Setting
This study was carried out in Ain Shams University Maternity Hospital Labor and Delivery Unit.

## Study Population
Subjects admitted to the labor and delivery unit in labor were screened for eligibility to participate in this study. A written informed consent to participate in this study was obtained.

All subjects underwent full medical interview and clinical examination to ensure eligibility for enrolment in the study.

### Inclusion Criteria
- Primiparity
- Active phase of labor (cervical dilatation of 3-5 cm, in the presence of adequate uterine contractions; lasting at least 40 seconds at intervals of 3-4 minutes)
- Maternal age between 20-29 years
- Singleton term pregnancy (37-42 weeks of gestation)
- Vertex-presenting fetus

### Exclusion Criteria
- Clinical evidence of cephalopelvic disproportion
- Scarred uterus; previous cesarean section, hysterotomy or myomectomy
- Medical disorders associated with pregnancy, especially gastritis, peptic ulcer, bronchial asthma or renal impairment
- Fetal distress
- Receiving any regional or parenteral analgesia before recruitment in the study
- Known hypersensitivity to the drug family

After enrolment, each participant was given the next available number in a computer-generated randomization plan which determined the group to follow.

**Study Interventions**

Intravenous administration of tenoxicam, a lyophilisate with 20 mg to be dissolved and diluted in 10 mL of sterile water (single dose), as an analgesic during the first stage of labor, given by a member of the study team. The process of labor was managed in both arms of the study according to the hospital protocol to ensure unified management of all cases. The use of additional medications was recorded.

**STUDY OUTCOMES**
**Primary Outcome Measure**

The efficacy of intravenous tenoxicam to supply adequate analgesia was indicated by changes in the pain intensity score using the visual analog scale and other pain intensity assessment tools (verbal and numeric rating scales). Assessment is to be done and followed up by the investigator at ¼, ½, 1, 2, 3 and 4 hours from drug administration. Drop-out rate or additional analgesia was also assessed.

**Secondary Outcome Measures**

Among the 2 groups, the following parameters will be assessed and compared:
- Duration of labor (1st and 2nd stages)
- Maternal side effects, e.g. gastric upset
- Postpartum hemorrhage
- Adverse neonatal outcomes
- Need for rescue medication

**Statistics**
**Sample Size**

The sample size was calculated using Stata version 10 (StataCorp LP, College Station, Texas, USA), setting power of the study $(1-\beta)$ at 90% and type-1 error $(\alpha)$ at 0.01. Data from a relevant study with similar prospect [9] indicated that the failure rate (use of rescue analgesic) was 14% in the study group after 1 h of receiving paracetamol.

According to these tenoxicam had comparable efficacy, a minimum of 50 women would be required in each arm of the study.

**Data Analysis**

Descriptive statistics for measured variables will be expressed as:
- Mean and SD for metric data
- Median and interquartile range for discrete data
- Number and proportions for categorical data

Demographic data, primary and secondary outcomes of both groups will be compared via:
$t$ test for quantitative parametric measures
Mann-Whitney U test for quantitative non-parametric measures
$\chi^2$ and Fisher's exact tests for categorical measures

A two-sided $P$ value < 0.05 will be considered statistically significant. Pearson's correlation coefficient (for metric variables) and Spearman's correlation coefficient (for rank variables) will be used to estimate association between variables.

Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) and IBM SPSS Statistics (IBM Corporation, Armonk, New York, USA) will be used for data presentation and statistical analysis.

**Ethical Considerations**

The procedures described in this study protocol gained approval by the Research Ethics Committee to ensure following the standard ethical principles governing research involving human subjects.

Before being admitted to the clinical study, the subject must consent to participate after the nature, scope and possible consequences of the clinical study have been explained in a manner understandable to her.

A consent document (in Arabic) containing all required elements was read by the patient, and signed by a dated formal signature of the patient and the information provider. If the patient is unable to read, information in the written consent form will be explained orally in the presence of an impartial witness, who should sign a dated formal signature together with the patient's legally-recognized alternative to her signature (e.g., the patient's thumbprint or stamp). The original signed consent documents will be retained by the principal investigator with data confidentiality guaranteed.

