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# The Effects of Intravenous Acetaminophen on Pain and Clinical Findings of Patients with Acute Appendicitis; A Randomized Clinical Trial

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## ABSTRACT

**Objective:** To determine the effects of intravenous Acetaminophen (Apotel®) on pain severity and clinical findings of peritonitis in patients with acute appendicitis.

**Methods:** This randomized cross-over clinical trial was carried out duringa 6-month period from August 2012 to February 2013 and comprised 107 patients diagnosed with acute appendicitis. Patients were randomly assigned to received placebo (n=54) or Apotel® (n=53). Patients were evaluated before, 30 minutes, 1 hour and 4 hours after administration of Apotel® or placebo,and were told to fill in two forms. The first form required patientsto measure their painintensityaccording to visual analogue scale (VAS). The second form was filled by a surgeon who examined the patients and recorded his or her findings using Alvarado score criteria for diagnosis of acute appendicitis at foregoing time points.

**Results:** Of 72 patients, 37 (51.4%) were men and 35 (48.6%) were women. The mean age of the patients was 34.1±13.5 years. The mean pain score in 107 patients included in this study was 7.96±2.3. Those who received Apotel® had significantly lower pain scores when compared to placebo at 30 minutes ($p$<0.001), 1 hour ($p$<0.001) and 4 hours of administration. There was no significant difference between two study groups regarding the frequency of Alvarado score; however the frequency of fever was significantly lower in those who received Apotel® ($p$<0.001). We found that Apotel® was not associated with resolved physical findings of acute appendicitis in different time intervals.

**Conclusion:** Apotel® does not affect the clinical findings of acute appendicitis and dos not interfere with the accurate diagnosis. Therefore, it could safely be used as a reliable pain relieving agent, in patients with acute appendicitis.

**Keywords:** Acute appendicitis; Apotel®; Clinical findings; Analgesic.

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## Introduction

Inflammation of the appendix or acute appendicitis is among the emergencies of the general surgery, for which the treatment of choice is appendectomy [1].Acute pain is one of the main symptoms of acute appendicitis and in almost every case is the chief complaint. Appendicitis pain, as well as any other pain due to acute abdomen are persecutory and unbearable by the patients, and are an annoying issue in the emergency room (ER) [2]. Administration of different analgesics for pain control in these patients has alwaysbeen most challenging and a matter of controversy among surgeons. In this regards, many physicians and surgeons believe that giving analgesic

to these patients will change the pain pattern and clinical findings of peritonitis and interfere with the proper diagnosis and management [3-6]. Such perspective caused reluctance in administering analgesics to patients with acute appendicitis admitted to our center. However the administration of analgesics should be supported by clinical evidence of not interfering with accurate diagnosis.However, having proved the innocuous property of analgesics and their lack of interference with accurate diagnosis of acute appendicitis, the administration of analgesics would help patients better tolerate the associated pain prior to surgery [2-6].

Many studies have been designed to show that analgesics do not affect clinical findings and can be administered safely to alleviate the pain intensity in acute appendicitis [2-8]. Another study showed that minor changes caused in clinical findings were negligible and did not interfere with the diagnosis and management in those with acute abdomen [5]. Also, some blinded clinical trials have demonstratedthe efficacy of analgesics in decreasing pain when compared to placebo in patients with abdominal pain without interference with the clinical management and decision making [9]. Previous lines of evidence also suggest that patient satisfaction and safety is increased when analgesics are prescribed [10]. The present study was thus carried out to determine the effects of intravenous administration of acetaminophen (Apotel®) on pain severity, and clinical findings in patients with acute appendicitis.

