Article type : Original Article

Efficacy of post-operative oral metronidazole for haemorrhoidectomy pain: a randomised double-blind, placebo-controlled trial

Short title: Post-haemorrhoidectomy Oral Metronidazole RCT

Dr Bruce D Wilkie MBBS[1,2], Mr Raaj Chandra, MBBS FRACS FCSSANZ[1,2,5], Mr Jonathon Chua, MBBS FRACS[1], Mr David CS Lam, MBBS FRACS[1,3], Dr Elizabeth D Paratz, MBBS (Hons) FRACP[4], Mr Vinna An, MBBS FRACS FCSSANZ[1,5], Mr James O Keck, MBBS FRACS FCSSANZ[1,4]

1. Department of Surgery, Eastern Health, 8 Arnold St Box Hill, Melbourne, Australia
2. Royal Melbourne Hospital, 300 Grattan St, Melbourne, Australia
3. Department of Surgery, Northern Health, 185 Cooper St Epping, Melbourne, Australia
4. St Vincent's Hospital Melbourne, 41 Victoria Parade Fitzroy Melbourne, Australia
5. Monash University, Wellington Rd, Clayton, Victoria, Australia

Corresponding Author: Dr Bruce Wilkie, Eastern Health, 8 Arnold Street, Box Hill, Victoria 3128, Australia. email: brucedwilkie@gmail.com Tel: +61 431 235 672

Conflicts of interest and source of funding: The authors of this report have nothing to disclose. This paper is not based on a communication to a society or meeting. Partial funding was provided by an Eastern Health Foundation Research grant.

Tables and Figures:

Word Count:

Abstract: 229 words

Text: 2529 words

References: 25

Abstract

Aim: To examine the efficacy of oral metronidazole in reducing post-haemorrhoidectomy pain versus placebo.

Method: Forty patients were randomised to either metronidazole and standard care or placebo and standard care (21 metronidazole, 19 placebo) in a double-blinded, randomised controlled trial. The main outcome measure was post-haemorrhoidectomy pain scores over twenty-one days, measured on a ten-point Likert scale.

Results: There were no significant differences between groups with regards to age, gender, smoking status, self-reported general health or quality of life, haemorrhoid-related pain, haemorrhoid-related impact on quality of life, reported satisfaction with surgery, experience of surgery, median overall pain score, or likelihood of recommending surgery to others.

For reported median worst pain scores and defaecation-related pain, a trend to significance was identified between groups on days 16 and 18-21 with the metronidazole group reporting less pain. However, these differences were not significant when pre-specified Bonferroni correction criteria were used. Using multilevel mixed effects modelling, the impact of time on median worst pain score was identified to be highly significant ($p<0.0001$) whereas treatment allocation (placebo versus metronidazole) did not significantly affect the improvement in patients' reported pain ($p=0.8837$).

Conclusion: Our data do not support the hypothesis that post-operative metronidazole has a clinically meaningful effect on post-haemorrhoidectomy pain. This study adds to the previous literature, and implies that it should not be routinely used as an analgesic adjunct.

Keywords: Haemorrhoidectomy, pain, metronidazole

What does this paper add to the literature?

This is a well-designed clinical trial and analysis that provides additional countervailing evidence to the previous clinical trials that have influenced current practice. In the era of antibiotic stewardship, it is critical that widespread antibiotic use be carefully examined and supported by high quality evidence.

Introduction

Symptomatic haemorrhoids are common, with an estimated prevalence of up to 4.4% in the adult population in the United States.[1] A European prevalence study of 976 patients undergoing colorectal cancer screening found 38.9% (380) had haemorrhoids of some degree, with 44.7% (170) of those with haemorrhoids reporting symptoms.[2] Post-operative pain is an expected consequence of haemorrhoid surgery, and its optimal evidence-based reduction has been the subject of multiple studies. Several randomised-controlled trials (RCTs) have specifically examined metronidazole as an analgesic adjunct, but with heterogeneous results.[3,4,5,6,7] Subsequent meta-analyses have thus provided equivocal conclusions.[8,9,10] The two largest worldwide multicentre trials on haemorrhoid surgery, HubBLE and eTHoS, did not establish a clear benefit from novel surgical approaches (haemorrhoidal artery ligation and stapled haemorrhoidectomy respectively) in terms of either pain, cost, recurrence or complication rates.[11,12]

Post-haemorrhoidectomy pain is likely multifactorial, encompassing the direct surgical insult to the highly sensate anorectal mucosa below the dentate line, anal sphincter spasm, post-operative inflammation, surgical technique and individual experience of pain. Evidence-based analgesic guidelines recommend a multimodal pre-, intra- and post-operative protocolised regimen.**Error! Bookmark not defined.** Pain typically peaks at days 3-5 postoperatively, with average return to work or resumption of normal activities occurring at approximately 2 weeks.[13] .[14]

The hypothesis of how oral metronidazole contributes to reducing post-operative pain is unclear. Two mechanisms have been proposed; direct anti-inflammatory action versus the

secondary effect of decreasing bacterial colonisation of anal wounds and micro-abscess formation.[10,15] Despite an unclear hypothesis of efficacy and limited high-quality data, post-operative metronidazole is routinely administered to Australian patients after haemorrhoidectomy.

The aim of this trial therefore is to provide further clinical data and re-examine metronidazole's efficacy as an analgesic adjunct in an era of heightened antibiotic stewardship.

Methods

This study was an investigator-led and departmentally-funded double-blind randomised controlled trial approved by the Eastern Health Research and Ethics Committee (Approval number E02/2014). The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000735156). Recruitment occurred from April 2015 to February 2018, and was ceased when a pre-specified number of patients had been recruited.

Patients were allocated to either intervention or placebo in a 1:1 manner. Cochrane database risk of bias criteria were consulted and adhered to.[16]

The null hypothesis was that oral metronidazole is not superior to placebo as an analgesic adjunct following haemorrhoidectomy. Primary outcome was worst pain experienced (measured daily) on a validated 10-point numerical rating pain scale from days 0-21 post-operatively [17]. Secondary outcomes included expected pain, and defaecation-related pain, reported side effects of metronidazole, post-operative complications and overall satisfaction with the surgery.

Sample size calculations incorporated an alpha level of 0.05 and power of 0.8 with an anticipated one-point difference in median pain scores and a standard deviation of 1.5 points – this indicated that a minimum of thirty-five patients in each arm would be required. An anticipated drop-out rate of up to twenty percent was then incorporated, resulting in a final intended sample size of forty-four patients in each group.[18] Previous trials calculated that only seventeen patients were required in each group when anticipating a twenty-percent difference between groups at an equivalent alpha and power level; however their studies did not support such a marked difference.