Any measures required specifically for the clinical study was not be performed until valid consent has been obtained. During the study, every parturient has the right to discontinue irrespective of the reasons.

**RESULTS**

The following figure summarized the study flow starting from initial patient recruitment until the final analyzed cases.
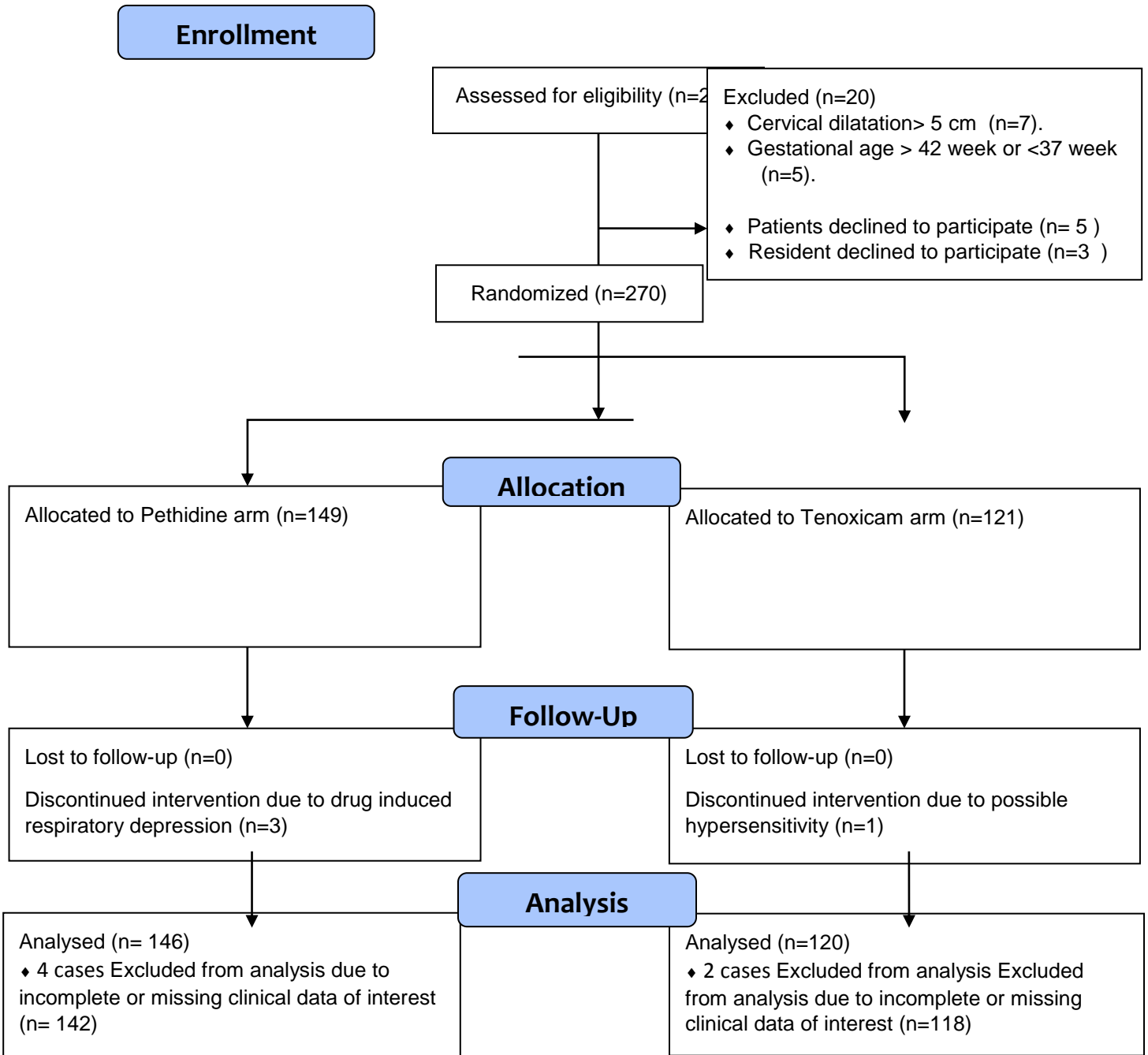
**Enrollment**

Assessed for eligibility (n=2...