## Materials and Methods

*Study Population*

This was a cross-over randomized clinical trial being performed in Shahid Faghihi hospital, a tertiary health care center affiliated with Shiraz University of Medical Sciences during a 6-month period, from August 10th, 2012 to February 10th, 2013. We included 107 patients with diagnosis of acute appendicitis. Patients were diagnosed by a surgeon or a senior surgical resident, using Alvarado score, in the emergency and were scheduled for appendectomy operation. Patients were selected randomly on days of selection using a random number table. Patients included in the study were hemodynamically stable on arrival having systolic blood pressure >90 mmHg and heart rate <100 beat/minute, feeling the intensity of pain more reliably, and diagnosed with acute appendicitis by the surgeon or a senior surgical resident. Patients excluded from the study were those with unstable hemodynamic, under 16 years, having pain in another region of their body besides abdomen, unable to easily communicate, having a prior medical condition which had caused peripheral neuropathy or changes in pain perception such as diabetes mellitus or opium consumption, using analgesics or anti-inflammatory drugs such as corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) during last 12-hours before diagnosis of acute appendicitis and finally patients who were unwilling to enroll in the study or even subjects which decided to quit the study during evaluation. The study protocol was approved by the institutional review board and the medical research ethics committee of Shiraz University of Medical Sciences and all the patients provided their informed written consents before inclusion in the study.

*Study Protocol*

We included 107 patients with acute appendicitis who were admitted to our emergency room. The patients' characteristics such as age, gender, signs and symptoms, duration of symptoms, co-morbidities and history of previous surgeries were recorded on admission. All the patients underwent complete physical examination by a senior general surgery resident and the findings were recorded in a data gathering form. Patients were randomly assigned to two study groups based on their admission order. We used a computer based random digit generator for assigning the patients to two study groups. Those who were assigned to first group received intravenous distilled water as placebo (n=54) while those in the second group received 1 gr intravenous Acetaminophen (Apotel®) during 15-20 minutes after inclusion in the study (n=53). The placebo or Apotel® were administered by a nurse who was blinded to the study and the administered drug.

Patients were evaluated before, 30 minutes, 1 hour and 4 hours after administration of Apotel® or placebo and asked to fill in two forms. The first form required themto measure their pain intensity by using 0-10 numerical visual analogue scale (VAS) at a forementioned times. The second form was filled in by a surgeon who examined the patients and recorded his or her findings using Alvarado score criteria for diagnosis of acute appendicitis at foregoing time points. The study was double-blinded and both surgeon and patients were unaware of administered substance. Indeed, when patients stayed in the emergency room for less than 4 hours, they were evaluated just before going to operating room rather than 4 hours after the intervention.

*Statistical Analysis*

In order to have 85% power to detect 5% difference between the corresponding variables, 50 patients were calculated to be required for each study groups. In order to compensate for non-evaluable patients, we included 107 patients. The statistical analysis included independent t-test and chi-square tests, with the statistical package for Social Science, SPSS for

Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Also MedCalc version 8.0.0.0 (MedCalc, Mariakerke, Belgium) statistical software was employed for comparison of proportions. A two-sided *p*-value less than 0.05 were considered statistically significant.

## Results

Over the course of six months, 143 patients diagnosed withacute appendicitis were admitted to the emergency room of the Shahid Faghihi hospital. Of these, 107 patients [72 (67.3%) men and 35 (32.7%) women] met the inclusion criteria and were gradually enrolled in the study. Placebo group included 54 patients and 53 patients were allocated to Apotel® group. The patients aged from 16 to 56 year with mean age of 34.2 ± 13.6 years.

Male and female patients waited for an average of 6.4±2.6 and 4.8±1.8 hours respectively, before referring to emergency room. According to 0-10 VAS score, the pain score ranged from 5 and 10 among all 107 patients with the mean pain score of 7.96±2.7 at the time of diagnosis and before administration of drugs (hour 0). On admission (hour 0), 95 (88.75%) patients had right lower quadrant (RLQ) tenderness. All 107 patients had rebound tenderness, 91 (85.02%) had elevated body temperature (higher than37.3°C). Of 107 patients, 103 (96.3%) had anorexia, 75 (70.1%) had positive history of nausea and vomiting, 105 (98.1%) exhibited leukocytosis marked by their complete blood count and 94 (87.82%) had positive history of migratory pain frompre-umbilical area to RLQ. All Alvarado criteria were also checked 30 minutes, 1 and 4 hours after giving drugs, except for leukocytosis which was only checked on admission and migration which had happened before admission and did not occur subsequently. The baseline characteristics of the patients are summarized in Table 1. There was no significant difference between two study groups regarding the baseline characteristics.

