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Safety and impact on diagnostic accuracy of early analgesia in suspected acute appendicitis: A meta-analysis

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ABSTRACT

Background: The safety of early analgesia in patients suspected to have acute appendicitis (AA) is still controversial.
Methods: Double blind randomized clinical trials comparing patients receiving or not receiving opiates for early analgesia in suspected AA were selected for meta-analysis according to PRISMA guidelines. Primary outcomes were the number of patients with AA confirmed by histology and the number of patients undergoing surgical intervention. Secondary outcomes were missed diagnoses, false positive AA and complication rate. Effect sizes were calculated using a Mantel-Haenszel fixed effects model.
Results: Previously published papers mostly analyzed surrogate end-points such as physician's confidence about the diagnosis or the alteration of clinical signs, subjective parameters dependent on personal perception. Our article focused on clinical outcome and specifically investigated those potentially related to AA instead of unspecified abdominal pain. Opiate administration did not have an impact on the number of histologically proven AA (OR = 1.196 [0.875–1.635]; $P = 0.261$). Differences in appendectomy rates were only slightly above the threshold for statistical significance (OR = 1.350 [0.966–1.887]; $P = 0.079$), suggesting that analgesia might influence the treatment approach. On the other hand missed diagnoses (OR = 0.509 [0.087–2.990]; $P = 0.455$) and false positive AA (OR = 1.071 [0.596–1.923]; $P = 0.818$) ascertained by histologic examination were unaffected, so diagnostic accuracy was retained. Safety was not compromised by opiates, as the difference in complication rates did not reach statistical significance (OR = 0.615 [0.217–1.748]; $P = 0.372$).
Conclusion: Early analgesia with opiates in suspected AA might influence the approach to treatment, but does not appear to alter diagnostic accuracy or surgical outcome. To support our findings, further trials on larger sample sizes from different age groups and both genders are needed.

1. Introduction

The safety of early analgesia in patients referred with abdominal pain has been long debated, but the question still remains controversial. The issue was first discussed in 1921 by Cope et al.,[1] who maintained that analgesia could alter or mask clinical signs during physical examination. Since then, the usual morphine dosage has decreased from a maximum of 30 mg in total, down to 0.05–0.1 mg/kg^{-1} and the majority of recent papers support the idea that withholding analgesia does not stand on scientific grounds.[2] On the other hand, flaws in study conception, low statistical power and arguable choice of surrogate markers instead of surgical outcomes have meant favorable results have been greeted with skepticism. Clinical practice is therefore still dependent on a surgeon's personal belief. The aim of this work was to assess the safety and impact of early pain relief on surgical outcome using a meta-analysis of double-blind randomized clinical trials (RCT) which enrolled patients complaining of abdominal pain who might have acute appendicitis (AA).

2. Materials and methods

Double-blind controlled RCTs comparing patients receiving or not receiving opiates (or receiving a placebo) for abdominal pain were sought through PubMed/Medline, Embase and Cochrane databases using the key words and phrases —appendicitis‖, —analgesia‖, —morphine‖, —opiate‖, —right lower quadrant pain‖, —abdominal pain‖ in combination with Boolean operators to obtain papers containing one or more of the listed key-words/free text terms. Further results were obtained by manual selection of articles found in bibliographies. Search and data extraction were independently performed by the authors and conflicts were resolved by consensus. Validation and appraisal were performed according to pre-established criteria.

The literature search spanned from inception to current date (early 2013). No restriction was applied for publishing status, language or number of included

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patients. Studies involving NSAIDs instead of opiates were excluded because their effects are not comparable due to different mechanisms of action. At the first level of filtering, titles and abstracts were screened to identify studies related to the subject of our inquiry. Secondly, all forms of clinical investigation other than RCTs such as retrospective studies, observational studies and non-blinded clinical trials were excluded. Finally, RCTs were further analyzed to assess study quality, design and comparability of results with respect to inclusion/exclusion criteria and patient-presenting conditions at the emergency department (ER). Reports and analyses were in accordance with the PRISMA statement.[3] Variables selected for extraction were descriptive (population, age groups, treatment drug and dosage) and methodological quality related (generation of the randomization sequence, allocation concealment and blinded outcome).[4]

Statistical analysis was performed with Comprehensive Meta-Analysis v. 2.0. Odds ratio (OR) was calculated (95% CI). Effect sizes were calculated for each outcome using the Mantel-Haenszel fixed effects model. Heterogeneity was assessed with the Q test (significant if $P < 0.05$) and the influence of heterogeneity on OR value with I^2 test. We intended to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, as appropriate given the known limitations of these methods. Results were presented in a forest plot.