Excluded (n=20)
- Cervical dilatation> 5 cm  (n=7).
- Gestational age > 42 week or <37 week (n=5).

- Patients declined to participate (n= 5 )
- Resident declined to participate (n=3  )

Randomized (n=270)

**Allocation**

Allocated to Pethidine arm (n=149)

Allocated to Tenoxicam arm (n=121)

**Follow-Up**

Lost to follow-up (n=0)

Discontinued intervention due to drug induced respiratory depression (n=3)

Lost to follow-up (n=0)

Discontinued intervention due to possible hypersensitivity (n=1)

**Analysis**

Analysed (n= 146)
- 4 cases Excluded from analysis due to incomplete or missing clinical data of interest (n= 142)

Analysed (n=120)
- 2 cases Excluded from analysis Excluded from analysis due to incomplete or missing clinical data of interest (n=118)

**Figure 1: study flow chart**

**Table 1: comparing baseline and clinical outcomes in tenoxicam and pethidine groups**

| Variable | Tenoxicam arm (n=118) | Pethidine arm (n=142) | P-value* |
|---|---|---|---|
| Maternal age (years) | 23.74 ± 3.76 | 23.99 ± 3.5 | 0.57 (N.S) |
| Gestational age (months) | 39.04 ± 1.42 | 38.93 ± 1.5 | 0.55 (N.S) |
| Birth weight (Kg) | 3.43 ± 0.26 | 3.41 ± 0.26 | 0.5 (N.S) |
| Fetal heart rate (beat/min) | 140.1 ± 17.12 | 138.1 ± 16.39 | 0.34 (N.S) |
| Cervical dilatation (Cm) | 4.19 ± 0.77 | 4.25 ± 0.7 | 0.57 (N.S) |
| Interval to delivery (Hours) | 5.89 ± 1.29 | 6.2 ± 1.62 | 0.08 (N.S) |

*Unpaired two tailed t-test was used in comparing the two groups.
**N.S:** non-significant.

**Table 2: comparing pain score at the different time points:**

| Outcome | Tenoxicam arm (n=118) | Pethidine arm (n=142) | RR* (95% CI) | P-value** |
|---|---|---|---|---|
| Baseline pain score | 5 (3-8) | 6 (4-8) | 1.13 (0.98-1.3) | 0.09 (N.S) |
| Pain score after 15 min | 4 (3-8) | 6 (4-8) | **1.3 (1.15-1.47)** | **<0.001 (Sig.)** |
| Pain score after 30 min | 6 (3-8) | 6 (4-8) | 1.22 (1-1.45) | 0.83 (N.S) |
| Pain score after 1 hr | 7 (4-8) | 6.5 (4-8) | 1.02 (0.8-1.3) | 0.72 (N.S) |
| Pain score after 2 hr | 6 (5-8) | 7 (4-9) | 1.23 (0.87-1.75) | 0.74 (N.S) |
| Pain score after 3 hr | 8 (6-9) | 8 (5-9) | 0.008 (0.01-0.64) | 0.85 (N.S) |
| Pain susceptibility* **(n, %) | 7 (5.9) | 7 (4.9) | 1.2 (0.43-3.33) | 0.72 (N.S) |

