Comparative effect of intraoperative propacetamol versus placebo on morphine consumption after elective reduction mammoplasty under remifentanil-based anesthesia: a randomized control trial [ISRCTN71723173]

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Abstract

Background: Postoperative administration of paracetamol or its prodrug propacetamol has been shown to decrease pain with a morphine sparing effect. However, the effect of propacetamol administered inoperatively on post-operative pain and early postoperative morphine consumption has not been clearly evaluated. In order to evaluate the effectiveness of analgesic protocols in the management of post-operative pain, a standardized anesthesia protocol without long-acting opioids is crucial. Thus, for ethical reasons, the surgical procedure under general anesthesia with remifentanil as the only intraoperative analgesic must be associated with a moderate predictable postoperative pain.

Methods: We were interested in determining the postoperative effect of propacetamol administered intraoperatively after intraoperative remifentanil. Thirty-six adult women undergoing mammoplasty with remifentanil-based anesthesia were randomly assigned to receive propacetamol 2 g or placebo one hour before the end of surgery. After remifentanil interruption and tracheal extubation in recovery room, pain was assessed and intravenous titrated morphine was given. The primary end-point was the cumulative dose of morphine administered in the recovery room. The secondary end-points were the pain score after tracheal extubation and one hour after, the delay for obtaining a Simplified Numerical Pain Scale (SNPS) less than 4, and the incidence of morphine side effects in the recovery room.

For intergroup comparisons, categorical variables were compared using the chi-squared test and continuous variables were compared using the Student t test or Mann-Whitney U test, as appropriate. A p value less than 0.05 was considered as significant.

Results: In recovery room, morphine consumption was lower in the propacetamol group than in the placebo group (p = 0.01). Pain scores were similar in both groups after tracheal extubation and lower in the propacetamol group (p = 0.003) one hour after tracheal extubation. The time to reach a SNPS < 4 was significantly shorter in the propacetamol group (p = 0.02). The incidence of morphine related side effects did not differ between the two groups.

Conclusions: Intraoperative propacetamol administration with remifentanil based-anesthesia improved significantly early postoperative pain by sparing morphine and shortening the delay to achieve pain relief.
Background
Postoperative administration of paracetamol or its prod-
rug propacetamol has been shown to decrease pain with a
morphine sparing effect [1-4]. The effect of propacetamol
administered intraoperatively on postoperative pain and
early postoperative morphine consumption has not been
clearly evaluated. However, for a predictable moderate
postoperative pain, intraoperative administration of non-
opioid analgesics such as paracetamol and postoperative
intravenous administration of morphine are recom-
manded in patients undergoing general anesthesia with
remifentanil [5]. Indeed, remifentanil differs from potent
mu agonists by its extremely short elimination half-life
[6]. The elimination kinetics of remifentanil is so fast that its
analgesic effect wears off abruptly, thus making the
management of postoperative pain critical.

In order to evaluate the effectiveness of intraoperative
paracetamol administration in the management of post-
operative pain and morphine consumption, a standard-
ized anesthesia protocol without long-acting opioid is
necessary. Thus, for ethical reasons, the surgical procedure
under general anesthesia with remifentanil as the only
intraoperative analgesic must be associated with a moder-
ate predictable postoperative pain.

Therefore, the present study was designed to evaluate the
effect of intraoperative administration of propacetamol
during remifentanil-based anesthesia on postoperative
pain in patients undergoing reduction mammoplasty.

Methods
Patients
After approval by the Local Ethical Committee and written
informed consent, 36 consecutive female patients who
underwent elective reduction mammoplasty were
included. Exclusion criteria were the preoperative use of
analgesic drugs; a body mass index ≥ 35, an American
Society of Anesthesiology physical status ≥ 3 and sensitiv-
ity to paracetamol. Pain evaluation using a Simplified
Numerical Pain Scale (SNPS) was explained to the
patient was transferred in the recovery room. The anes-
thesist, the patient and the nurse’s staff caring for the patients
in the recovery room were unaware of the treatment
type. In both groups, anesthesia was induced with pro-
pofo 2.5 mg.kg⁻¹ followed by a slow bolus (1 min) of
remifentanil 1 mcg.kg⁻¹. Tracheal intubation was facil-
itated by atracurium 0.5 mg.kg⁻¹. Anesthesia was main-
tained with remifentanil 0.1 mcg.kg⁻¹.min⁻¹ and
isoflurane (0.5–1.0% end-tidal) with nitrous oxide (N₂O)
in 50% oxygen. Remifentanil infusion rate was increased
or decreased by 0.05 mcg.kg.min⁻¹ in order to maintain an
arterial systolic pressure of 20% more or less than the
baseline value. One hour before the end of surgery, which
corresponded to the beginning of the skin closure,
patients received either propacetamol 2 g in 50 cc saline
(Propacetamol group) or 50 cc saline alone (Placebo
group) infused over 10 min. At the end of surgery, admin-
istration of isoflurane and N₂O were withdrawn and the
patient was transferred in the recovery room. The anaes-
thetist, the patient and the nurse’s staff caring for the patients
in the recovery room were unaware of the treatment
group. Remifentanil infusion was interrupted when the
patient arrived in recovery room. Tracheal extubation
was performed within a few minutes after remifentanil
discontinuation. Clinical monitoring included heart rate,
blood pressure, pulse oxymetry, respiratory rate, and seda-
tion score (0: awake, 1: drowsy and 2: asleep).

