# Influence of Ketoprofen on Drainage Volume After Radical Breast Cancer Surgery: A Prospective Randomized Clinical Trial [ISRCTN06628870]

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## Abstract

**Objective:** To determine the effectiveness of non steroidal inflammatory drug ketoprofen versus placebo in reducing postoperative drainage duration and volume after breast cancer surgery.
**Materials and Methods:** A single-centre prospective, randomized, double blind controlled study of women scheduled to undergo a simple or modified radical mastectomy. Patients were randomized into two groups given placebo or a single dose of 200 mg sustained release ketoprofen. Primary outcome measure was total drain volume; secondary outcomes were mean drainage periods, drained volume on postoperative days 1 and 2 and associated morbidity. A sample size and power calculation was undertaken to demonstrate a reduction of 20% between groups in primary outcome (power 0.80; significance level 0.05).
**Results:** Forty-eight patients were randomized to the ketoprofen group and 45 to the placebo group. The demographic characteristics of the two groups were similar. There was no difference between the two groups in the postoperative drainage volume: 540±152 ml in the ketoprofen group versus 585±195 ml in the placebo group ($p$=0.22) or period (respectively in days 6±2 versus 5.6±1.1; $p$=0.24). Finally complications did not differ in frequency between the two groups ($p$=0.54).
**Discussion:** A single dose of 200 mg sustained release ketoprofen did not result in a significant decrease in the postoperative drainage volume compared with placebo. However, the highly significant difference between groups during the first two postoperative days tends to confirm the inflammatory causes of the collected fluid, opening the door for future research.

**Keywords:** breast cancer surgery, anti-inflammatory agents, non-steroidal drains seroma

## Özet

### Ketoprofenin Radikal Meme Cerrahisi Sonrasında Drenaj Hacmine Etkisi: Randomize Kontrollü Bir Çalışma [ISRCTN06628870]

**Amaç:** Radikal meme cerrahisi sonrasında non-steroidal antienflamatuvar bir ilaç olan ketoprofenin postoperatif drenaj süre ve hacmine etkisini plasebo ile karşılaştırmak.
**Materyal ve Metot:** Tek bir merkezde basit veya modifiye radikal mastektomi yapılacak kadınlarda ileriye yönelik, randomize, çift kör bir çalışma planlandı. Hastalar plasebo veya tek doz uzun süre salınımlı (SR: sustained release) 200 mg ketoprofen gruplarına randomize edildi. Primer son nokta olarak drenaj hacmi; sekonder son noktalar olarak da ortalama drenaj periyotları, postoperatif 1. ve 2. gündeki drenaj hacmi ve morbidite belirlendi. Örneklem büyüklüğü ve güç analizi, gruplar arasında primer son nokta hedefinde %20'lik bir azalmayı gösterecek şekilde yapıldı (güç 0.80; anlamlılık derecesi 0.05).
**Sonuçlar:** Ketoprofen grubuna 48, plasebo grubuna 45 hasta randomize edildi. Her iki grubun demografik özellikleri benzerdi. Her iki grubun postoperatif drenaj hacmi (ketoprofen grubunda 540±152 ml, plasebo grubunda 585±195 ml; $p$=0.22) veya periyotları (ketoprofen grubunda 6±2 gün, plasebo grubunda 5.6±1.1 gün; $p$=0.24) farklı değildi. Her iki grup arasında komplikasyon oranları açısından da fark yoktu ($p$=0.54).
**Tartışma:** Tek doz uzun süre salınımlı 200 mg ketoprofen, plasebo ile karşılaştırıldığında postoperatif drenaj hacmini anlamlı derecede azaltmamaktadır. Bununla beraber, postoperatif ilk iki gün içindeki drenajlar arasındaki anlamlı farklılık enflamatuvar teorileri desteklemektedir. Bu da, sıvı toplanması ile ilgili ileri çalışmaların gerekliliğini göstermektedir.

**Anahtar sözcükler:** meme kanseri cerrahisi, non-steroidal antienflamatuvar ajanlar, drenaj, seroma

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## Objective

Modified Radical mastectomy remains one of the most performed procedures for breast cancer surgical treatment (1). This extensive surgery causes substantial post operative morbidity and is associated with an extended closed suction wound drainage (2) and an average hospital stay of a week (3). There are widely varying recommended techniques to reduce postoperative liquid formation (4-6) but there is no strong evidence to recommend any one of these techniques (7,8) and premature withdrawal of postoperative drains is accompanied by an increase in the incidence of axillary seromas (9).

