

Research Article

Efficacy and safety of intravenous acetaminophen versus intravenous butorphanol as post-operative analgesic in obstetrics and gynecology: a comparative study

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ABSTRACT

Background: The purpose of this study is to provide effective pain management by administration of an analgesic that gives the patients maximum satisfaction. The goal was to evaluate and compare the analgesics efficacy of acetaminophen with butorphanol; to determine if there is an overall decrease in opioid consumption and opioid-related adverse effects; and detect any adverse effects of acetaminophen as post-operative analgesics.

Methods: In this randomized parallel-group controlled trial, post-operative patients were given either 1 g intravenous (IV) acetaminophen or 2 g IV butorphanol as post-operative analgesics. The post-operative pain was evaluated by pain intensity scales and was measured at rest and during a deep breath over 24 h. If the reading in the pain intensity scale was above 5 then rescue medicine injection. Tramadol 100 mg IV SOS was given in both the groups. Any adverse effects reported by the patients were recorded.

Results: The butorphanol group achieved slightly better pain ratings in the first 2 h and acetaminophen group after 6 h post-operatively. The overall visual analogue scale score across time was significantly lower for acetaminophen group than the butorphanol group ($p = 0.02$). The secondary outcome measure, rescue analgesic consumption (injection tramadol) was comparable between the two groups. Side-effects were less in acetaminophen than butorphanol, predominantly headache and sedation which was seen in butorphanol but was absent in acetaminophen.

Conclusion: IV acetaminophen is an effective analgesic in obstetric and gynaecological surgeries with a good safety profile. When used in combination with opioids, they reduce opioid consumption, and this reduction is sufficient to reduce opioid-induced adverse effects.

Keywords: Intravenous acetaminophen, Opioid analgesic, Gynaecological surgeries, Post-operative analgesia

INTRODUCTION

Pain is an unpleasant feeling that causes discomfort to the person experiencing it. Pain is one of the primary affects after surgery. Pain management is very complex and challenging as the pathophysiology of pain is not very well-understood. Effective pain management is by providing an ideal analgesic that can reduce or eliminate pain without causing any adverse effects and without interfering in any pharmacological interactions. It should provide maximal efficacy with minimum toxicity. The failure to give good

analgesics will lead to adverse effects causing more distress, prolonging the duration of stay and increases the burden on the nursing staff.¹ The goal of every healthcare professional is to put in their best to relieve the patients pain and suffering. The American Pain Society has challenged the health care system to include pain as the fifth vital sign.²

The purpose of our study is to provide effective pain management by administration of an analgesic that gives the patients maximum satisfaction. The currently used combination in our hospital for all patients is undergoing

obstetric and gynecological surgeries (butorphanol-tramadol), while usually considered as effective, does raise issues about tolerability and adverse effects. This is because while butorphanol, an analgesic of the phenanthrene series, a synthetically derived opioid mixed agonist-antagonist with low intrinsic activity at receptors of the μ -opioid type (morphine-like) is a centrally acting weak opioid receptor agonist, it has all the known adverse effects of an opioid. The adverse effects can indeed be troublesome, which can cause greater distress to the patients than the pain itself.

Injectable acetaminophen (paracetamol) is a safer option, but its analgesic efficacy is often unclear in this scenario especially when used as a stand-alone analgesic. Acetaminophen is a para amino phenol drug derivative, which is a good analgesic and antipyretic with poor anti-inflammatory action. acetaminophen has been effectively used as an analgesic and antipyretic with well-established tolerability.³ In comparison to other analgesics, like opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen has a favorable safety profile.⁴ The drug is not associated with the increased incidence of nausea, vomiting, and respiratory depression that can occur with opioids, or platelet dysfunction, gastritis, and renal toxicity that are sometimes associated with NSAIDs. Acetaminophen is also said to reduce post-surgical pain intensity and reduce the opioid consumption⁵ further protecting the patients against opioid related adverse effects. Intravenous (IV) acetaminophen appears to avoid first-pass hepatic exposure and metabolism via portal circulation, which may reduce the potential for hepatic injury.⁶ IV acetaminophen is rarely associated with hepatotoxicity.