Prospective patients were screened for eligibility, counselled and invited to participate in the trial during a public hospital outpatient consultation with a colorectal registrar, fellow or consultant surgeon where the decision was made to proceed to haemorrhoidectomy. Patient information and consent was provided and patients were placed on an elective surgery waitlist.

On the day of surgery, patients who agreed to participate in the trial completed a screening questionnaire that confirmed they did not exhibit any exclusion criteria (age >70, severe aspirin-sensitive asthma, renal impairment (eGFR <50), congestive cardiac failure, history of recent acute coronary syndrome or unstable ischaemic heart disease, significant peptic ulcer disease, major depression or pregnancy) and provide information on general health, smoking status, alcohol use, and a subjective assessment of the pain and the impact of their haemorrhoids on their overall quality of life.

Under general anaesthetic, either Milligan-Morgan (open) or Ferguson (closed) haemorrhoidectomy using standard diathermy was performed at the discretion of the operating subspecialist colorectal surgeon. Patients were given a single dose of 500mg intravenous (IV) metronidazole as surgical prophylaxis, 1000mg IV paracetamol, intravenous non-steroidal anti-inflammatory (40mg IV parecoxib or 200mg IV celecoxib), and a pudendal nerve block with a long-acting local anaesthetic (either 0.5% bupivacaine with adrenaline or 0.75% ropivacaine).

At day one post-operatively, patients were randomised using a computer-generated random number sequence by the clinical trials pharmacist to receive either placebo (one tablet three times daily for seven days) or metronidazole (400mg three times daily for seven days) in addition to a script for 1000mg oral paracetamol four times daily, 50mg diclofenac three times daily, 5mg oxycodone as required, one 13.8g macrogol 3550 sachet daily. Both the metronidazole and placebo were manufactured by a single compounding pharmacist and blinded to patient, pharmacist and treating clinicians.

Patients were discharged with their take-home questionnaire at day 0 (day 1 post-operatively), with a standardised 10-point numerical rating pain (Likert) scales to be completed each day until the patient resumed full normal activities. Patients were asked to rate their “Expected Pain”, “Most pain experienced” and “Pain on defecation” on three separate scales.

Interim analysis at one year demonstrated a poor response rate with 13 of 42 patients recruited returning questionnaires (30%). The trial protocol was subsequently amended to exclude GTN ointment and docusate with senna from the analgesic regimen (due to cost, compliance and as a potential confounder), the questionnaire simplified (we had initially endeavoured to track opioid analgesia use and the occurrence of medication side-effects) and follow-up period shortened. Patients were initially followed up as routine at four to six weeks post-operatively, however this was amended to three to four weeks. Patients who had not returned a questionnaire or attended three subsequent follow-up appointments were contacted via mail. At follow-up, patients provided an overall subjective assessment of their pain, analgesia, and expectations related to the surgery. The response rate from the subsequent amended protocol cohort was 28 of 46 patients recruited (60%)

Continuous and ordinal variables were compared using a Mann-Whitney test, with reporting of median values and interquartile ranges. Categorical variables were compared using Fisher's exact test, with presentation of percentage values. To assess significance of change over the time-course of the trial of pain and defaecation pain scores, we employed multilevel mixed effects modelling utilising the "*xtmixed*" command in STATA. This permits assessment of the significance of changes in patients' individual pain scores as a function of time interacting with treatment allocation (placebo versus metronidazole).

The threshold for significance was set at $p< 0.05$ for the primary outcome of overall change in pain score using multi-level mixed effects modelling. For the comparison of daily pain scores over 21 days, a Bonferroni correction of $p<0.05/21$ was applied, setting a threshold of $p<0.002$ for significance. All statistical analysis was performed with STATA 2015 (STATACorp 2015, Texas USA).

Results

Of 88 patients enrolled in the study, forty patients (19 placebo patients, 21 metronidazole patients) completed the trial and returned a response (45.5%) (Figure 1). There were no significant differences between groups with regards to age, gender, smoking status, self-reported general health or quality of life, haemorrhoid-related pain, haemorrhoid-related impact on quality of life. There were no significant differences with grade of haemorrhoids, surgery received (Milligan-Morgan or Ferguson technique), suture ligation of pedicles, treating surgeon, rate of surgical complications or length of stay. Nor was there any

observable difference with the overall experience of surgery, median overall pain score, overall impression of pain control, or likelihood of recommending surgery to other patients (Table 1). No adverse effects related to metronidazole were reported to investigators.

When daily pain scores were compared over the post-operative 21 days, there was no difference in regards to anticipated pain scores (Table 2). With regards to reported median worst pain scores (Figure 2) and defaecation-related pain scores (Figure 3), there was a trend to reduced pain in the metronidazole group, although none of the daily differences in pain scores reached significance at the pre-specified Bonferroni-corrected level.

Multilevel mixed effects modelling was utilised to interrogate whether the trend for reduced pain and defaecation scores in the metronidazole group were significant when the interaction of time with treatment allocation was accounted for. The impact of time on median worst pain score was identified to be highly significant ($p<0.0001$) however treatment allocation (placebo versus metronidazole) did not significantly affect the improvement in patients' reported pain ($p=0.8837$). The impact of time on defaecation-related pain was again highly significant ($p<0.0001$) however treatment allocation (placebo versus metronidazole) did not significantly affect patients' reported defaecation pain ($p=0.9105$).

In regards to the GTN ointment allocation and subsequent amended trial protocol, 13 of 41 patients received GTN; 6 in the placebo group and 7 in the metronidazole group. There was no significant difference in allocation ratio when compared to the non-GTN group which had 14 patients in each arm ($p=0.906$). There was no significant difference in median overall 'average pain' scores between the GTN group (8, interquartile range [5-8]) and the non-GTN group (5 interquartile range [4-7.5]) ($p=0.2354$) or the likelihood of recommending surgery to others; GTN group (70%) and non-GTN group (75%) ($p=0.763$).

Discussion

Historical accounts describe post-haemorrhoidectomy pain that 'varies from discomfort to severe distress' and proposed various remedies from 'liberal doses' of morphine to more directed therapies such as cinchocaine-soaked gelatin dressings.[19] The modern approach includes a range of multimodal analgesics and analgesic adjuncts.