Primary outcomes were the number of patients with AA confirmed on pathologic examination and the number of patients undergoing either open or laparoscopic appendectomy. Secondary outcomes were complication rate (defined as the number of appendicular abscesses or perforated appendices observed at the time of surgical intervention[5–7]), missed diagnoses (defined as the number of patients readmitted to the same or nearby hospital and operated for proven AA within a month after discharge[5–8]), and false positive AA (diagnosis excluded by histologic examination[5–8]).

3. Results

The search produced 2187 articles. After the first screening, 24 potentially relevant articles were found and among them 14 RCTs were identified.[5–18] Two of them[16,18] were discarded because all patients were equally destined to have surgical intervention as a preliminary condition to enrollment. Seven other papers[9–14,17] were deemed to be biased as they addressed non-specific abdominal pain (NSAP), whereas our focus was on suspected AA. Although formally investigating NSAP, the studies conducted by Green at al.[5] and Kokki et al.[7] were considered eligible. Enrolled patients were in fact younger than 17 years and AA represents the most common indication for emergency laparotomy in this age group, indicating that the focus was implicitly on AA or mimicking conditions.[19] In addition, outcome measures in both studies related to the clinical features of AA (Fig. 1). Studies with usable information[5–8,15] presented a pooled population of 664 patients, 337 treated with opiates and 327 with placebo. Publication bias was not formally assessed as there were inadequate numbers of included trials to properly analyze a funnel plot or more advanced regression-based assessments. Descriptions of included papers are summarized in Table 1. Table 2 shows patient and outcome data, whereas Table 3 shows methodological quality evaluation data.

Information about the number of suspected AA confirmed by histologic examination was available for all eligible studies. Pooled data showed no significant difference between patients receiving opiates and those managed with a placebo (OR = 1.196 [0.875–1.635]; $P = 0.261$); there was no evidence of heterogeneity ($Q = 1.811$; $P = 0.770$; $I^2 = 0\%$). The number of patients undergoing appendectomy was only slightly above statistical significance (OR = 1.350 [0.966–1.887]; $P = 0.079$); values were available for four studies and heterogeneity was not present ($Q = 0.957$; $P = 0.812$; $I^2 = 0\%$). The complication rate was reported in four studies and did not reach statistical significance (OR = 0.615 [0.217–1.748]; $P = 0.372$); heterogeneity was not present ($Q = 0.059$; $P = 0.809$; $I^2 = 0\%$). Information regarding missed diagnoses was available in four studies. No difference resulted between the two groups (OR = 0.509 [0.087–2.990]; $P = 0.455$). Heterogeneity test was negative ($Q = 0.461$; $P = 0.794$; $I^2 = 0\%$). False positive AA values were reported in four studies and did not