Objectives

1. To evaluate and compare the analgesic efficacy of acetaminophen with butorphanol (an opioid)
2. To determine if there is an overall decrease in the use of opioid analgesics (tramadol, an iopioid used as a rescue medication in the study) and subsequent decrease in post-operative nausea and vomiting
3. To detect the adverse effects of acetaminophen in analgesic doses when given to post-operative patient.

METHODS

Materials

1. 100 mL glass vial containing 1000 mg (10 mg per mL) ready to use acetaminophen (no reconstitution or dilution is required)
2. 2 mg butorphanol
3. Injection tramadol 100 mg
4. Pain intensity scales
5. Informed consent and questionnaires.

Methodology

This was a single center, randomized, parallel-group controlled trial which took place in the Department of Obstetrics and Gynecology of Father Muller Medical

College. Approval for this study was obtained by the Institutional Ethics Committee, and the informed consent was obtained from the study subjects. The study population was female patients aged 18-65 years with moderate to severe post-operative pain. Data were collected from June 2013 and completed in August 2013. Data were completed by collecting the information from the patients with the help of questionnaires. Data were analyzed using Microsoft Excel 2013 and Statistical Package for Social Sciences (SPSS).

Inclusion criteria were female patients, aged 18-65 years who are scheduled to undergo elective caesarean sections and routine gynecological surgeries like vaginal hysterectomy, abdominal hysterectomy, laparoscopically assisted vaginal hysterectomy, total laparoscopic hysterectomy and laparotomy for ovarian tumors, tubo ovarian masses; body mass index was between 18 and 35; ability to read, understand and provide informed consent to study procedures; and ability to understand the use of pain intensity scale to grade pain.

The exclusion criteria was known case of hypersensitivity to acetaminophen or butorphanol; those with chronic pain conditions or any significant medical disease requiring pain control; abnormal liver functions, active hepatic diseases, clinically significant liver disease, cirrhosis or hepatitis; known or suspected alcohol, drug or opiate abuse or dependence, or participation in other clinical study within 30 days of surgery and renal dysfunction.

On the day before the surgery, the patient was explained about the nature and purpose of the study. The informed consent included the briefing on the test drug (acetaminophen) and control drug (butorphanol). Using sealed envelopes the patients were randomized to receive either IV acetaminophen or IV butorphanol as post-operative analgesic.

Patients received either regional/general anesthesia prior to surgery. No regional anesthesia technique or local wound infiltration was used intraoperatively to reduce post-surgical pain. After the surgery in the post-operative care unit a random group of 51 women were given acetaminophen contained in a 100 mL glass vial containing 1000 mg (10 mg/mL) ready-to-use acetaminophen (i.e., no reconstitution or dilution is required). The entire dose of IV acetaminophen was administered over 15 min, and the infusion was vented for proper delivery. Acetaminophen is given 1 mg intravenously every 8 h (Group A; $n = 51$). The other random group of 50 women acted as the parallel group who received butorphanol 2 g intravenously for every 12 h (Group B; $n = 50$) as a post-operative analgesic administered 15 min after the end of the surgery. The post-operative pain was evaluated by pain intensity scales and was measured at rest and during a deep breath at 30 min, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h. If the reading in the pain intensity scale was above five then rescue medicine injection. Tramadol 100 mg IV SOS was given (maximum dose of 300 mg in 24 h) in both the groups.

Assessment of pain is difficult as the pain is a subjective phenomenon. For a health care worker to know the efficacy of analgesics for subsequent treatment or in cases of clinical

trials, the pain intensity should be expressed objectively. This is done by using pain intensity scales. In our study, we used different types of pain score scales. They are faces pain scale, numerical rating scale, and color pain scale, all which are based on the visual analogue scale (VAS) (10). This scale has 0 at one end indicating no pain and 10 at the other end indicating worst imaginable pain.

Figure 1 shows Wong Baker’s faces pain scale, which relates the expression on the faces in terms of how the patient is feeling.

Figure 2 shows the numerical rating scale that was based on the VAS that had number ratings from 0 to 10.^{7,8}

Figure 3 shows the color scale, which is also based on VAS. This scale uses color to grade the increasing severity of pain instead of number ratings. Red is associated with severe pain and green is associated with no pain.