The changes in VAS score after administration of placebo or Apotel® is summarized in Table 2. The VAS score in patients decreased for 0.35 of score from admission (hour 0) to 30 minutes after receiving placebo ($p$=0.009). The mean score decreased for 1.98 in Apotel® group after 30 min ($p$<0.001). Mean VAS score increased for 0.07 in placebo group between hours 0 and 1 hour ($p$=0.696) and decreased in Apotel® group for 3.86 scores during the same time ($p$<0.001). Mean VAS score increased in placebo group for 1.24scores between hours 0 and 4 hours ($p$=0.003), and decreased for 5.52 scores in Apotel® group in the same timeperiod ($p$<0.001). The frequency of Alvarado score between two groups in different time periods is demonstrated in Table 3. There was no significant difference between two study groups regarding the frequency of Alvadaro score except for fever which was significantly lower in those who received Apotel®, 30 minutes ($p$<0.001), 1hour ($p$<0.001) and 4 hours ($p$<0.001) after administration of Apotel® (Figure 1).

As another major part of our study we sought to compare the prevalence of Alvarado criteria with each other in the two groups at specified time. This was done by comparing the proportions with MedCalc 8.0.0.0 (MedCalc, Mariakerke, Belgium) statistical software that enabled us to see if administration of Apotel® or placebo significantly changes a particular criterion among our patients over time. As shown in Table 3, 46 patients (86.7%) in group 2 had RLQ tenderness on admission, and 30 minutes after administration of Apotel® they still exhibited this criterion. But 4 hours after administration of Apotel®, RLQ tenderness was found in 43 patients (81.2%). According to MedCalc software, there was no statistically significant difference in RLQ tenderness in group 2 between 0 time and 4 hours ($p$=0.6092). Table 4 shows that comparison of proportions of other criteria in both groups at different times showed that neither placebo nor Apotel® caused any significant changes in Alvarado criteria. In other words, Apotel® had no effect on clinical findings in patients with

**Table 1.** Baseline characteristics of the 107 patients with acute appendicitis in two study groups.

| | Placebo (n=54) | Apotel® (n=53) | *p*-value |
|---|---|---|---|
| **Age (years)** | 32.6 ± 10.9 | 33.6 ± 8.3 | 0.579 |
| **Sex** | | | |
| Men (%) | 35 (64.8%) | 37 (69.8%) | 0.681 |
| Women (%) | 19 (35.2%) | 16 (30.2%) | |
| **Duration of symptoms (hours)** | 5.7 ± 2.4 | 6.1 ± 2.6 | 0.624 |
| **Pain intensity on admission (VAS[a] score)** | 7.7 ± 0.85 | 8.1 ± 0.71 | 0.061 |
| **Alvadaro criteria** | | | |
| RLQ[b] tenderness (%) | 53 (98.1%) | 52 (98.1%) | 0.999 |
| Reboundtenderness (%) | 54 (100%) | 53 (100%) | 0.999 |
| Fever (%) | 53 (98.1%) | 52 (98.1%) | 0.999 |
| Anorexia (%) | 53 (98.1%) | 50 (94.3%) | 0.363 |
| Nausea and vomiting (%) | 51 (94.4%) | 51 (96.2%) | 0.997 |
| Leukocytosis (%) | 53 (98.1%) | 52 (98.1%) | 0.999 |
| Pain migration (%) | 53 (98.1%) | 52 (98.1%) | 0.999 |