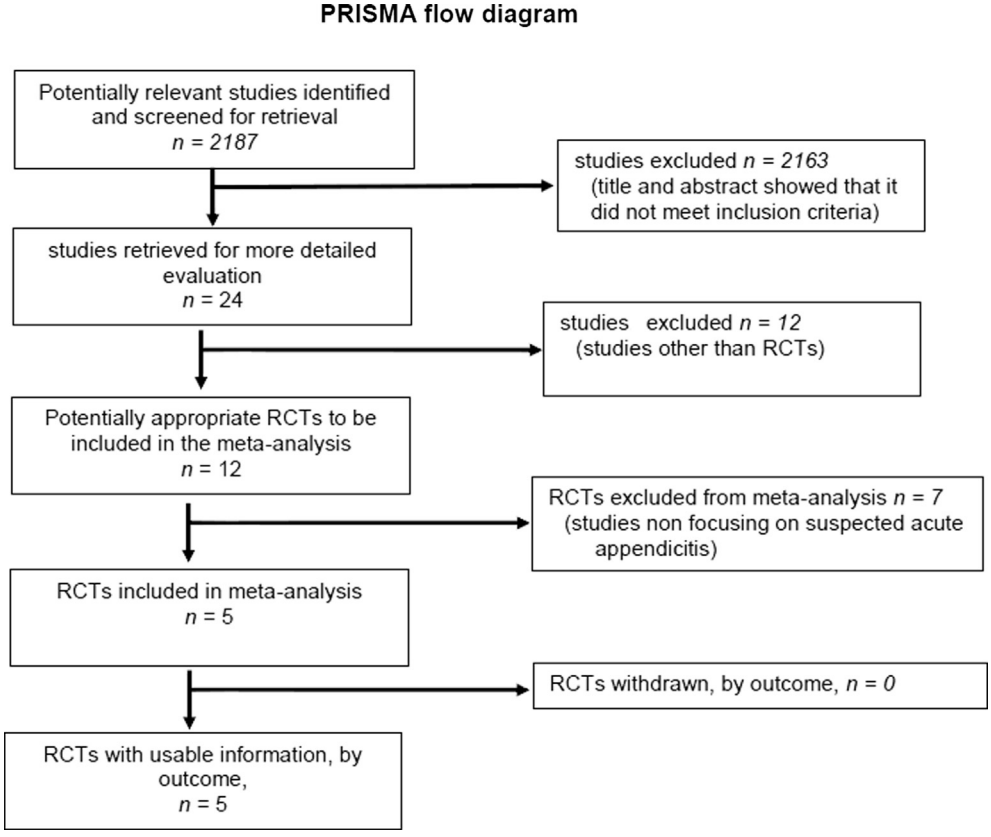

Fig. 1. PRISMA flow diagram representing literature evaluation and selection process.

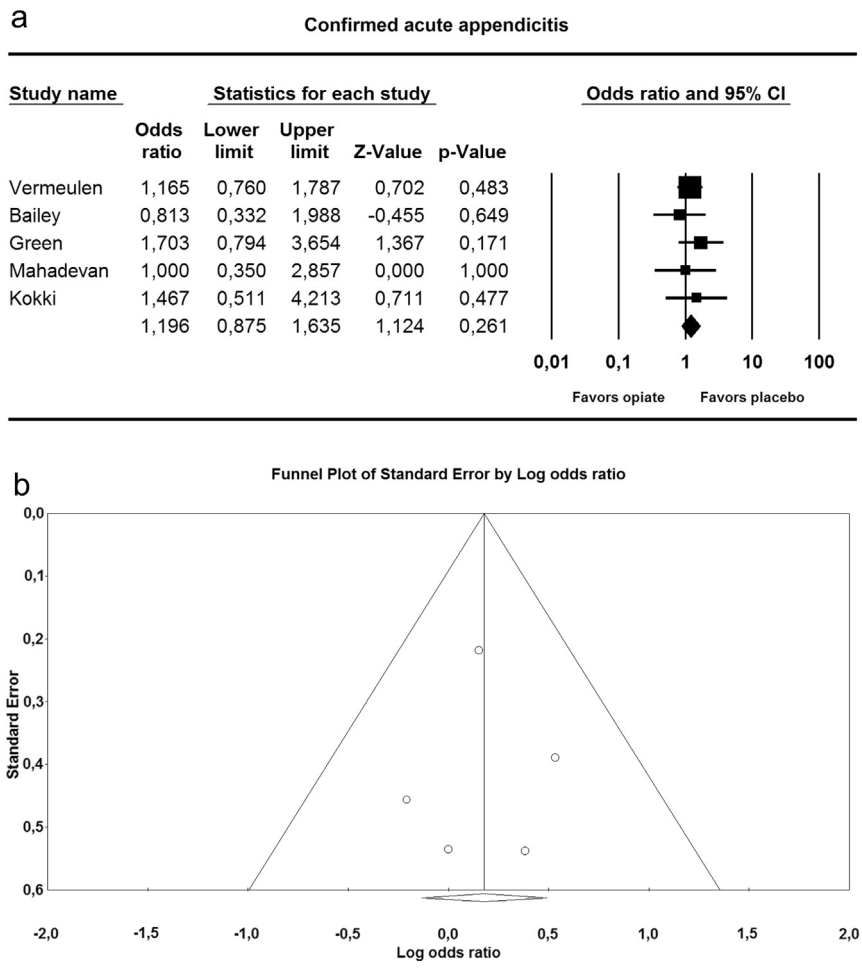

Fig. 2. a: Forest plot of histologically confirmed acute appendicitis. b: Funnel plot for publication bias evaluation about histologically confirmed acute appendicitis.

show statistical significance (OR = 1.071 [0.596–1.923]; $P = 0.818$); there was no evidence of heterogeneity ($Q = 1.837$; $P = 0.607$; $I^2 = 0\%$) (Figs. 2–6).