Efficacy measurements

The study drug was administered 15 min after the end of the surgery in the post-operative ward. The time of drug administration was taken as time 0 and the pain intensity readings was taken for 30 min, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h after the administration of the first drug. The pain intensity readings were recorded using three VAS (i.e. faces pain scale, numerical pain scale and color pain scale) and the average was taken at that time and compared between the test and control. The acceptance of rescue medication and the time at which the rescue medicine is first administered is also recorded over a 24 h study.

Safety assessments

Adverse effects of the test and the control drug were monitored during the 24 h study. The safety was also

assessed by the vital sign measurements (blood pressure, heart rate and respiratory rate) and the infusion site examination.

Statistical analysis

Intent to treat analysis was performed using SPSS software version 21.

The primary outcome was to compare the efficacy of acetaminophen versus butorphanol as measured by a change pain intensity scores on the VAS 0.5 h, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h after the drug administration. The secondary outcome included the acceptance for rescue medicine, the time at which the rescue medicine was first administered and the adverse effects seen during the study.

When the pain intensity data were subjected to Kolmogorov–Smirnov test for normality, most of the pain score distributions at various time points were found to deviate significantly from the normal distribution. Hence, parametric statistical analysis was not pursued. The groups were thus compared with the mean of the two groups by non-parametric test (Mann–Whitney U-test).

- H₀: Both drugs had same efficacy
- H₁: Both drugs had different efficacy.

Significance level for statistical tests was alpha = 0.05. The hypothesis is rejected or failed to reject based on the following rules.

- If $p < 0.05$, reject the null hypothesis
- If $p > 0.05$, fail to reject the null hypothesis.

For categorical comparisons Chi-square test or Fisher’s exact test was used wherever necessary.

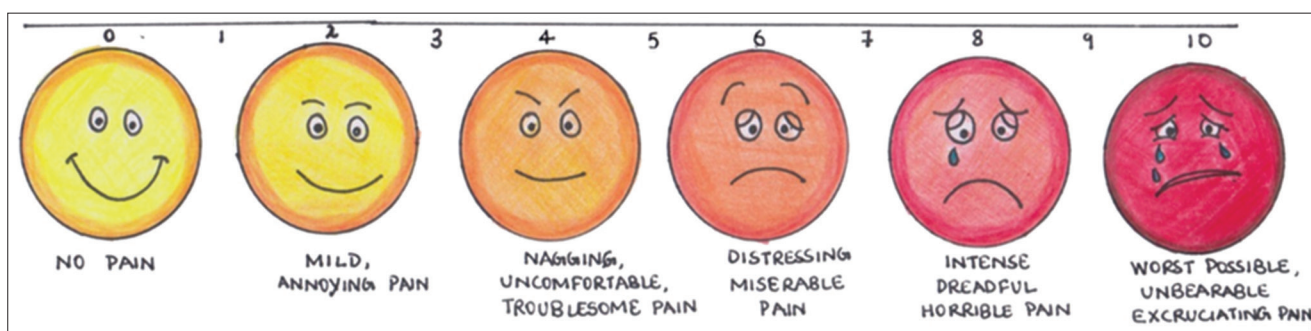


Figure 1: Wong Baker’s faces.

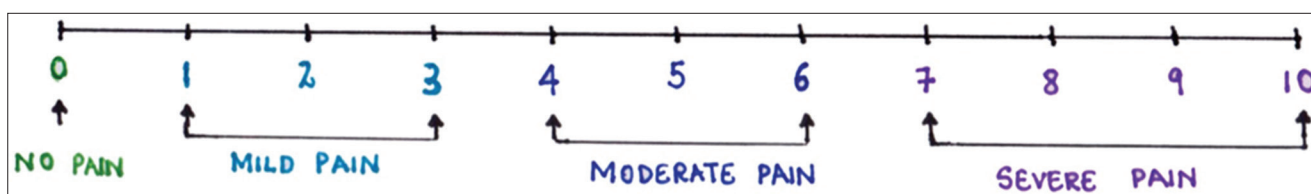


Figure 2: Numerical rating scale.