From the time of extubation, pain was evaluated on using a
SNPS (from 0, no pain to 10 the worse pain) and intra-
venous 2 mg morphine was administered on request every
5 min until pain relief (SNPS<4). When pain relief was
reached, SNPS was subsequently evaluated every 15 min.
Morphine was interrupted when the sedation score went
up to 1, systemic arterial pressure < 80 mmHg or respira-
tory rate less than 8/min. During the data collection
period, intravenous morphine titration was further
administered if SNPS was up to 4. Patients did not receive
antiemetic prophylaxis. If post-operative nausea and vom-
iting (PONV) occurred, metoclopramide 10 mg and ondan-
setron 4 mg if necessary were intravenously ad-
ministered.

Patients fulfilling Aldrete criteria [7] were discharged from
recovery room.

Measurements
Morphine requirement, pain and sedation scores were
measured every 5 min until pain relief was obtained. When
SNPS was below 4 during 15 min, parameters were
subsequently recorded every 15 min. Morphine side
effects (nausea, vomiting, urinary retention, shivering and
itching) and need for supplemental medications (e.g.,
antiemetics) were also recorded.

The total dose of morphine in recovery room was the pri-
mary end point. Pain scores after extubation and one hour
after tracheal extubation, delay for morphine require-
ment, delay for pain relief and incidence of morphine side
effects were recorded.

**Statistical analysis**

Data are expressed as mean (± standard deviation) for
quantitative variables normally distributed, or otherwise
as median (25th – 75th percentiles) when data were not
normally distributed, and as percentage for categorical
variables. Data were analyzed using Statview 5.0 software
(SAS Institute Inc, USA). For intergroup comparisons, cat-
egorical variables were compared using the chi-squared
test and continuous variables were compared using the
Student t test or Mann-Whitney U test, as appropriate. A p
value less than 0.05 was considered as significant. Antici-
pating a standard deviation of 2.49 [8], it was calculated
that 15 patients at least were necessary to show a differ-
ence between groups in morphine consumption of 4 mg
(considered as a clinically relevant difference) with a 80%
power and a 5% type 1 error.

**Results**

Thirty-six patients were included during a 12 months
period: 19 in Propacetamol group and 17 in Placebo
group (Table 1). There was no significant difference
between the groups concerning clinical characteristics,
anesthesia duration and total amount of remifentanil
administered. In all patients, extubation was obtained
within 7 ± 3 min (Table 1) after remifentanil discontinu-
ination.

In recovery room, cumulative morphine consumption
was significantly lower in the Propacetamol group than in
the Placebo group (Table 2). Five minutes after ex-
tubation, pain scores were similar in both groups (SNPS = 6).
Pain scores one hour after tracheal extubation were signif-
ically lower in the Propacetamol group than in the Pla-
cebo group (Table 2). Moreover, the time to reach a SNPS
score less than 4 was significantly shorter in Propacetamol
group compared to the Placebo group. All the patients
received intravenous morphine titration in the first hour
after extubation and three patients (one in Placebo group
and two in Propacetamol group) required a morphine
titration over one hour after extubation. Once a SNPS
value less than 4 was obtained, pain scores remained sta-
ble and similar in both groups except in one patient in
Placebo group who required an additional 2 mg intrave-
nous bolus of morphine 80 min after extubation.

The incidence of morphine adverse effects was similar in
both groups: 5 patients had nausea (3 in Propacetamol
and 2 in Placebo group, p=NS) and 4 patients had vomit-
ing (2 in each group, p=NS), no other side effects were
observed. In one patient receiving placebo, morphine
titration was interrupted because of nausea and vomiting.

**Discussion**

This study shows that propacetamol administered one
hour before end of surgery reduced the morphine dose
given over the first four postoperative hours and short-
ened the elapsed time to obtain a SNPS under 4 in
patients undergoing elective reduction mammoplasty. In
our study, surgical technique and anesthetic protocol were
similar in both groups. Remifentanil was the only analge-
sic used during anesthesia period and was interrupted
before morphine administration. Thus, the beneficial
effect on postoperative pain observed is clearly linked to
intraoperative administration of propacetamol.