A systematic review of procedure-specific pain management found paracetamol alone to be ineffective and recommended as part of a multimodal approach; intraoperative perianal & pudendal/ischiorectal long-acting local-anaesthetic infiltration, NSAIDS/selective COX-2 inhibitors including intraoperative parenteral NSAIDS to cover the immediate post-operative

period, opiates for breakthrough pain, topical GTN, and laxatives with oral metronidazole 'ideally' commenced prior to surgery.**Error! Bookmark not defined.** A survey of colorectal surgeons in Australia demonstrated that 50% of respondents use metronidazole as an analgesic adjunct either 'often' or 'routinely' after any anorectal surgery (not specific to haemorrhoids).[20]

A perhaps underappreciated issue with post-operative analgesia, particularly in the day-case or overnight-stay setting, is the relative complexity of the analgesic regimen and patient compliance. Our trial protocol was amended early to exclude GTN and additional laxatives in order to simplify the regimen, improve compliance and reduce potential confounders. The groups (GTN and non-GTN) were evenly matched and in addition to earlier follow-up, this improved the response rate from 30% to 60% at the completion of the trial without a significant impact on average pain scores or likelihood of recommending surgery to others. While topical GTN ointments may alter wound healing and reduce post-operative pain,[21, 22] it remains an adjunct to an adequate standardised regimen of multimodal analgesia. Patients were counselled prior to their enrolment regarding perioperative pain and the need to strictly adhere to the prescribed regimen.

The mechanism by which metronidazole may reduce post-operative pain has not been fully elucidated. There is some limited evidence that metronidazole has an antioxidant effect and anti-inflammatory properties in certain clinical settings i.e. NSAID-induced enteropathy,[23] or in active Crohn's disease.[24] Metronidazole may reduce neutrophil-released reactive oxygen species, and exhibit direct antibacterial properties, reducing colonisation or the formation of 'micro-abscesses in anal wounds. However, increasing awareness of the importance of antibiotic stewardship means that antibiotic therapy should not be used as an analgesic adjunct unless it demonstrates compelling and irreplaceable clinical benefits. Metronidazole is the cornerstone of treatment of anaerobic bacterial infections worldwide, and over-use will contribute to resistance in pathologically significant bacteria.[25]

Two major double-blinded randomised controlled trials of oral metronidazole as an analgesic adjunct following haemorrhoidectomy have been published thus far. Carapeti et al (n=40) found that a 7-day course of oral metronidazole resulted in a reduction in pain at days 5-7 post-open haemorrhoidectomy, earlier return to work (15 vs 18 days) and higher overall satisfaction.[3] Balfour et al (n=35) found no statistically significant difference in pain, return to work or overall satisfaction after closed haemorrhoidectomy.[4] Our study used similar methodology modified for local prescribing and operative practice and increased the length of follow-up. Both trials included similar numbers of patients to our study.

Of remaining RCTs examining oral metronidazole, the study by Solorio-Lopez et al (n=44) was placebo-controlled but not double-blinded and found patients undergoing closed haemorrhoidectomy under spinal anaesthetic consistently reported lower mean pain scores in the metronidazole group. The study by Ng et al (n=52) which did not determine an analgesic benefit from metronidazole was not placebo controlled and had short-term follow-up (2 days). A Saudi Arabian trial that found a benefit from metronidazole days 0-7 was neither blinded nor placebo-controlled and included a number of methodological issues that resulted in a high risk of bias.[7]

The marked heterogeneity between these studies makes comparison difficult. As a result, three recently published meta-analyses have arrived at differing conclusions. Wanis et al identified improvements in pain severity on postoperative days 1 and 4 and earlier return to work, but after sensitivity analysis excluding the trial with the largest risk of bias, found no benefit. Xia et al included both oral and topical metronidazole in their meta-analysis of 9 RCTs, finding benefit between days 1-14. Lyons et al also found that metronidazole reduced pain on post-operative days 1, 2, and 7 and on first defecation using similar methodology and inclusion criteria to Xia[8].

The relative strengths of our study include the study design and the comparability to earlier studies by Carapeti and Balfour. The double-blinding and placebo control reduce the risk of bias and this is supported in evenly matched study and control groups. The extended period of follow-up between days 1 and 21 also captured a period beyond the previous benchmark of 14 days. Multilevel mixed effects modelling conducted in the analysis of our results accounts for time with the relatively large number of data points. When assessing the strength of our randomized controlled trial and its conduct according to the Cochrane Risk of Bias Criteria, it would appear that our results have a low risk of bias.[16]

The major limitation in our study was patient loss to follow-up (54.5%). This trial design enrolled a young population undergoing minor surgery with a prolonged outpatient follow-up; all features creating vulnerability to loss to follow-up. However, drop-out rates were balanced between allocation groups, reducing the risk of bias. It is important to note that the complete published literature of oral metronidazole in post-haemorrhoidectomy pain currently consists of only 335 patients according to the meta-analysis performed by Wanis et al.[9] In this context, our RCT still contributes substantial patient data for inclusion in future meta-analyses.

Conclusion

Oral metronidazole compared to placebo therapy resulted in a non-significant trend to improved pain and defaecation-related pain scores post-haemorrhoidectomy. The major determinant of improving pain scores post-haemorrhoidectomy was time elapsed since surgery. Despite common practice and the favourable safety profile of metronidazole, our data does not support the routine use of post-operative metronidazole as an analgesic adjunct, especially in an era of increased antibiotic stewardship.

Acknowledgements

The authors would like to acknowledge the assistance of Dr Chris Steen and Dr Anshini Jain, and Senior Clinical Trials Pharmacist, Ms Paula Lee, in conducting this study.