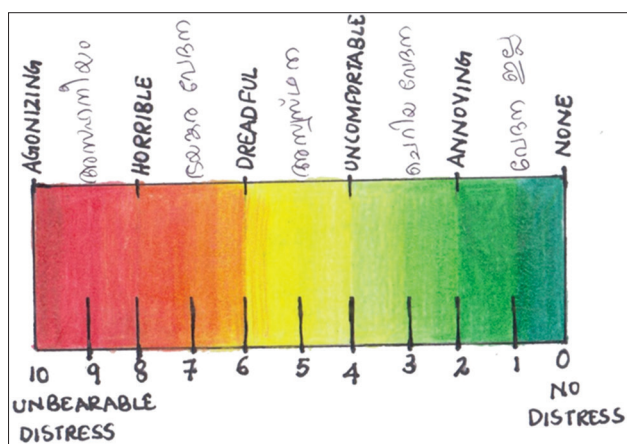


Figure 3: Colour scale.

All the required statistical values from SPSS were then put into a brief table using Microsoft Excel.

RESULTS

One hundred and nine patients were invited to participate in this study. Eight patients were excluded, out of which six did not meet the inclusion, and two patients refused to participate. This left us with 101 consenting participants. The patients were then randomized into two groups. The index group consisted of 51 women aged 18-65 years undergoing elective caesarean section or routine gynecological procedures as listed in the inclusion criteria, who received injectable acetaminophen. One patient was excluded because of anaphylactic reaction to antibiotic. The control group consisted of 50 women of the same age range as that of the index group, who received injectable butorphanol after randomization. The data were collected from June 2013 to August 2013. The index and control groups were comparable on all other sample characteristics including demographic, clinical and surgery-related characteristics (Table 1).

The consolidated standards of reporting trials flow diagram is shown in Figure 4.

Table 2 shows the pain scores in the two groups across the seven time points of observation. The overall pain ratings were low in both the groups. Median pain scores ranged from 0 to 4 (out of 10) in both the groups. The upper limit of pain score (95% confidence interval upper bound) ranged from 0 to 5 in both groups indicating good pain control. The butorphanol group however achieved slightly better pain ratings in the first 2 h. Pain rating scale (VAS) within each group decreased over time during the post-operative period. The overall VAS score across time was significantly lower for acetaminophen group than the butorphanol group ($p = 0.02$). There was statistical difference between the two groups at 6 h, 8 h and 24 h (Table 3). In all the other instances (4 out of 7 time points comparison) the p -value was statistically non-significant.

The secondary outcome measure, rescue analgesic consumption (injection tramadol) was comparable between

Table 1: Demographic data.

Baseline characteristics	Acetaminophen (n=51)	Butorphanol (n=50)
Age (mean±SD)	32.07±12.67	36.22±10.74
Weight (mean±SD)	55.42±8.0	56.98±8.85
Type of surgery		
Caesaran section	14	14
Laparascopy	28	30
Laparotomy	3	6
Duration of surgery	46.72±6.70	48.50±5.56
Pulse rate	62.8±4.87	68.76±4.46
Systolic blood pressure	120±7.00	124±6.06
Diastolic blood pressure	77±4.63	78±3.28
Respiratory rate	14.04±1.37	13.54±1.20

SD: Standard deviation

the two groups. There were very few side-effects in the acetaminophen group; nausea (4%), vomiting (3%), sleep disturbance (8%). None of the patients had headache and sedation. Butorphanol group experienced relatively more side-effects, especially nausea (14%), headache (6%), sleep disturbance (25%) and sedation (47%) (Tables 4 and 5, Figures 5-7).

DISCUSSION

Our study demonstrates that IV acetaminophen is a safe and effective IV, non-opioid analgesic for the treatment of post-operative pain in patients recovering from obstetrics and gynecological surgeries. This study shows that the acetaminophen group was significantly better than the butorphanol group as regards overall pain control. The highlight of our study is that it is finding out the differences between two active treatments (acetaminophen and butorphanol) unlike many other studies (active treatment and placebo). There are few studies comparing acetaminophen with opioid when used as a monotherapy for pain relief in post-operative period. Major obstetrics and gynecological surgery is extremely painful, and monotherapy with acetaminophen would not be expected to provide complete relief. Therefore, in the current investigation, we have used tramadol, an opioid as a rescue medication. This allowed the evaluation of the monotherapeutic efficacy of IV acetaminophen in reducing pain intensity in comparison with butorphanol.