[a]VAS: Visual Analogue Scale; [b]RLQ: Right Lower Quadrant

**Table 2.** Changes in VAS score in 107 patients with acute appendicitis after receiving placebo or Apotel®.

| | Placebo (n=54) | Apotel® (n=53) | *p*-value |
|---|---|---|---|
| **VAS[a] score** | | | |
| On admission | 7.7 ± 0.85 | 8.1 ± 0.71 | 0.061 |
| After 30 minutes | 7.4 ± 0.95 | 6.2 ± 0.76 | <0.001 |
| After 1 hour | 7.8 ± 1.27 | 4.3 ± 0.77 | <0.001 |
| After 4 hours | 8.4 ± 1.34 | 2.6 ± 0.97 | <0.001 |

[a]VAS: Visual Analogue Scale

acute appendicitis other than significantlydecreasing body temperature ($p<0.001$).

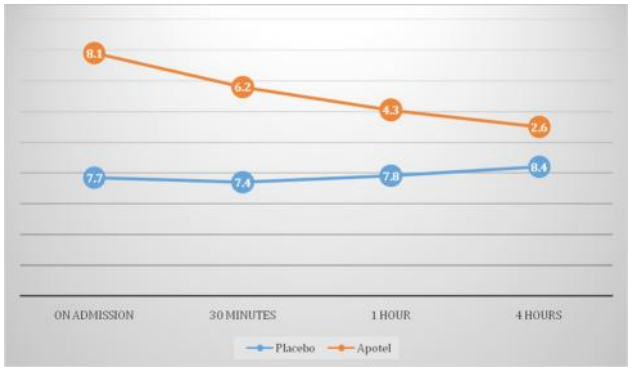


**Fig. 1.** Changes in visual analog scale (VAS) score in 107 patients with acute appendicitis receiving placebo or Apotel® as analgesic.

## Discussion

Pain management in patients with acute appendicitis before surgery is not included in the conventional ER management policies. There could be several reasons for with holding analgesia from these patients. It could mostly concern changes in the physical findings, and interference with the proper diagnosis [3-6,11]. In another study, Stalnikowicz *et al*. found a difference in evaluating pain intensity by the patients and medical personnel [12]. Perhaps this disparity in evaluation by staff and nurses is an additional reason for reluctance in prescribing analgesics.

Some previous studies have shown that management of pain in these patients does not interfere with the accurate diagnosis andwould merely help the patient tolerate the situation much easier [2-6]. Many studies have been done on the effect of analgesia on physical examination of ER patients. Attard *et al*. concluded that early administration of opiates to patients with acute abdominal pain can reduce their painwithout interference with correct diagnosis. On the contrary, such treatment may even facilitate the diagnosis [13]. Thomas *et al*. reviewed the results of 8studies regarding the effect of analgesia on accuracy of physical findings and proper diagnosis, and found no association between analgesia and misdiagnosis [14]. The study of Ranji and colleagues showed that opiate administration may alter the findings of physical examination, but these changes did not resultin any significant increase in management errors [5]. In the other hand, LoVecchio *et al*. reported changes in physical examination following administration of analgesics to patients with acute abdominal pain [15]. To design a unified protocol for pain management in these patients, different drugs and their effect on pain intensity, physical examination and vital signs have to be tested along with sufficient control trials. Mahadevan *et al*. in their blinded study, reported striking effects of analgesics on alleviating pain in these patients, compared with placebo without any problems in patients' management [9]. On the other hands,Thomas *et al*. assessed analgesic effects of morphine in patients with undifferentiated abdominal pain compared with placebo. The results showed no change in physical examination and no interference with diagnostic accuracy after administration of morphine, andsupported early administration of