Table 1. Baseline characteristics of patients

	Placebo	Metronidazole	Significance
Number	19	21	
Male (%)	12 (63.2%)	13 (62.0%)	P = 1.00
Median Age (years)	44 [32-58]	45 [34-60]	P = 0.822
Smoker	3 (15.7%)	3 (14.3%)	P = 1.00
Cigarettes per day if smoker	10 [10-10]	10 [10-10]	P = 1.00
General health	7 average 7 good 2 excellent	6 average 8 good 2 excellent	P = 1.00
General quality of life	1 not good 3 average 9 good 3 excellent	0 not good 0 average 13 good 3 excellent	P = 0.239
Haemorrhoid-related pain	5 not too much 3 a fair bit 5 a little 3 a lot 0 unbearable	2 not too much 8 a fair bit 3 a little 2 a lot 1 unbearable	P = 0.264
Haemorrhoid-related impact on quality of life	2 not too much 6 a little 5 a fair bit	1 not too much 2 a little 8 a fair bit	P = 0.341

	3 a lot	5 a lot	
Number of haemorrhoids	2 [2-3]	2 [2-3]	P=0.1741
Haemorrhoid grade	3 [3-4]	3 [3-4]	P = 0.5042
Milligan-Morgan or Ferguson operation	5 Ferguson 14 Milligan-Morgan	2 Ferguson 18 Milligan-Morgan	P = 0.235
Pedicles suture ligated	9 (47.4%)	10 (47.6%)	P = 0.65
Operative complications	1 (5.3%)	1 (4.8%)	P = 1.00
Surgeon	Surgeon 1: 1 Surgeon 2: 5 Surgeon 3: 1 Surgeon 4: 1 Surgeon 5: 0 Surgeon 6: 1 Surgeon 7: 10 Surgeon 8: 0	Surgeon 1: 1 Surgeon 2: 1 Surgeon 3: 2 Surgeon 4: 1 Surgeon 5: 1 Surgeon 6: 0 Surgeon 7: 13 Surgeon 8: 1	P=0.528
Length of stay (days)	1 [1-1]	1 [1-1]	P = 1.00
Satisfaction with surgery	1 slightly dissatisfied 4 not sure 0 slightly satisfied 9 satisfied 1 very satisfied	0 slightly dissatisfied 1 not sure 1 slightly satisfied 9 satisfied 8 very satisfied	P= 0.030
Experience of surgery	7 worse than expected 4 about what expected 4 better than expected	3 worse than expected 7 about what expected 9 better than expected	P = 0.193
Median overall 'average pain' score	6.5 [5-9]	5 [4-8]	P = 0.1558
Was pain adequately controlled	13 (86.7%) yes	15 (78.9%) yes	P = 0.672
Would recommend surgery to others	9 (60.0%) yes	16 (84.2%) yes	P = 0.139
Numbers are presented as n (%) for categorical values, and median [interquartile range] for continuous or ordinal values.			

Table 2. Median pain scores

	Anticipated pain			Reported actual worst pain			Defaecation pain		
	Metronidazole	Placebo	Significance	Metronidazole	Placebo	Significance	Metronidazole	Placebo	Significance
Day 0	7 [4-9]	7.5 [5-9]	P = 0.3505	6 [1.5-7]	5 [3-6]	P = 0.6898	5 [4-7]	3 [1-5.5]	P = 0.3369
Day 1	7 [5-7]	6 [5-9]	P = 0.4512	3 [2-5]	3 [3-7]	P = 0.3196	5 [4-8]	7 [5.5-8.5]	P = 0.3252

Day 2	5 [4-7]	7 [3-9]	P = 0.9755	4 [2-8]	5.5 [4-8]	P = 0.2383	7 [3-9]	7 [3-9]	P = 1.00
Day 3	6 [4-7.5]	6 [4-7]	P = 0.7223	5 [2-9]	6.5 [5-8]	P = 0.2938	8 [4-9]	8 [6-8]	P = 0.9854
Day 4	5 [3-8]	5 [3-7]	P = 0.6346	5 [4-9]	5.5 [3-7]	P = 0.6810	8 [5-9]	7 [6-8]	P = 0.6257
Day 5	6 [3-7]	5 [3-7]	P = 0.8771	6 [3-8]	5.5 [4.5-7]	P = 0.9877	7 [5-8]	6 [5-9]	P = 0.5604
Day 6	5 [3-7]	5.5 [3-7]	P = 0.9876	4 [2.5-8]	5 [3.5-7]	P = 0.4232	6 [3-9]	6 [4.5-8]	P = 0.6288
Day 7	5 [3-6]	4.5 [2-6]	P = 0.5816	4 [2-7]	6 [3.5-7]	P = 0.2934	6 [4-9]	6 [5-7]	P = 0.9442
Day 8	4.5 [2-6.5]	5 [3-7]	P = 0.6841	4.5 [2-6]	5 [3-8]	P = 0.1906	6 [3-7]	7 [5-9]	P = 0.1860
Day 9	5 [2-6]	4 [3-7]	P = 0.3286	5 [2-6]	6.5 [3-7]	P = 0.1578	5 [3-8]	5.5 [4-8]	P = 0.5289
Day 10	4 [2-5.5]	4 [3-7]	P = 0.9174	3 [1-5]	4 [3-7]	P = 0.2289	5 [3-8]	5 [3-7.5]	P = 0.8061
Day 11	4 [2-5]	3.5 [2-5]	P = 0.6677	2.5 [1-5]	4 [2-5]	P = 0.2885	3 [1-5]	4 [3-6]	P = 0.3255
Day 12	3 [1-5]	3 [2-5]	P = 0.8581	2 [1-4]	4.5 [1.5-5]	P = 0.2021	3.5 [2-5]	5 [4-7]	P = 0.1163
Day 13	4 [1-5]	3.5 [2-4]	P = 0.7782	3 [1-4]	4 [2-5]	P = 0.2008	3 [2-4]	3.5 [3-7]	P = 0.3323
Day 14	3 [1-4]	3 [2-4]	P = 0.2124	2 [1-4]	4 [3-6]	P = 0.1524	3 [2-4]	4 [4-6]	P = 0.0737
Day 15	2 [1-4]	3 [2-5]	P = 0.1142	2 [1-4]	4 [3-7]	P = 0.0644	3 [2-6]	5 [3-7]	P = 0.0855
Day 16	2 [1-4]	3 [2-5]	P = 0.2020	1 [1-3]	4 [3-6]	P = 0.0089	2 [1-3]	4 [3-6]	P = 0.0098
Day 17	2 [1-3]	2 [2-5]	P = 0.1333	2 [1-3]	3 [2-5]	P = 0.0742	2 [1-3]	2.5 [2-5]	P = 0.1837
Day 18	2 [1-3]	2 [2-5]	P = 0.0849	1 [1-3]	4 [2-6]	P = 0.0102	2 [1-3]	4 [2-6]	P = 0.0410
Day 19	1 [1-3]	2.5 [2-4]	P = 0.1559	1 [1-3]	3.5 [2-5]	P = 0.0035	1.5 [1-2]	3 [2-4]	P = 0.0044
Day 20	1 [1-3]	2 [1-3]	P = 0.2785	1 [1-2]	3.5 [2-6]	P = 0.0159	2 [1-3]	3 [2-6]	P = 0.1049
Day 21	1 [1-3]	2 [1-3]	P = 0.2785	1 [1-2]	3 [2-5]	P = 0.0253	1.5 [1-2]	2.5 [2-4]	P = 0.0733
Significance threshold was set at $p<0.002$ (Bonferroni correction for 21 days of assessment)									