Our study found that both acetaminophen and butorphanol combinations effectively controlled pain in this sample. Pain scores, were in the lower range in both of the groups (mean pain scores <4). Regarding the pain score ratings, as mentioned earlier, the butorphanol group fared better in the first few hours than the acetaminophen group, with a trend of lower pain scores in the first 2 h following the first administration of the drug when compared to acetaminophen group. However acetaminophen group scored better after 6 h

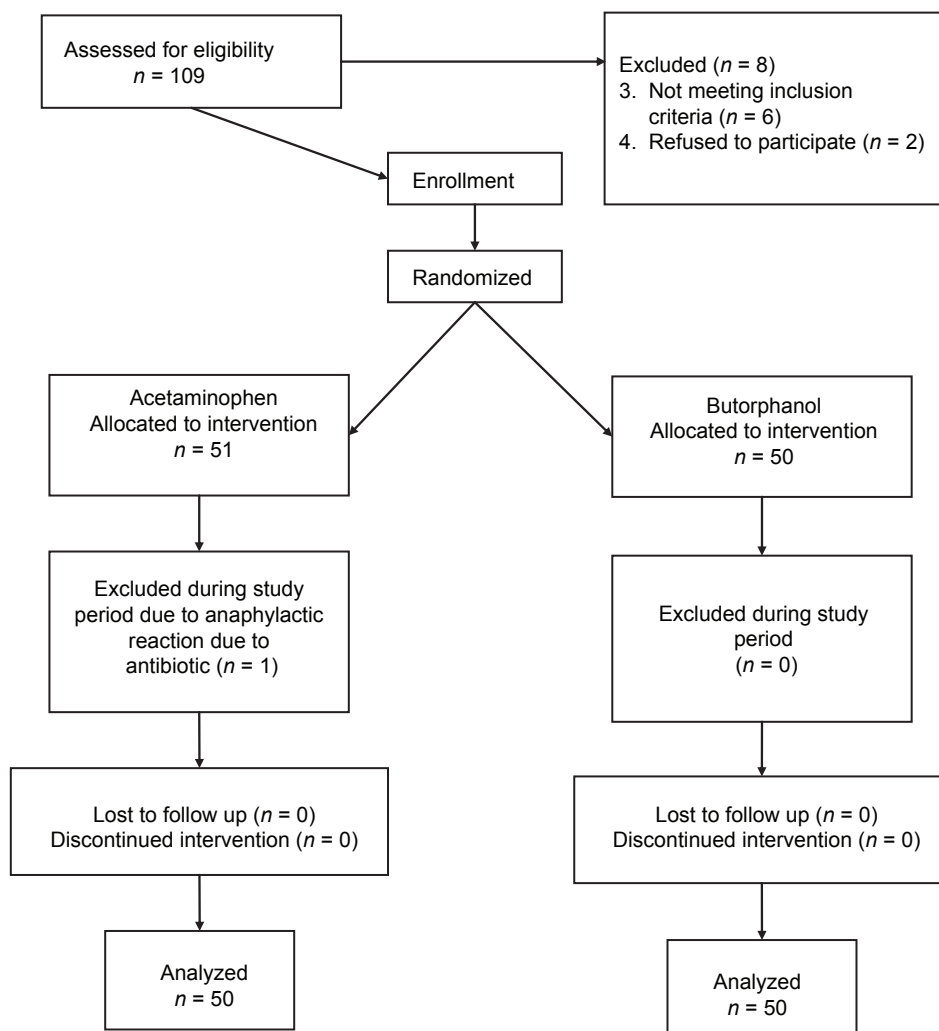


Figure 4: Consort flow diagram.

Table 2: Pain scale - descriptive statistics.