The origin of drained liquid is controversial; some suggest that lymph might contribute (10,11) but in an earlier study Watt-Boolsen et al. (12) investigated the nature of post-mastectomy seroma and concluded that it's an exudate and thus is the result of an acute inflammatory reaction. In a more recent study McCaul et al. (13) analyzed the fluid composition after breast cancer surgery and demonstrated a minimal contamination with whole blood, but containing more inflammatory components other than lymphocytes; they also concluded post mastectomy seroma is the result of an acute inflammatory exudative process.

We hypothesized that by reducing this acute inflammatory process it could be possible to reduce the post operative drainage. We therefore performed this double-blind, controlled trial to assess the effect of a Non Steroidal Inflammatory Drug (NSAID) on post-operative drainage, its duration and volume, as compared with a placebo, after radical breast cancer surgery. The study also compared immediate postoperative morbidity between the two groups. To the best of our knowledge no previous study has attempted to answer this hypothesis.

## Materials and Methods

This single-centre double-blinded study was conducted in the Gynecology and Obstetrics Department of the F. Hached University Teaching Hospital in Sousse, Tunisia.

Eligible participants were female, 20-years or older, scheduled to undergo a simple or modified radical mastectomy. Patients were excluded if they had a history of asthma, bleeding disorder, gastrointestinal ulceration or bleeding, known Crohn's or liver disease, creatinemia above 110 mmol/l, platelet count less than 100 000/mm$^3$. Pregnant or lactating women or those receiving anticoagulant or NSAID within the last 72 hours were also excluded.

Women were randomly assigned to one of two groups: one who received 200 mg of a generic sustained release ketoprofen or the other group who received a placebo. Assignment to one of the two study groups was generated using a table of random numbers (www.randomization.com). The assigned treatment was placed in sealed and opaque envelopes numbered in sequence. Each envelope corresponded to a package of identical oral pills prepared by an independent physician. Placebo capsules were filled with lactose and were indistinguishable from the active treatment. Persons involved in the conduct of the study and the patients were blinded regarding the group assignment. Each patient received either ketoprofen or the placebo. Subjects received the single dose of medication orally just before the procedure. Patients were operated by four different surgeons familiar with the technique. Cases of modified radical mastectomies were associated with a standard level II axillary dissection. In cases of palpable nodes in level III, these were cleared. Electrocautery and ligation were the techniques used; after simple mastectomy only one pectoral suction drain (12Fr) was placed, whereas two drains were placed after modified radical mastectomy (12Fr; axillary and pectoral drains).

Our institution's standard analgesic post operative treatment after breast surgery includes 1000 mg intravenous paracetamol (Prefalgan®) every 8 h.

During the first 72 hours external compression dressings were provided and patients were encouraged to perform active shoulder exercises, the total drain output was measured and recorded daily. A volume of 30 ml/24 h is our institutional guideline for timing of drain removal; drains are systematically removed on day 8.

The primary outcome variable was total drain volume; secondary outcome variables were mean drainage periods, drained volume on postoperative days 1 and 2, and associated morbidity; the latest being defined as the occurrence of wound infection, seroma formation or haematoma. Serious adverse events were also noted.

The study was approved by the local Ethical Committee and all patients enrolled in the study gave written informed consent. The trial was registered in the International Standard Randomized Controlled Trial Number Register (ISRCTN06628870). Financial support was provided by the Gynecology and Obstetrics Department only and we do not report any conflict of interest.

No stratification was performed according to whether simple or modified radical mastectomy was performed. A sample size and power calculation was undertaken according to a previous study performed in our department (14) and it was determined that 45 patients in each group was of sufficient power (power of 0.80; significance level of 0.05) to demonstrate a reduction of 20% between groups in total drained volume. The data were analysed for statistical significance by using the Student *t* test, the $\chi^2$ test, and Fisher's exact test. $p<0.05$ was considered significant. Analyses were performed on an intent-to-treat basis. SPSS version 13.0 was used for analyses.

## Results

During the 12-month period (from May 2005 to June 2006), there were 153 modified radical or simple mastectomies in our department of which 110 were eligible for this study. Seventeen were not randomized in the study, or declined

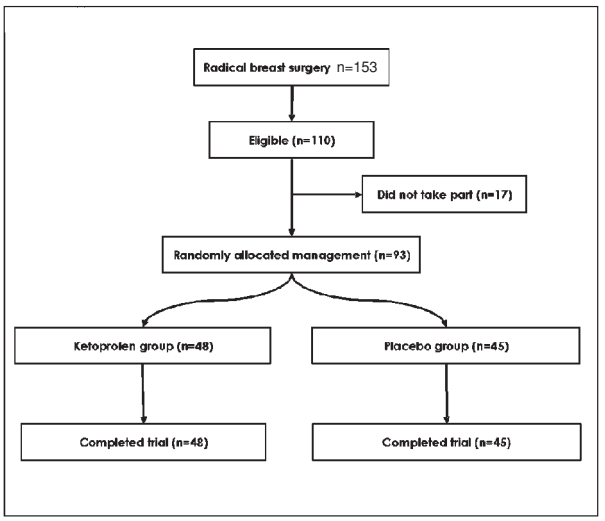


**Figure 1.** Trial profile.

participation, leaving a total of 93 women. A total of 48 women were enrolled in the ketoprofen group and 45 in the placebo group (Figure 1).