References

[1] Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation: an epidemiologic study. *Gastroenterology* 1990; 98: 380-6.
[2] Riss S, Weiser FA, Schwameis K et al. The prevalence of haemorrhoids in adults. *Int. J. Colorectal Dis*. 2012; 27: 215-20.
[3] Carapeti EA, Kamm MA, McDonald PJ, Phillips RKS. Double-blind randomised controlled trial of effect of metronidazole on pain after day case haemorrhoidectomy. *Lancet* 1998; 351: 169-72.
[4] Balfour L, Stojkovic SG, Botterill ID, Burke DA, Finan PJ, Sagar PM. A randomized, double-blind trial of the effect of metronidazole on pain after closed hemorrhoidectomy. *Dis. Colon Rectum* 2002; 45: 1186-91.
[5] Ng SSM, Lee JFY, Cheung KY, Leung KL, Yiu RYC, Lau WY. Preemptive analgesia and metronidazole on post-haemorrhoidectomy pain control. *Surg. Pract.* 2006; 10: 102-5.
[6] Solorio-López S, Palomares-Chacón UR, Guerrero-Tarín JE, *et al*. Efficacy of metronidazole versus placebo in pain control after hemorrhoidectomy: results of a controlled clinical trial. *Rev. Esp. Enferm. Dig.* 2015; 107: 681-5.
[7] Al-Mulhim AS, Ali AM, Al-Masuod N, Alwahidi A. Post hemorrhoidectomy pain: a randomized controlled trial. *Saudi Med. J*. 2006; 27:1538-41.
[8] Lyons N, Cornille JB, Pathak S, Charters P, Daniels IR, Smart NJ. Systematic review and meta-analysis of the role of metronidazole in posthaemorrhoidectomy pain relief. *Colorectal Dis*. 2017; 19: 803-11.
[9] Wanis K, Emmerton-Coughlin H, Coughlin S, Foley N, Vinden C. Systemic metronidazole may not reduce posthemorrhoidectomy pain: A meta-analysis of randomized controlled trials, *Dis*. *Colon Rectum* 2017; 60: 446-455.
[10] Xia W, Manning J, Barazanchi A, Su'a B, Hill A. Metronidazole following excisional haemorrhoidectomy: a systematic review and meta-analysis, *ANZ J. Surg.* 2018; 88:408-414
[11] Brown S, Tiernan J, Biggs K, et al. The HubBLe Trial: haemorrhoidal artery ligation (HAL) versus rubber band ligation (RBL) for symptomatic second- and third-degree haemorrhoids: a multicentre randomised controlled trial and health-economic evaluation. *Health Technol Assess.* 2016 Nov;20(88):1-150.
[12] Watson A, Hudson J, Wood J, et al. Comparison of stapled haemorrhoidopexy with traditional excisional surgery for haemorrhoidal disease (eTHoS): a pragmatic, multicentre, randomised controlled trial, *Lancet* 2016; 388: 2375–85.
[13] Hollingshead JRF, Phillips RKS. Haemorrhoids: modern diagnosis and treatment. *Posgtrad. Med. J.* 2016; 92: 4-8.
[14] Puigdollers A, Cisternas D, Azpiroz F. Postoperative pain after haemorrhoidectomy: role of impaired evacuation. *Colorectal Disease* 2011; 13: 926-929.
[15] Miyachi Y. Potential antioxidant mechanism of action for metronidazole: implications for rosacea management. *Adv. Ther.* 2001; 18: 237-43.
[16] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*; in press. Available online at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0
[17] Cardno N, Kapur D. Measuring pain. *Br. J. Anaesth.* 2002; 2(1); 7-10.
[18] Sakpa T, Sample Size Estimation in Clinical Trial, *Perspect Clin Res* 2010; 1(2): 67-69.
[19] Lee M, Pain after haemorrhoidectomy: use of prolonged wound anaesthesia. *Lancet* 1954; 266(6801): 22-3
[20] Lam D, Keck J. Pain Management in Anorectal Surgery: CSSANZ Survey, *ANZJS* May 2015 85:S1 p.28 https://doi-org.ezproxy.surgeons.org/10.1111/ans.13081
[21] Tan KY, Sng KK, Tay KH, Lai JH, Eu KW. Randomized clinical trial of 0·2 per cent glyceryl trinitrate ointment for wound healing and pain reduction after open diathermy haemorrhoidectomy, *Br. J. Surg.* 2006; 93: 1464-1468
[22] Karanlik H, Akturk R, Camlica H, Asoglu O. The Effect of Glyceryl Trinitrate Ointment on Posthemorrhoidectomy Pain and Wound Healing: Results of a Randomized, Double-Blind, Placebo-Controlled Study, *Dis. Colon Rectum* 2009; 52 (2): 281-285
[23] Bjarnason I, Hayllar J, Smethurst P, Price A, Gumpel MJ. Metronidazole reduces intestinal inflammation and blood loss in non-steroidal anti-inflammatory drug induced enteropathy. *Gut* 1992; 33(9): 1204-8.

[24] Freeman CD, Klutman NE, Lamp KC. Metronidazole: a therapeutic review and update. *Drugs* 1997; 54: 679-708.
[25] Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections." *Clin. Infect. Dis.* 2010; 50 (Suppl 1): S16-S23.