Drug	Statistics	0.5 h	2 h	4 h	6 h	8 h	12 h	24 h	Overall
Acetaminophen	Mean	0.673	4.020	4.447	4.287	4.167	0.003	2.187	3.292
	Std. error	0.207	0.320	0.275	0.194	0.249	0.276	0.216	0.117
	95% CI LB	0.256	3.377	3.893	3.898	3.665	2.713	1.754	3.062
	95% CI UB	1.090	4.663	5.000	4.676	4.668	3.821	2.620	3.522
	SD	1.467	2.264	1.948	1.369	1.764	1.949	1.524	2.189
	Minimum	0.000	0.000	0.000	2.000	0.000	0.000	0.000	0.000
	Maximum	5.333	8.000	8.333	7.667	7.667	7.667	5.333	8.333
Butorphanol	Mean	0.560	3.613	4.420	4.947	5.087	4.087	3.073	3.684
	Std. error	0.176	0.274	0.280	0.233	0.158	0.326	0.229	0.120
	95% CI LB	0.205	3.062	3.857	4.478	4.769	3.432	2.613	3.448
	95% CI UB	0.915	4.165	4.983	5.416	5.405	4.741	3.534	3.920
	SD	1.248	1.939	1.979	1.650	1.118	2.302	1.621	2.243
	Minimum	0.000	0.000	0.000	2.000	2.000	0.000	0.000	0.000
	Maximum	4.667	8.000	8.000	8.333	7.000	7.667	8.000	8.333

LB: Lower bound, UB: Upper bound, CI: Confidence interval, Std.: Standard, SD: Standard deviation

post-operative period. The intergroup difference reached a statistical significance at 6, 8 and 24 h post-operatively with

regard to pain out of the total of seven sets of post-operative observations.

Table 3: Pain scale - Mann-Whitney test.

Statistics	0.5 h	2 h	4 h	6 h	8 h	12 h	24 h	Overall
Mann-Whitney U	1217.50	1106.50	1229.50	951.00	819.00	1000.50	867.00	54907.50
p value	0.75	0.31	0.89	0.04	0.00	0.08	0.01	0.02

Table 4: Adverse effects across seven time points.

Drug	Nausea	Vomiting	Sedation	Headache	Sleep disturbance
Acetaminophen (%)	4	3	0	0	8
Butorphanol (%)	14	2	47	6	25
p value	0.000	0.806	0.000	0.000	0.000

Table 5: Incidence of acceptance of rescue medicine.

Drug	Not needed	Needed
Acetaminophen (%)	32	68
Butorphanol (%)	8	92
p value	0.003	

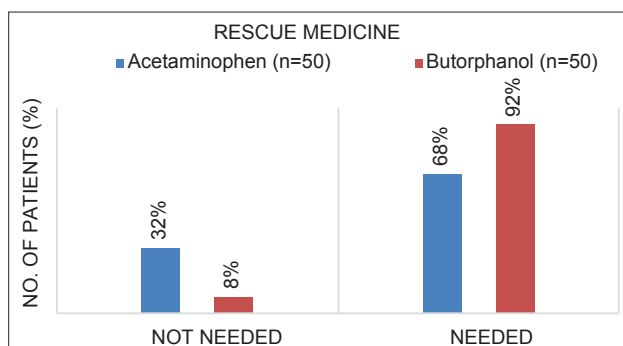


Figure 5: Incidence of acceptance of rescue medicine.

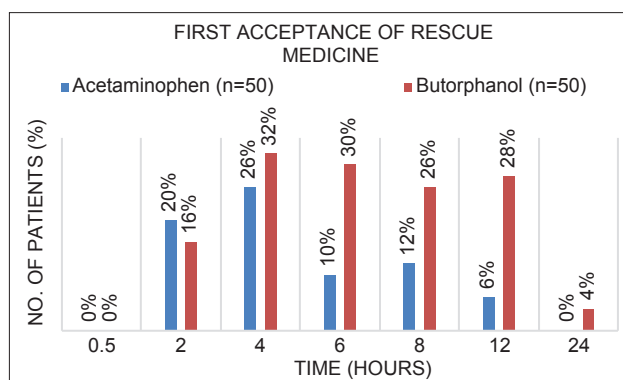


Figure 6: Percentage of patients that accepted rescue medicine in acetaminophen and butorphanol across seven time points.

