Effects of Intravenous Morphine on Physical Examination Findings in suspected Acute Appendicitis: A Randomised Conctrolled Clinical Trial.

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Back ground: Use of analgesics in patients with undiagnosed acute abdominal pain is marked by long standing controversy over the effects of analgesia on physical examination findings. Analgesics are often with held for fear that they may mask physical examination findings and lead to delayed or missed diagnosis. This study aimed at determining the effects of intravenous Morphine on the physical examination findings in patients with clinically suspected acute appendicitis admitted at Mulago hospital Accident and Emergency Department and surgical wards of Mulago hospital.
Methods: This study was a randomized controlled clinical trial. Patients were randomized to receive intravenously either 0.15mg/kg (maximum 1ml) of morphine sulphate (n = 28) or an equal volume of water for injection (placebo) (n = 32).
Results: A total of 60 patients 28 males (46.7%) and 32 females (53.3%) aged between 7 years to 79 years with acute right lower abdominal pain suspected to be due to appendicitis were included in the final analysis. The study findings demonstrated that I.V morphine provided substantial and statistically significant pain reduction (P=.00) in patients with acute abdominal pain due to appendicitis without blunting their physical examination findings. Those who received placebo had fractional pain VAS reduction which were not statically significant (P = 0.610). Effects of I.V morphine and placebo on the rebound tenderness and muscle guarding showed that there was no statically significant change in these two important physical signs for both study groups.
Conclusion: The study has objectively demonstrated that when compared with placebo judicious administration of I.V morphine provides significant pain reduction without adversely affecting the physical examination findings in patients presenting with acute abdominal pain due to suspected appendicitis.

Introduction

Many clinicians have been reluctant to use analgesics while evaluating patients with presumed acute appendicitis or undifferentiated abdominal pain. The chief concern has been that pain medication may mask and blunt signs of the underlying pathology and hinder the ability to make a definitive diagnosis or lead to delay in diagnosis[1]. This view has been dispelled recently, several clinical trials have suggested that expeditious pain relief in patients with acute abdominal pain does not lead to delay in diagnosis or interfere with the physical examination findings[2,3,4,5,6].

Currently, surgical literature emphasize that unrelieved pain can have profound psychological effects on the patients and is associated with increased stress and makes the patient uncooperative during physical examination[7,8,9]. Despite the safety and advantages pointed out in previous studies[2,4,5,6,10], the concept of early pain relief in patients presenting with acute abdominal pain is still novel in Africa. Therefore a randomized controlled clinical trial was designed to determine the effects of I.V morphine on physical examination findings in patients with suspected appendicitis. The study focused on clinically suspected acute appendicitis because it is one of the commonest causes of acute abdominal pain in our environment and abdominal signs in acute appendicitis are easily elicitable and lead to correct diagnosis[11].

Materials and Methods

This study was a randomized, double blind placebo controlled clinical trial. The study was conducted at Mulago national hospital Kampala, Uganda. All patients who were 7 years to 80

years old with right lower abdominal pain suspected to be due to appendicitis and who scored 5–6 by the Modified Alvarado Score System (MASS) [12] were eligible for the study. All eligible adult patients were asked for the informed written consent. For children, informed written consent from parent and assent from the patient was obtained.

The screening process entailed identification of all patients with acute right lower abdominal pain presenting at the Accident and Emergency (A & E) department. All patients with history of allergy to morphine, those with suspected pregnancy and those who had shortly used opioid analgesia prior to their arrival to A & E department were excluded. In order to make a provisional diagnosis, a detailed history and through physical examination plus appropriate investigations were carried out. Total white blood cell count (WBC) was carried out for all patients. Abdominal ultrasonography was done to those patients with equivocal presentation. Patients with acute right lower abdominal pain suspected to be due to appendicitis were scored by using the MASS; those who scored 5–6 were considered eligible for the study.

A computer program (random number generator, Microsoft excel 5.0) was used to generate random number list, whereby patients were assigned to either of the two groups i.e. A (I.V morphine) or B (placebo). Adequate double blinding was employed; whereby both the patients and the principal investigator (PI) were blinded i.e. treatment identity to the study subject was hidden. The PI who was the chief assessor was blinded to avoid assessment bias.

After initial evaluation, assessment for eligibility and making of a provisional diagnosis, the patients' baseline vital signs and pains score using 10cm visual analogue scale (VAS)[13], were recorded. The abdominal physical examination findings prior interventions were recorded as well. These focused on three explicit signs commonly found in acute appendicitis namely, muscle guarding in the right iliac fossa (RIF), rebound tenderness in the RIF and localization of site of maximal tenderness to percussion in the RIF. Location of exact abdominal site with maximum tenderness was measured in centimeters using a tape measure. The point of reference was the distance from the midline and this was an imaginary straight line joining the pubic symphysis, umbilicus and xiphisternum. Guarding and rebound tenderness were graded as being present or absent. Patients then received either I.V morphine 0.15mg/kg (maximum 1ml) or an equal volume of water for injection (placebo), depending on whether patient belonged to group A or B.

Thirty minutes after administration of morphine or placebo, patient's pain scores, vital signs and physical examinations findings were re – evaluated and again recorded. Patients admitted to the hospital were followed up for a period of two weeks for final diagnosis, and this was made in regard to operative findings, histology results or postmortem findings. Patients discharged home from the A & E department had their presumptive diagnosis recorded but they were not followed up.