- *For design of contingency table for relative risk calculation, pain data were dichotomized considering pain score=6 as a cut-off value.
- **Mann-Whitney U test was used for comparing ordinal pain data.
  ***Chi-square test with Yates correction was used for comparing the proportions.
  **C.I:** confidence interval, **N.S:** non-significant, **RR:** relative risk, **Sig.:** significant.
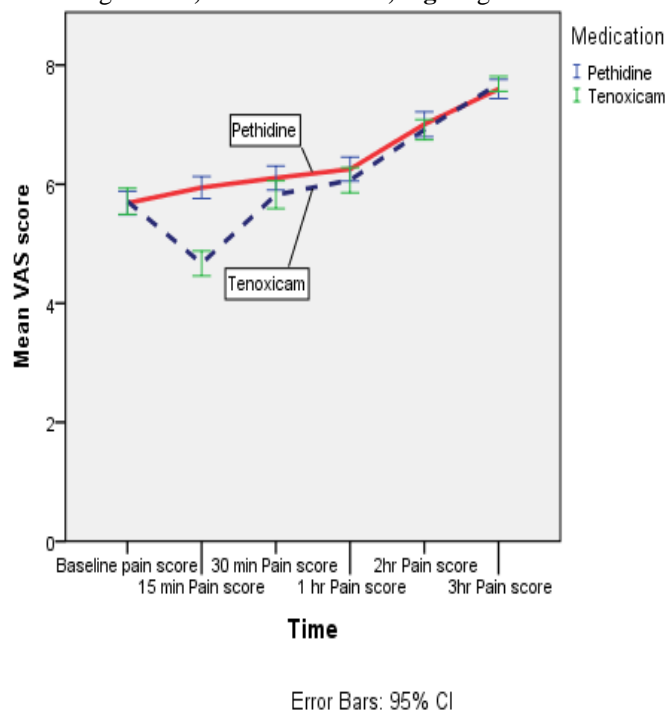


Error Bars: 95% CI

**Figure 2 :** over all pain control profiles in both pethidine group (represented with the solid red line) and tenoxicam group (represented with dotted blue line). It could be seen clearly the superior clinical efficacy of tenoxicam in controlling the pain over pethidine.

**Table 3: comparing the neonatal outcome in pethidine and tenoxicam groups**

| Outcome (n, %) | Tenoxicam arm (n=118) | Pethidine arm (n=142) | RR (95% CI) | P-value* |
|---|---|---|---|---|
| NICU | 14 (11.9) | 21 (14.8) | 0.8 (0.43-1.51) | 0.47 (N.S) |
| APGAR Score less than 7 in 1 min | 23 (19.5) | 35 (24.6) | 0.79 (0.5-1.26) | 0.32 (N.S) |
| APGAR Score less than 7 in 5 min | 14 (11.9) | 21 (14.8) | 0.8 (0.43-1.51) | 0.47 (N.S) |

*Chi-square test was used for comparing the proportions.
**CI**: confidence interval, **NICU:** neonatal intensive care unit admission, **N.S:** non-significant, **RR:** risk ratio.

**Table 4: comparing Bishop Scores between tenoxicam and pethidine groups**

| Bishop profile | Tenoxicam arm | Pethidine arm | RR (95% CI) | P-value* |
|---|---|---|---|---|
| Baseline Patients with Bishop score > 6 (n, %) | 14 | 14 | 1.2 (0.6-2.4) | 0.604 (NS) |
| 2-hr Bishop score >6 (n, %) | 36 (30.5) | 28 (19.7) | 1.55 (1.007-2.375) | **0.031 (Sig)**. |
| 4-hr Bishop score >6 (n, %) | 97 (82.2) | 72 (50.7) | 1.62 (1.35-1.95) | **<0.001 (Sig)** |

*Chi-square test was used for each pair of comparison.

## DISCUSSION

This study was conducted to evaluate the analgesic effects and the safety of I.V tenoxicam versus pethidine as control in women undergoing normal vaginal delivery. This randomized double-blinded controlled clinical trial carried on Ain Shams University Maternity Hospital, Labor and Delivery Unit from June 2016 to June 2017.

After obtaining consent from each participant, all the subjects included in this study were assessed for baseline criteria including: maternal age, birth weight, cervical dilatation, interval to delivery and initial Bishop scores and statistical comparison were made between the study group with regard to baseline criteria to confirm the homogeneity and all baseline comparisons were statistically non-significant (P<0.05). Although being effective analgesic in rheumatologic and post-operative settings, tenoxicam was little evaluated as obstetric analgesic in labor pain [10-11], and all the previous trials studied the analgesic effect in women undergoing caesarian section mainly as adjunct to opioid analgesics and none of them investigated their efficacy and (or) safety profile in case of normal vaginal delivery.