4. Discussion

The diagnosis of AA is often challenging as a result of the variability of clinical and laboratory findings. First level imaging techniques such as ultrasonography (US) also fail to provide sufficient information to prove the diagnosis due to the lack of distinguishing features. Palpation is considered a fundamental step in the physical examination and the decision-making process, and therefore the fear of altering peritoneal signs has led to frequent withholding of early analgesia.[20] When the issue was first raised, it had a reasonable basis in that the morphine dosage could reach 30 mg in adults, altering patient responses and cognitive function. Current dosages are considerably lower and recent studies suggest that the problem no longer exists on scientific grounds.[2] Some papers showed paradoxical results[9,10] in that tenderness could be better appreciated after opiate administration, facilitating diagnosis. According to Mahadevan et al.,[15] pain relief improved patient collaboration and diagnostic accuracy. All other cited RCTs showed that early analgesia did not influence diagnostic accuracy.

Published papers analyzed the variation of clinical signs or surgeon's confidence to commit to a decision. Both these endpoints are subjective and do not provide a real assessment of accuracy. Clinical signs may be differently interpreted among examiners and are dependent on physician's perception. For example Kim et al.[14] showed that after analgesia administration, pediatric emergency physicians noticed a decrease in areas of tenderness whereas surgeons did not. Moreover, even an actual alteration of physical signs does not necessarily imply a variation of treatment strategy or predict a worse outcome. In fact some works revealed that changes on physical examination did occur, but concluded that diagnostic accuracy was not affected.[12,14,15] Surgeon's confidence is not necessarily related to accuracy and delay of surgical intervention does not imply an incorrect treatment strategy unless it affects morbidity.

Histologic proof is the most reliable confirmation of AA. In our article, comparison with final pathologic examination results demonstrated that opiate administration did not impair surgeons' ability to diagnose AA correctly. Treated and untreated groups were also confronted to verify differences in treatment approach: patients receiving morphine underwent appendectomy more frequently. The difference in rates of surgical intervention between the groups was just inferior to statistical significance ($P = 0.079$), suggesting that early analgesia might influence the surgeon's decision, but not to an extent sufficient to affect accuracy and morbidity. In fact neither complication rates, nor false positive AA, nor missed diagnoses reached a statistically significant value.

Recent studies have proposed the introduction of CT scan for the routine diagnosis of AA, diminishing the impact of physical examination on treatment strategy.[21] None of the patients included in