As shown in Table 1, demographics were similar between the two groups.

There was no difference between the two groups in the post-operative drainage volume (primary outcome): 540±152 ml in the ketoprofen group versus 585±195 ml in the placebo group; $p$=0.22. There was a significant difference between groups in the drained volume at postoperative day 1: 157±35 ml versus 191±38 ml in ketoprofen and placebo groups respectively ($p$<0.001); this difference remained significant at post operative day 2 ($p$<0.05) but was not found for other days (Figure 2).

**Table 1.** Demographic characteristics of the two groups

| | Ketoprofene group n=48 | Placebo group n=45 | *p* |
|---|---|---|---|
| Mean Age (years) | 52.3±12.8 | 51.6±13.8 | 0.8 |
| Mean Weight (kg) | 66.5±19.8 | 70.9±15.1 | 0.18 |
| Diabetes | 5 | 8 | 0.37 |
| Hypertensive disorder | 6 | 6 | >0.99 |
| Menopausal | 27 | 17 | 0.16 |
| NACT | 12 | 15 | 0.36 |
| Tumour size | 3.5±2.1 | 4.4±2.3 | 0.06 |
| Surgery (MRM) | 38 | 45 | 0.39 |
| No. of lymph nodes resected (mean) | 12.5±3.7 | 12.5±4.1 | 0.98 |
| With positive lymph nodes (%) | 21 | 19 | 0.97 |

BMI: body mass index; MRM: modified radical mastectomy
Continuous data presented as mean ± standard deviation and dichotomous data presented as number (percent).

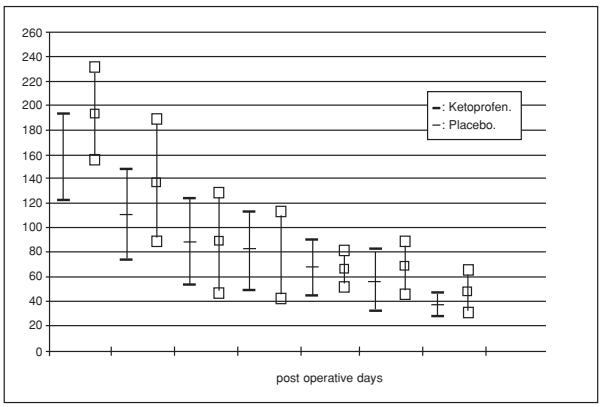


**Figure 2.** Variations in drained volume during post operative period in the two treatment groups. Expressed as Mean ±SD and $p$ value. (* Significant)

No significant difference between groups was observed in the mean drainage period (days): 6±2 versus 5.6±1.1; $p$=0.24.

Complications did not differ in frequency between the two groups: 5 versus 4 in ketoprofene and placebo groups respectively ($p$=0.54). One patient in each group needed a further operation for a haematoma formation. We did not report any serious adverse event.

## Discussion

Simple or modified radical mastectomy is usually followed by a post operative use of closed suction drainage because it has been shown to reduce the incidence of seroma formation (2,15). Some authors advocate discharge with the drains *in situ* (16,17) but patients with suction drains are generally managed in the hospital with an average stay of 7 days (3); this is particularly true in developing countries, since patients come from distant rural regions where medical facilities are limited (3,18). Morbidity is a function of the length of time of drainage (19) but premature withdrawal postoperative drains seems to be associated with a higher incidence of seroma formation (9,20).

Varying techniques have been proposed to reduce the volume of post operative drainage, to diminish the duration of suction drainage, and to lower the incidence of seroma formation (21). Chintamani et al. (3,18) found that half of the usual negative suction effective in reducing hospital stay but their findings are challenged by those of Bonnema et al. (6) who compared high versus low vacuum drainage in 141 patients and found no significant difference in the volume of fluid production or duration of drainage between the two randomized groups. There is thus no strong evidence to recommend high or low pressure of suction (20).

The use of a pressure garment has not been shown to reduce post-operative drainage volumes (22), and obliteration by fibrin sealant did not result in a clinically significant decrease in seroma formation (23). Therefore this costly and cumbersome

technique does not seem to be a viable option to supplant drain placement in breast surgery at this time (24). Finally, Pogson CJ et al. (20) reviewed in an interesting paper, the available evidence and concluded that shoulder movement restriction and delayed shoulder mobilization are of little benefit on seroma formation. From a review of the above data, it seems that evidence is lacking that suggests it's possible to reduce the volume and duration of drainage. We therefore intended to analyse the potential benefit of a NSAID.