Reported adverse effects in a post-operative pain study may reflect a number of factors. The Adverse effects may be residual effects of anesthesia and surgery. To remove this confounding factor, all patients received injection ondansetron 4 mg immediately after the surgery. Side effects of the medications were less in the acetaminophen group;

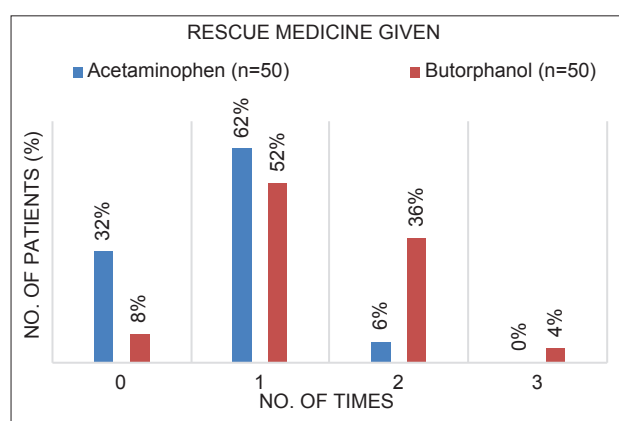


Figure 7: Number of times the patients (%) accepted rescue medicine.

headache and sedation which was a predominant side-effect in butorphanol group was never seen. Significantly more patients in the butorphanol group reported nausea. The fact that differences in the side effects between the groups were found despite ondansetron given to all patients may suggest that the difference in side-effects between butorphanol and acetaminophen in reality might be larger than the differences demonstrated in the present study. The injectable form of acetaminophen drug was found to be safe during the study period, although observation over longer term would be needed to confirm this.

The secondary outcome measure, rescue analgesic consumption (injection tramadol) was statistically significant between the two groups. 68% needed the drug in the acetaminophen group while majority of the patients (92%) in butorphanol group asked for rescue medication. The first acceptance of rescue medication was comparable between the two groups. Majority of the patients took rescue medication in the acetaminophen group only once as against the butorphanol group which took more than 2 times. Hence, we establish that IV acetaminophen reduces opioid consumption to an extent that opioid-induced adverse effects are reduced. Our study differs from Remy et al's systematic review of seven randomized controlled trials which documents that post-operative acetaminophen combined with patient controlled analgesia morphine

provides a statistically significant morphine-sparing effect but does not decrease the incidence of morphine side effects.⁹

The present study differs from the other studies on IV acetaminophen by using a different, and more competitive, comparator group being butorphanol, an opioid. In effect, then, our study has “raised the bar” for demonstrating the analgesic efficacy of acetaminophen when compared to an opioid. The study power and the differences between the groups might have been larger if only butorphanol and acetaminophen were used as test drugs. However, studying only butorphanol versus acetaminophen was not ethically justifiable because both of them are mild analgesics. Therefore another opioid (tramadol) was added as a rescue medication. Further, the currently used standard combination in our hospital is butorphanol-tramadol (as multimodal analgesia) and we wanted to compare this combination with acetaminophen-tramadol combination. As shown in the results, both the groups were effective in maintaining overall low pain scores. It must be stressed; however, acetaminophen-tramadol group was significantly better than the butorphanol-tramadol group as regards overall pain control.

Our results are in line with recent publications that suggest that acetaminophen not only reduces post-surgical pain intensity but also reduces the opioid consumption^{5,10} further protecting the patients against opioid related adverse effects. We now extend this finding to obstetrics and gynecological cases as well.

The service related implications of this study is that in circumstances where opioid use is considered unsafe or risky were in patients who are sensitive to opioid induced sedation, confusion, respiratory depression, and gastrointestinal complications, injectable acetaminophen can provide an acceptable safe alternative. Thus, the results of this study expand our therapeutic options and further empower the clinician in the management of this important group of patients

The limitation of our study

It has lower overall number of patients, so the best point estimate may be less accurate. There is a need for better designed large-scale studies to establish whether adding acetaminophen with an opioid does or does not decrease opioid consumption and its side-effects.

CONCLUSION

In conclusion, our analyses suggest that IV acetaminophen is an effective analgesic in obstetric and gynecological surgeries with a good safety profile. Given alone, they are unlikely to provide sufficient analgesia in surgery, which produces moderate-to-severe pain. If used in combination with opioids, they reduce opioid consumption, and this reduction is sufficient to reduce opioid-induced adverse effects. Larger trials are required.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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