Tenoxicam exhibits dual benefit as labor analgesic; first: As NSAID, it reduces the nociceptive pain associated with prostaglandin release during the labor, Second: It reliefs the uterine cramps, possible by its effect on PGE2 responsible for the uterine contractions during the different stages of labor [12].

**Elhakim *et al*. ** [13] studied the analgesic efficacy of a single I.V. dose of tenoxicam 20 mg, given 10 min before induction of anesthesia in 25 patients underwent elective caesarean section. Another group of 25 similar patients served as the controls. Nalbuphine consumption in the first 24 h after operation was reduced by 50% when tenoxicam was given. The median time to first request for analgesia was increased from 25 to 110 min in the tenoxicam group. Subjective experiences of pain and sedation were significantly greater in the control group up to 24 h after operation. The hemodynamic variability after intubation was of shorter duration in the tenoxicam group. There was no significant difference in incidence and severity of

postoperative nausea and vomiting between the two groups. The surgeon's assessment of uterine relaxation and bleeding, using a visual analogue score, and infant well-being, as judged by Apgar score and cord blood-gas analysis, showed no significant difference between the two groups. There was no evidence of premature closure of the ductus arteriosus or pulmonary hypertension. They concluded that a single I.V dose of tenoxicam is a useful pretreatment to minimize the hemodynamic variability of light general anesthesia at induction-delivery and in reducing 24 h postoperative opioid consumption and hence they are considered as effective labor analges.

Pethidine is the most common opioid administered during delivery. In many hospitals, particularly in those with low numbers of deliveries, this drug is the analgesic of choice [14]. Neonatal respiratory depression and hypothermia remain major concerns of pethidine therapy. It was estimated that it can take a newborn three to six days to eliminate pethidine and its metabolite, norpethidine, from its system. The analgesic effect of pethidine starts within 10 - 20 minutes and lasts two to four hours after being administered intramuscularly [15]. Pethidine has been shown to significantly affect fetal heart rate variability, accelerations and decelerations, during labor [16]. Changes in normal fetal heart indices have consequences for the woman. She was required to have electronic fetal heart rate monitoring if she was in hospital and transfer to hospital if she was in the community.

Through this study we introduced the concept of **"dynamic statistics"** where each step in the trial undergone the statistical evaluation and the results of the statistical analyses at each level provided a basis for inclusion, exclusion, addition of subjects or modifying the planned methodology. In other words, the results of the statistical analysis for different phases of this trial guided the next steps. For example, sample size was initially calculated to be 50 patients in each arm based on the previous study conducted by **Abd-El-Maeboud et al.** [17] who compared paracetamol to pethidine for control of labour pain. At the start of the trial we conducted a pilot study on 38 subjects allocated equivalently into each arm, the estimated sample size based on the findings of the pilot statistics were 240 patients, so the study plan was modified and ultimately conducted on the higher sample size estimated based on the results of pilot statistics. All sample size calculations

followed the pupliushed guidelines for sample size calculation [18]. Another implementation of dynamic statistical analysis was carried out during the final evaluation of the results of the trial. Inspite of following the computerized randomization throughout the subject's allocation, the statistical comparison of the study arms demonstrated a statistically significant difference between the study groups with regard to some of baseline criteria, namely, the birth weight and maternal age. This was treated by adding additional 20 subjects with very strict inclusion criteria with regard to this two variables and following their randomization to the study arms, the results were re-evaluated and confirmed the statistical balancing of the two study groups regarding to each pair of comparison of the baseline criteria prior to carrying out inferential statistical tests for comparing the outcomes between the two study groups.

In the current study, it was noted remarkably that the interval to delivery was higher than the similar studies [18-19]. This can be explained by that the fact that both the study medications are well-known to prolong the labor. NSAIDs reduce the uterine contractions by its inhibitory effect on PGE2 (the principle mediator of normal uterine contractions) [20] and pethidine due to its sedative action [21]. However, comparing their intrinsic effects on duration to labour; we found that there was non-statistically significant difference between them (p=0.08).