In a recent study [9], Verchère and colleagues failed to
demonstrate a postoperative analgesic effect of intraoper-
ative propacetamol administration, after remifentanil
anesthesia for supratentorial craniotomy. Pain after
supratentorial neurosurgery was too severe and paraceta-
мол was insufficient to relieve it. In our study
mammoplasty was chosen because postoperative pain is
moderate [10], and intravenous administration of mor-
phine was used in recovery room. Thus, the morphine
sparking effect of intraoperative administration of para-
cetamol could be really evaluated with respect of ethical
requirement.

Our results are apparently at variance with those of other
previous studies. Paracetamol given rectally immediately
after induction of anesthesia [11] or at the end of gyneco-
logical surgery [12] and orally before surgery [13-16]
failed to improve early postoperative analgesia. The nega-
tive results of these studies may be ascribable to several
causes such as the low initial pain score in the control
group [11,12,15,17], and the difference in the route used
for paracetamol administration [11-16]. An other hypoth-
esis to consider is the use of long-acting opioid such as
fentanyl that might have contributed to the early postop-
erative analgesia [14,18].

Cobby and colleagues observed a morphine sparing effect
when paracetamol 1.3 g was administered rectally at the
end of hysterectomy [19]. One explanation is that plasma
concentration after 1.3 g paracetamol was sufficient to
achieve opioid sparing effect comparable with that of
intravenous propacetamol. This hypothesis is strength-
ened by the results of another trial showing that after rec-
tal administration of a high dose of paracetamol (40 and
60 mg kg⁻¹) pain score and analgesic demand were signif-
ically reduced in the early postoperative period [20].

The presently observed incidence of postoperative nausea
and vomiting was of 25% and was similar to that of a pre-
vious study [21]. Despite the reduced dose of postopera-
tive morphine in the Propacetamol group, the incidence of
postoperative nausea and vomiting was not dimin-

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ished. Our results are in agreement with the recent study of Aubrun and co-workers [4] who observed that postoperative intravenous propacetamol allowed a morphine-sparing effect but did not reduce the incidence of morphine-related adverse effects in patients undergoing general surgery.

Propacetamol was administered at the beginning of skin closure, which corresponds to one hour before the end of surgery. This delay may be insufficient to achieve pain control immediately after tracheal extubation, as the peak effect of intravenous propacetamol was shown to occur only two hours after its administration [22]. Nevertheless, we considered that it was not feasible to administer propacetamol earlier, as in our practice duration of surgery was unpredictable.

In summary, intraoperative propacetamol administration in women undergoing reduction mammoplasty improved significantly early postoperative pain in recovery room, and should be recommended for postoperative pain management.

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Table 1: Demographic characteristics and perioperative parameters.

|                              | Placebo Group (n = 17) | Propacetamol Group (n = 19) |
|------------------------------|------------------------|-----------------------------|
| Age (years)                  | 41 (16)                | 34 (14)                     |
| Body mass index (kg.m−2)     | 26 (4)                 | 25 (3)                      |
| Duration of anesthesia (min) | 245 (55)               | 245 (80)                    |
| Remifentanil consumption (µg.kg−1.min−1) | 0.150 (0.055)         | 0.155 (0.040)               |
| Final intraoperative corporeal temperature (Celsius) | 36.8 (0.4)            | 36.7 (0.5)                  |
| Delay before extubation after remifentanil interruption (min) | 7 (3)                 | 7 (3)                       |

Data are expressed as mean (standard deviation) for age, body mass index, final intraoperative corporeal temperature and delay before extubation. Other data are expressed as median (interquartile).

Table 2: Postoperative intravenous morphine requirement and pain scores in recovery room.

|                              | Placebo Group (n = 17) | Propacetamol Group (n = 19) | p value |
|------------------------------|------------------------|-----------------------------|---------|
| Morphine consumption in recovery room (mg) | 16 [8–34]             | 10 [6–28]                   | 0.01    |
| Delay between extubation and first morphine administration (min) | 5 [5–20]              | 5 [3–15]                    | NS      |
| SNPS score five minutes after extubation | 6 [0–9]                | 6 [0–10]                    | NS      |
| SNPS score one hour after extubation | 3 [2–6]               | 2 [0–4]                     | 0.003   |
| Delay between extubation and obtaining a SNPS score < 4 (min) | 40 [20–85]            | 30 [15–70]                  | 0.02    |

Data are expressed as median [25th–75th percentile]. P < 0.05 was considered as statistically significant. Pain score was evaluated on using a Simplified Numerical Pain Scale (SNPS: from 0, no pain to 10 the worse pain).
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