Figure 1

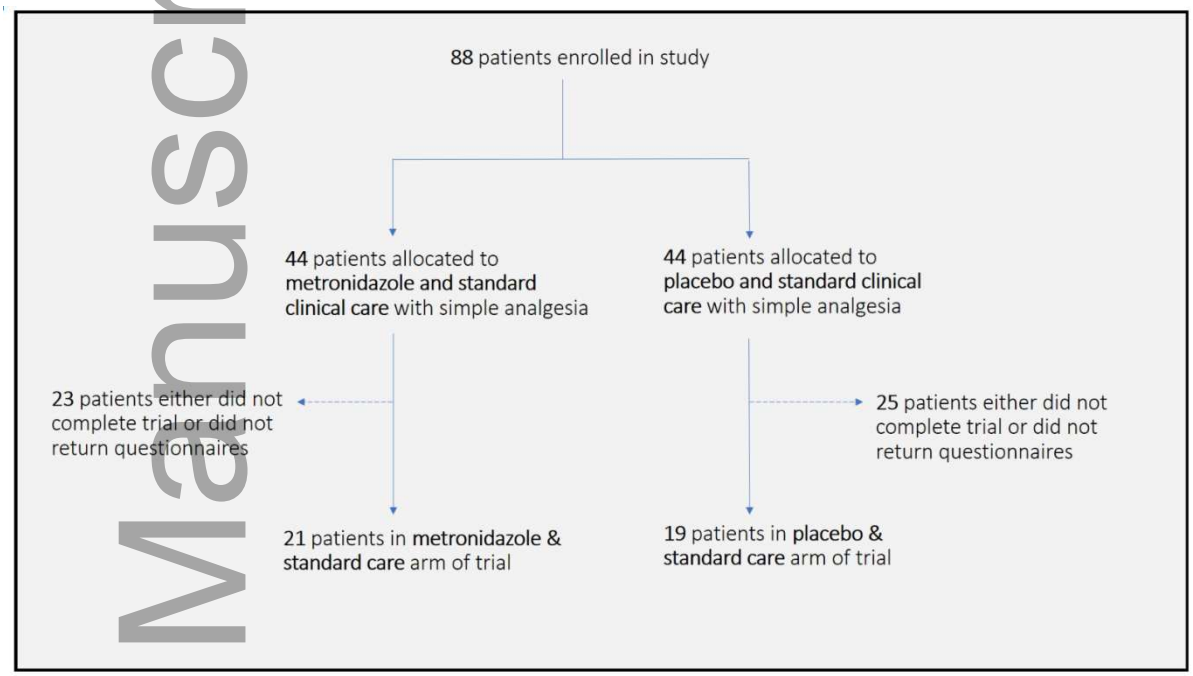


Figure 2

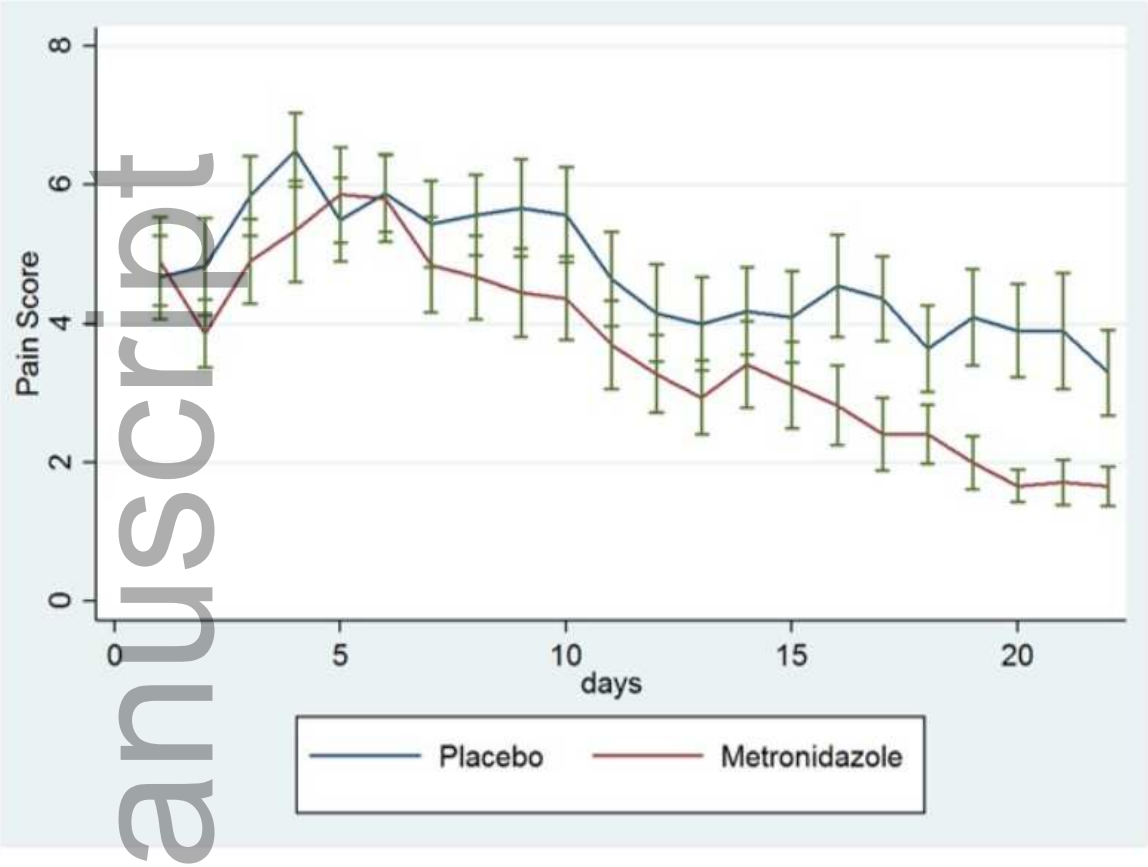