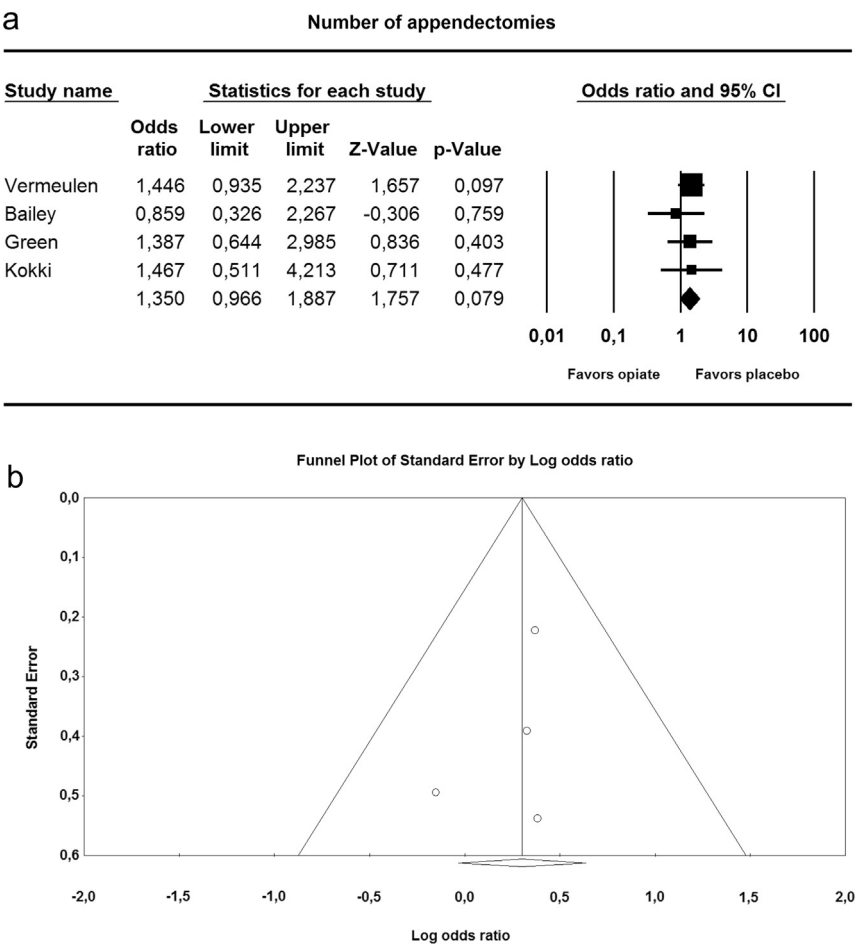

Fig. 3. a: Forest plot of number of appendectomies. b: Funnel plot for publication bias evaluation about number of appendectomies.

our article underwent CT scan. Patients enrolled in the study performed by Vermeulen et al.[8] underwent US, a first level imaging technique that may have influenced the final surgical decision. This should not be considered a bias because US is a well-established examination in routine investigation for suspected AA and our goal was to assess the impact of early opiate administration in customary situations in the ER.

A limitation of our study was the diversity of patient age groups among the RCTs reviewed, since differential diagnoses and relative prognoses vary according to age. To support our findings, further trials on larger sample sizes from different age groups/genders are needed, based on the intention to treat and per-protocol analysis. Focus on pain related to suspected AA represented a limitation as well, but NSAP may portend diverse and potentially life threatening conditions. Therefore, the risk to alter the clinical signs under these circumstances renders unethical the enrollment of patients in clinical trials.

5. Conclusions

According to our data, early analgesia with opiates in suspected AA might influence the approach to treatment, but does not alter diagnostic accuracy or surgical outcome. Further trials are needed to confirm or refute our findings.

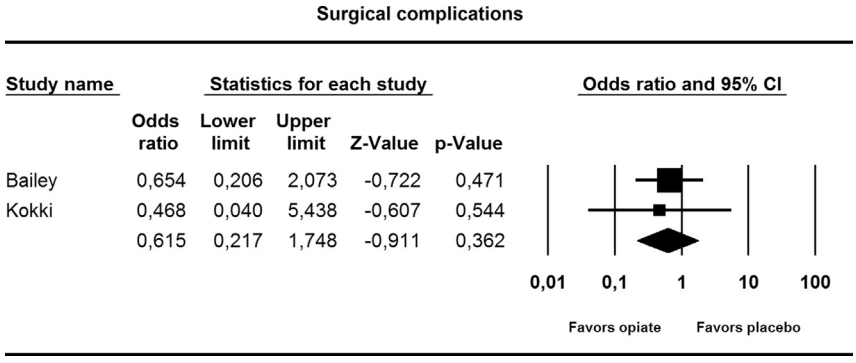

Fig. 4. Forest plot of surgical complications.

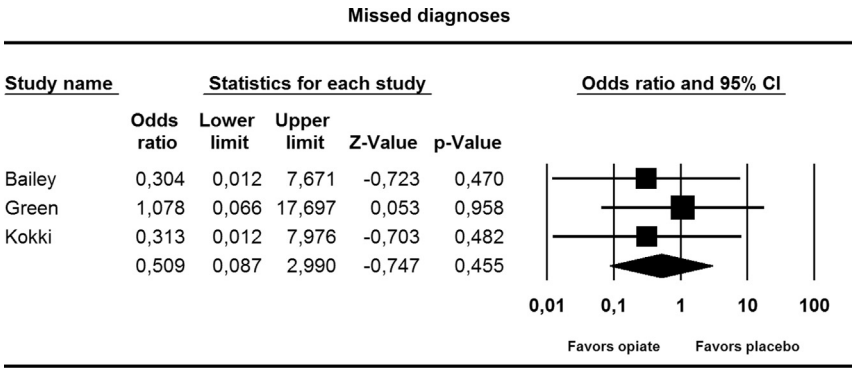

Fig. 5. Forest plot of missed diagnoses.