**Table 3.** The changes in Alvarado Score in 107 patients with acute appendicitis after receiving placebo or Apotel®.

| | Placebo (n=54) | | | Apotel® (n=53) | | |
|---|---|---|---|---|---|---|
| | 30 minutes | 1 hour | 4 hours | 30 minutes | 1 hour | 4 hours |
| **RLQ[a] tenderness (%)** | 54 (100%) | 53 (98.1%) | 50 (92.6%) | 52 (98.1%) | 53 (100%) | 49 (92.5%) |
| **Reboundtenderness (%)** | 54 (100%) | 52 (96.3%) | 53 (98.1%) | 52 (98.1%) | 52 (98.1%) | 52 (98.1%) |
| **Fever (%)** | 50 (92.6%) | 41 (75.9%) | 37 (68.5%) | 24 (45.3%)* | 7 (13.2%)* | 6 (11.3%)* |
| **Anorexia (%)** | 52 (96.3%) | 50 (92.6%) | 47 (87.0%) | 50 (94.3%) | 48 (90.6%) | 46 (86.8%) |
| **Nausea and vomiting (%)** | 49 (90.7%) | 50 (92.6%) | 45 (83.3%) | 51 (96.2%) | 49 (92.5%) | 49 (92.5%) |
| **Leukocytosis (%)** | 53 (98.1%) | 54 (100%) | 54 (100%) | 52 (98.1%) | 53 (100%) | 53 (100%) |

[a]RLQ: Right Lower Quadrant; (Significantly lower when compared to placebo group ($p<0.05$)).

**Table 4.** Comparison of proportions of Alavarado criteria in 107 patients with acute appendicitis receiving placebo or Apotel® for pain relief.

| | Placebo (n=54) | Apotel® (n=53) |
|---|---|---|
| | *p*-value | *p*-value |
| **RLQ[a] tenderness** | | |
| Changes in 30 min | 0.9928 | - |
| Changes in 1 hour | - | 0.9962 |
| Changes in 4 hours | 0.5719 | 0.6092 |
| **Rebound tenderness** | | |
| Changes in 30 min | - | 0.9944 |
| Changes in 1 hour | 0.4761 | 0.4707 |
| Changes in 4 hours | 0.9794 | 0.9979 |
| **Fever** | | |
| Changes in 30 min | 0.6027 | < 0.0001 |
| Changes in 1 hour | 0.0134 | < 0.0001 |
| Changes in 4 hours | 0.0024 | < 0.0001 |
| **Anorexia** | | |
| Changes in 30 min | 0.9870 | - |
| Changes in 1 hour | 0.3680 | 0.7239 |
| Changes in 4 hours | 0.0672 | 0.3232 |
| **Nausea and Vomiting** | | |
| Changes in 30 min | 0.8424 | - |
| Changes in 1 hour | 0.9861 | 0.8352 |
| Changes in 4 hours | 0.3135 | 0.7121 |

[a]RLQ: Right Lower Quadrant; (*Proportion of each group which had a criterion on admission, was compared to that proportion, in that group, in other times. ** Note that (-) means proportions have been the same in two times.)

analgesics to patients with undifferentiated abdominal pain [16].

There are very few reportson assessing the effect of intravenous administration of Acetaminophen Apotel®) on pain intensity and other aspects of diagnosis and treatment. We preferred to use Apotel® because of its lesser adverse effect on patients than narcotic analgesics. This study aimed to highlight the actual effect of intravenous Acetaminophen (Apotel®) on pain intensity and clinical findings in patients with acute appendicitis scheduled for surgery, compared to those receiving placebo. The results obtained showed a compelling evidence of pain-relieving property of Apotel® ($p<0.001$).

In conclusion, Apotel® did not cause any significant changes in the clinical findings and did not interfere with accurate diagnosis. Therefore, it could be used safely, as a reliable pain relieving agent, in patients with acute appendicitis. This drug inevitably lowers body temperature which is due to its antipyretic property.

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**Conflict of Interest:** None declared.

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