The main outcome measurements were presence or absence of rebound tenderness, presence or absence of muscle guarding, pain scores by using a 10cmVAS before and after administration of Morphine or placebo and localization of site of maximal tenderness. Data was collected by using structured questionnaires, SPSS version 10 programs was used to enter data and for analysis. Continuous variables such as pain scores and changes in pain scores were analyzed using means, standard deviation (SD) and compared using the independent sample t–test. Categorical variables such as changes in localization of site with maximal tenderness to percussion, presence or absence of rebound tenderness and presence or absence of guarding were analyzed using frequencies and percentages and compared using the chi – square test. The 95% confidence interval (95% CI) was calculated where appropriate, statistical significance was set at $P < .05$ (two tailed).

Results

A total of 63 eligible patients admitted to Mulago hospital with clinically suspected acute appendicitis were approached to participate in this study. Out of those 63 eligible patients, two patients did not consent to take part in the trial and one patient dropped out before enrolment, hence 60 patients 32 females (53.3%) aging between 7 years to 79 years were enrolled and consented to participate in the study. Twenty eight patients were eventually randomized to the morphine group and 32 patients to the placebo group. No randomized patients withdraw from the study. All 60 patients were included in the subsequent analysis. Thirty minutes post intervention there was a significant change in pain VAS scores especially in the morphine group (P= .00) Never the less, fractional pain reduction scores were observed on the placebo group with mean VAS score of 1.0cm (P=0.610) which was not statistically significant. Generally children had high VAS scores compared to their adults' counterparts.

With regard to comparison between the effects of I.V morphine and placebo on the abdominal signs, there was no statistically significant change in patients' physical examination findings after receiving either morphine or placebo for each of the abdominal sings assessed. Odds ratio (OR) for rebound tenderness was 2.315 with 95% confidence interval (0.14 – 13.02) and P= 0.331 in both study groups, whereas the odds ratio (OR) for muscle guarding was 0.873 with 95% CI (0.13–2.49) and P= 0.799

Comparison of I.V morphine and placebo effects on the site of localization of maximum tenderness to percussion revealed no statistically significant change. The mean in the morphine group was found to be 1.9cm whereas the mean for placebo group was 2cm (P=0.122)

Discussion

The use of analgesics in patients with acute abdominal pain has traditionally been condemned world wide. Classic teaching in surgery has dictated that the use of analgesics should be with held from patients with acute abdominal pain until a surgeon establishes a definitive treatment plan[1,14,15]. This anecdotal based teaching and practice has been challenged. Several studies suggest that the administration of analgesia does not adversely affect the physical examination findings or delay diagnosis[2, 3,4,5,6]. In this cohort, the two study groups had similar demographic characteristics, comparable initial pain scores, base line vital signs, physical signs and presenting symptoms. Unaltered baseline vital signs following administration of opioid analgesia has been reported in previous studies [2,3,16].

Morphine causes analgesia (relief of pain without the loss of consciousness), by both raising the pain threshold at the spinal cord level and more importantly by altering the brains perception of pain. Patients treated with morphine are still aware of the presence of pain but the sensation is not unpleasant[17.] This property makes morphine an appropriate analgesic in patients with acute abdominal pain as it allows abdominal signs to be easily elicited.

The study showed that the three physical examination findings commonly found in acute appendicitis namely, muscle guarding in the RIF, rebound tenderness in the RIF, and localization of site of maximum tenderness to percussion in the RIF were not interfered following morphine or placebo administration. This therefore alleviates fears that analgesia use in patients with acute abdominal pain does mask physical signs and hence delay diagnosis. Similar outcomes were reported by earlier investigators[2,3,16].

The fractional pain VAS score reduction in the placebo group could only be ascribed to the "psychological soothing" as patients in both study groups were adequately blinded and did not know what has been administered to them at the time of intervention. This finding is also

consistent with what the earlier investigators observed[3, 10]. High VAS pain scores observed in children can be attributed to the fact that children have low pain threshold compared to their adult counter parts, however children responded similarly to adults following placebo or I.V morphine administration.

With regard to physical examination findings, children had comparable outcomes to adults. These findings militates against the myths that children do not feel pain in the same way adults do and that pain has no untoward consequence in children. Generally, patients' pre – intervention and post–intervention diagnosis did not change in both study groups due to the fact that key abdominal signs were unaltered even after morphine administration, these findings are consistent with what was reported earlier [2,3,15].

Although pharmacokinetically morphine overdose may lead to depression of respiratory rate and hypotension, these adverse effects were not encountered in this study probably due to judicious administration. The study had some limitations, firstly, use of opioid analgesia in patients with acute appendicitis may not be generalized to other abdominal conditions in which use of opioid analgesia is questionable e.g. in biliary and pancreatic problems. Secondly, small sample size might have failed to demonstrate adverse effects associated with administration of opioid analgesia.

However, homogenous patient's enrollment, recruitment of patients with elicitable abdominal signs and those who clinically needed analgesia were the study's main strengths. In future, a multi–center, large–scale clinical trial involving both adults and children is required to show effects of analgesia on physical examination findings in our setting.

Conclusion

The study has objectively demonstrated that when compared with placebo judicious administration of I.V morphine provides significant pain reduction without adversely affecting the physical examination findings in patients presenting with acute abdominal pain due to suspected appendicitis.

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