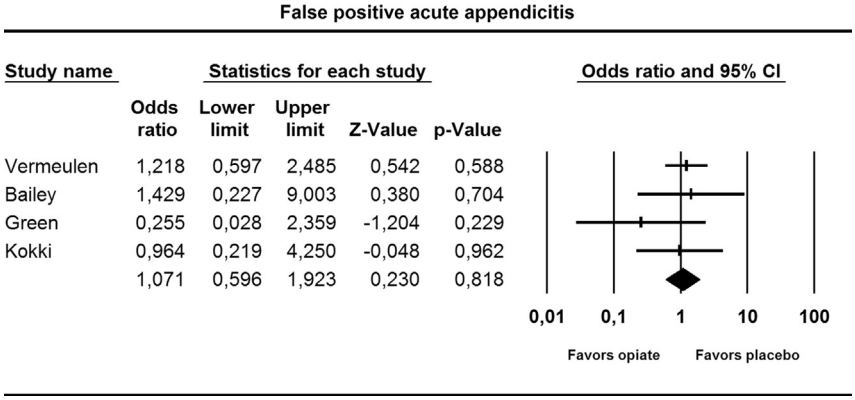

Fig. 6. Forest plot of false positive acute appendicitis.

Table 1
Included studies description.

Author (country)	Year	Age group	Inclusion criteria	Exclusion criteria	Intervention	Outcome measures
Mahadevan (Singapore)	2000	>11	RLQ pain <week's duration (nontraumatic in origin) suggestive of AA.	Not specified.	1 mg/kg^{-1} tramadol vs "normal saline made up to an equal volume" placebo.	Pain score VAS, physical examination findings, performance of each physical finding in the evaluation of AA.
Vermeulen (Switzerland)	1999	>16	RLQ pain.	Previous appendectomy; clinical presentation highly negative predictive for AA (e.g., renal colic or extrauterine pregnancy); renal, hepatic, respiratory insufficiency; psychotropic medication.	0.1 mg/kg^{-1} morphine IV vs 0.9% NaCl IV	Pain score VAS, sensitivity and specificity of US for the diagnosis of AA. Positive and negative predictive value of US.
Bailey (Canada)	2007	8–18	RLQ pain <72 h duration presumed to be appendicitis, pain score ≥5 on VAS.	AA already proven by US or CT, previous analgesia, hemodynamically unstable, sepsis, immunocompromised, history of sickle cell anemia, abdominal surgery, IBD, pancreatic or biliary disease, allergy to morphine, pregnancy.	0.1 mg/kg^{-1} morphine sulfate IV vs "similar looking" placebo	Pain score VAS, physical examination findings, clinical outcome, diagnostic accuracy. Time to final surgical decision.
Green (Canada)	2005	5–16	Abdominal pain <48 h duration thought to be of possible surgical origin.	Allergy to opiates, previous opiate use within the past 4 h, hypotension, or the absence of a parent.	0.05 mg/kg^{-1} morphine sulfate IV vs 0.9% NaCl IV	Pain score CAS, missed appendicitis rate, physician confidence in diagnosis, diagnosis delays, perforation rate.
Kokki (Finland)	2005	4–15	Abdominal pain <7 days' duration, pain scores 5 cm or higher on a 10-cm long VAS.	Abdominal trauma, asthma, hypotension (systolic blood pressure 90 mm Hg), known contraindication to oxycodone, and analgesia use prior to ED arrival.	Buccal 0.1 mg/kg^{-1} of oxycodone hydrochloride vs the same volume of 0.9% sodium chloride.	Maximal pain intensity difference, summed pain intensity difference, presence of abdominal guarding before and after medication, diagnostic accuracy.

Table 2
Patient and outcome data.

	Group	Study name					
		Mahadevan	Vermeulen	Bailey	Green	Kokki	Total
Population	Opiate	33	175	45	52	32	337
	Placebo	33	165	42	56	31	327
Confirmed appendicitis	Opiate	10	83	29	31	12	165
	Placebo	10	72	29	26	9	146
Complications	Opiate			6	15	1	22
	Placebo			8	12	2	22
Appendectomies	Opiate		113	33	32	17	195
	Placebo		92	32	30	14	168
Missed diagnoses	Opiate		0	0	1	0	1
	Placebo		0	1	1	1	3
False positive AA	Opiate		19	3	1	4	27
	Placebo		15	2	4	4	25

Table 3
Methodological quality evaluation data.

	Mahadevan	Vermeulen	Bailey	Green	Kokki
Randomization	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Yes	Yes	Yes	Yes
Blind evaluation	Yes	NS	Yes	Yes	Yes
Statistical methods description	Yes	Yes	Yes	Yes	Yes
Clinical homogeneity	Yes	Yes	Yes	Yes	Yes

NS: not specified.

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Author contribution

Andrea Ciarrocchi conceived the study, collected and analyzed the data, wrote the paper.

Gianfranco Amicucci collected the data and revised the paper.

Conflicts of interest

The authors declare no conflict of interest.

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