Our study failed to demonstrate a significant benefit of the use of a single dose of 200 mg of sustained release ketoprofen in the reduction of the amount or duration of exudate drainage. However, we believe that a very interesting finding of our study is the highly significant difference in the volume of exudate drainage on post operative day 1 and 2. This seems to confirm the "inflammatory reaction theory" of the origin of collected fluid after large breast cancer surgery.

To the best of our knowledge based on extensive research, no previous study has attempted to analyze the influence of NSAIDs on wound drainage volume or duration. Legeby M et al. (25) assessed the postoperative influence of diclofenac 50 mgx3 on post operative pain as a primary outcome after breast cancer surgery with immediate reconstruction in 50 women. Interestingly these authors analysed post operative volume drainage as a secondary outcome and found that diclofenac seemed to increase volume drainage particularly after axilary lymph node dissection (796±355 versus 462.2±206.1 (ml) respectively; $p$=0.032). Surprisingly, and as we previously noted (26), the authors considered that post operative drainage reflected bleeding. These findings are in contradiction with ours, however one can suppose that immediate breast reconstruction with sub muscular implants can modify the composition of liquid drainage by increasing the proportion of red cells and decreasing the exudation by reducing dead space (27); on the other hand, the pharmaceutical regimen tested was analgesic and therefore may not have had an important anti-inflammatory action.

The physiopathology of fluid drainage formation remains uncertain; earlier studies suggested that the fluid originates from blood ultrafiltration; but more recently it has been assumed that the fluid is due to drainage of lymph from transected lymphatics (28).Our review of the literature failed to produce strong evidence to confirm this theory (29).

On the basis of laboratory analysis, Watt-Boolsen S et al. (30) were the first to demonstrate that seroma is an exudate resulting from an acute inflammatory reaction of the first phase of wound repair. Mc Caul JA et al. (31) compared drain fluid concentration to plasma concentration, for a number of haematological and biochemical parameters following surgery for primary breast cancer. The authors found a mean haemoglobin concentrations of 0.55 g/dl demonstrating a minimal contamination with whole blood. They also demonstrated the presence of more inflammatory components, other than lymphocytes meaning that that clearance reflected an acute inflammatory exudative phase.

Based on the previously mentioned studies (30,31), we postulated that acute inflammation that occurs during the 24 first hours was responsible for the majority of the collected liquid. Ketoprofen 200 mg LP is a once-daily oral administrated NSAID that ensures therapeutic activity for 24 h. It achieves a plasma steady-state within 2 h after administration and maintains it for about 12-14 h. During a 24 h period after administration, mean ketoprofen plasma levels never fall under 2 µg/ml which is the reported active concentration (32).

Inflammation can be divided into several phases (33). The first is acute vascular response with vasodilatation and increased capillary permeability leading to an increase in blood flow and to the entry of fluid into the tissues. The acute cellular response takes place over the next few hours with appearance of granulocytes and fibrinogen.

Our results are in accordance with the inflammatory theory and early administration of NSAID initially reduced liquid formation. From our data, we can not extrapolate whether continuous administration of ketoprofen for 5 days might lead to a decrease in the total drained volume of exudate without impairment in wound healing. In this protocol we decided to administer NSAID for the 24 first hours not only because we postulated that early 24 first hours acute inflammation was the most critic period, but also to avoid inhibition of chronic cellular response which is very important in remodelling and healing and plays a pivotal role in defence against infection (34).

Mastectomy wounds are vulnerable to hypoxia and some suggested that NSAID impede growth stimulation of the epidermis (35); we therefore restricted administration to the acute inflammatory phase to allow a decrease in collagen degradation (36) and to avoid delay in tissue regeneration and granuloma formation.

Finally, in this study, one patient in each group presented a haematoma. One of the concerns regarding the use of preoperative ketoprofen is the risk of decreased haemostasis. Although it has been found that NSAIDs prolong bleeding times secondary to a reversible impairment of thromboxane-dependent platelet aggregation, values generally remain below the superior limits (37). Furthermore, NSAIDs action is more of an anti-inflammatory effect than an anti-platelet activity because they inhibit both the cyclo-oxygenase and lipo-oxygenase transformations of arachidonic acid (38).

In conclusion, a single 200 mg dose of sustained release ketoprofen administered orally before radical breast surgery does not appear to have an effect on total post operative drainage volume and duration, or on the incidence of post operative complications. However our study is the first to prove the inflammatory cause of the collected fluid, since we found a highly significant difference of the drained volume

between groups during the first two postoperative days. This open the doors to future research based on mechanical or medicinal therapeutics to reduce intra-operative inflammation and therefore preventing accumulation of postoperative fluid.

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