In this study, pain severity, which was defined according to a patient's VAS pain score, was significantly lower in patients who received I.V tenoxicam 15 minutes after intervention, but there was not a significant difference in the severity of pain between the patients at 30 minutes, 1 hour, 2 hours and 3 hours intervals post-dose for each intervention, p-values were 0.83, 0.72, 0.74, 0.85, 0.72 respectively. The possible explanation for the significant pain management found in patients on tenoxicam therapy over those administered pethidine is that in the management of post-cesarean analgesia is that uterine contraction pain involves several chemical nociceptive mediators such as bradykinins, leukotrienes, prostaglandins, serotonin, lactic acid and substance P [12] that are well known to be directly affected by tenoxicam and little affected by pethidine. Another possible hypothesis for the superiority of tenoxicam over pethidine in pain control during Labour is most likely emphasized by that NSAID in general suppress prostaglandin production, including

prostaglandin E2 which has substantial effect in promotion of uterine contractions during labor, so NSAIDs may exhibit additional mechanism for labor analgesia by inhibiting the physiological uterine contraction besides its action on reducing the sensitivity of nociceptive receptors which are the key player in peripheral pain [12]. This interpretation was supported by the results of **Abdollahi *et al.*** [22] who concluded that intravenous paracetamol was more effective than intramuscular pethidine at relieving labor pain in normal vaginal deliveries.

The findings of our work demonstrated that the differential longitudinal pain scores of the tenoxicam arm vs pethidine arm was 5 (3-8) vs 6 (4-8) at baseline assessment, 4 (3-8) vs 6 (4-8) after 15 minutes of administration , 6 (3-8) vs 6 (4-8) after 30 minutes of administration, 7 (4-8) vs 6.5 (4-8) after 1 hour of administration, 6 (5-8) vs 7 (4-9) after 2 hours of administration, 8 (6-9) vs 8 (5-9) and 7 (5.9) 7 (4.9) after 3 hours of administration. Despite of the clinical superiority in pain relief at 15 minutes, 2 hours of drug administration, only the results of 15-minute pain assessment was statistically significant (odds of adequate pain control defined as VAS score $\leq 6$ was 1.3 (1.15-1.47), $p < 0.001$. To best of our knowledge, there were no detectable comparisons concerning I.V tenoxicam vs pethidine in relief of labour pain.

Opioids especially pethidine have been implicated in causing neonatal respiratory depression. It has been postulated that this effect is mainly evident on intravenous administration of the drug and if the fetus is delivered within two to three hours following the drug use [23], but numerous studies have reported that Apgar scores were not altered and respiratory depression requiring resuscitation was not observed with pethidine and tramadol [24]. Our results support these previous data. The mean Apgar scores at 1 and 5 minutes were comparable between the 2 groups, indicated absence of any neonatal adverse effects with the use of either of the 2 drugs. We found that 1 min Apgar score was less than 7 in 19.5% of tenoxicam group vs 24.6% in pethidine group (p=0.32), 5-minute Apgar score was less than 7 in 11.9% of tenoxicam group vs 14.8 in pethidine group (p=0.47) and overall rate of neonatal admission to ICU for all reasons was 11.9% in tenoxicam group vs 14.8 % in pethidine group (p=0.47). This also agrees with the results of **Othman *et al.*** [25] who found that there was no evidence of a difference in Apgar scores for any of the comparisons of non-

opioid drugs with placebo or different types of non-opioids˙

To the best of our knowledge, this is the largest trial to investigate the potential role of tenoxicam in control of labor pain during different stages. It is also the only trial evaluating the analgesic effect of tenoxicam in normal vaginal deliveries, as most of the few studies evaluating tenoxicam in labor was carried out in cesarean section settings, so it the analgesic efficacy of tenoxicam by reducing the physiological pain due to uterine contractions was obviously confounded by presence the wound pain.

## CONCLUSION

Tenoxicam (20 mg iv), a long acting NSAID that induces analgesia by inhibiting peripheral prostaglandin synthesis, reduced postpartum uterine contraction pain without apparent maternal or neonatal adverse effects. Furthermore, tenoxicam exhibits superior analgesic properties over the routinely used pethidine as labor analgesic. Further studies should evaluate analgesic effects vs side effects of iv tenoxicam as a function of dosage or as part of combination therapy with different opioid analgesics.

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