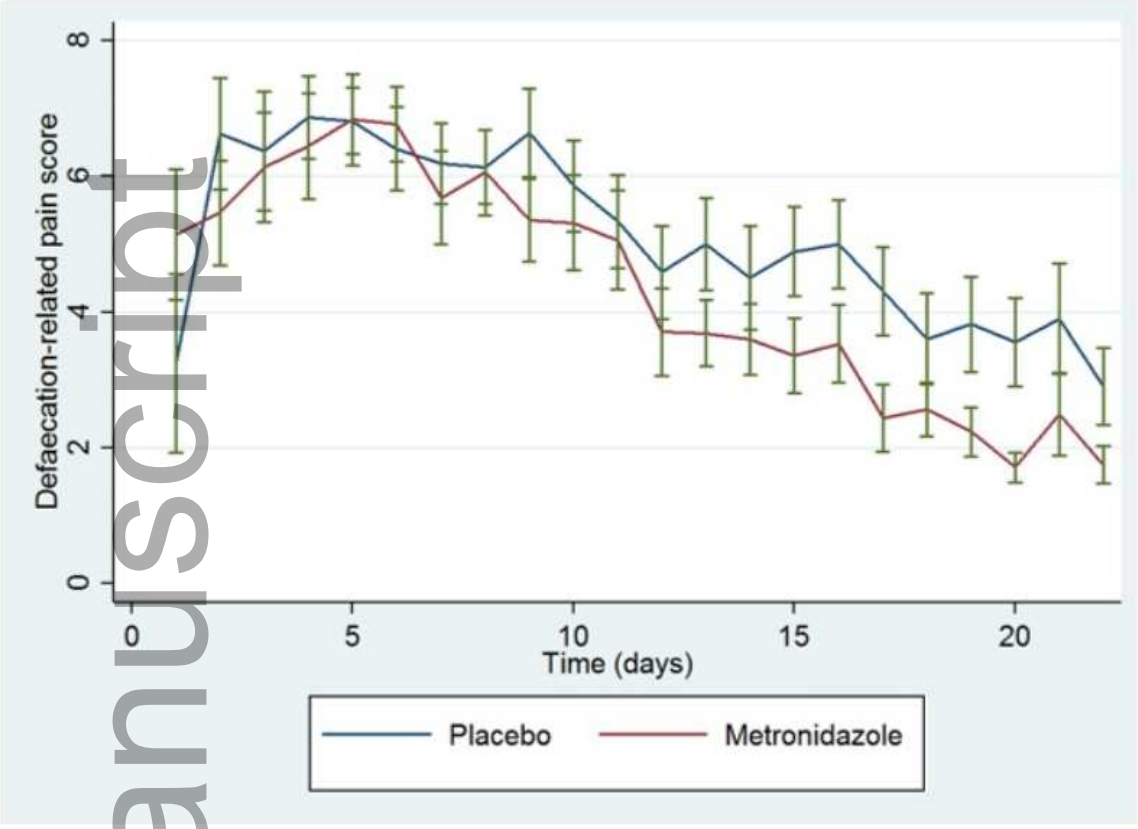
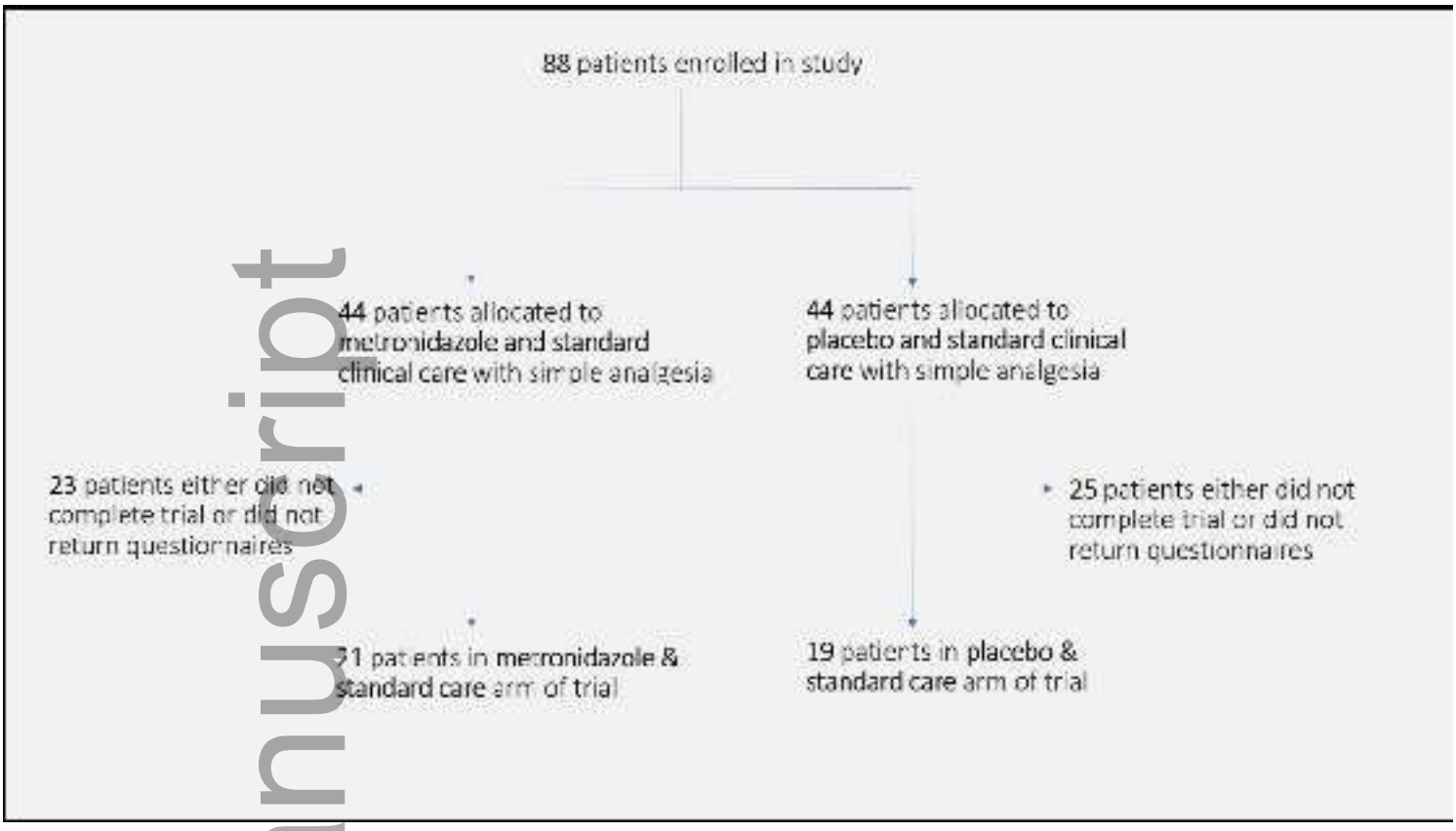
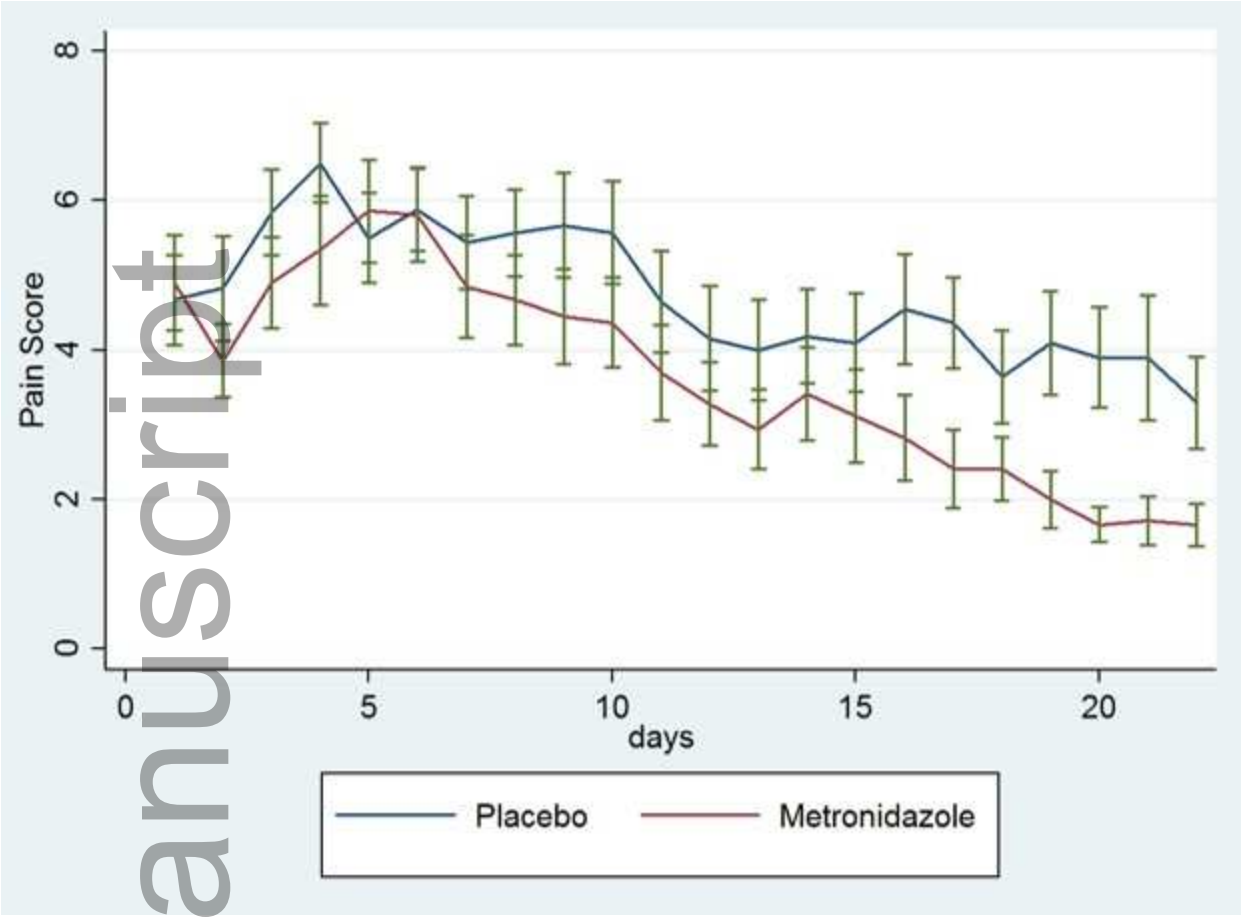


Figure 3

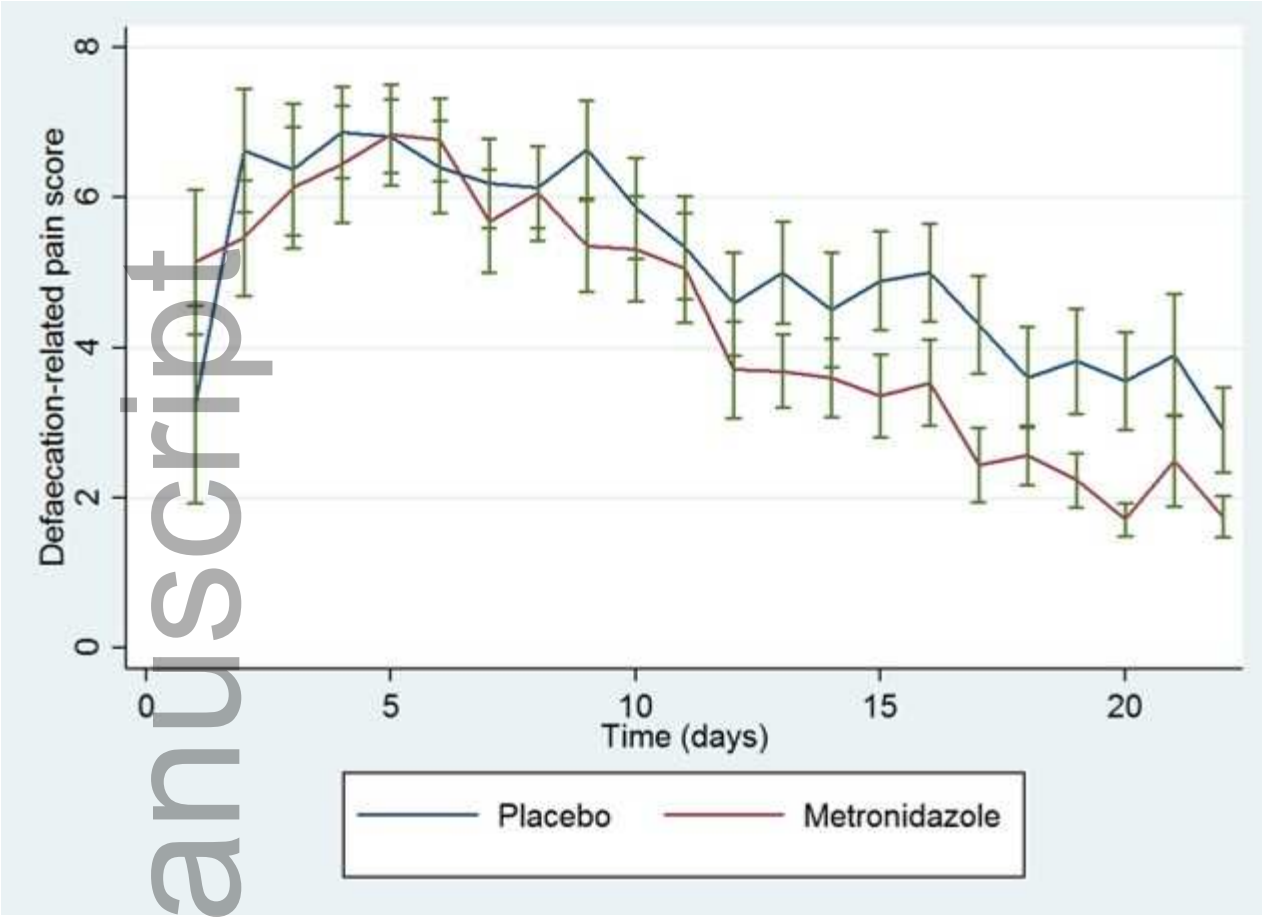




codi_15291_f1.jpg



codi_15291_f2.jpg



codi_15291_f3.jpg