# Comparison of efficacy of icchabhedirasa with bisacodyl in addressing Opioid induced Constipation (OIC)

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## Introduction

Morphine is the prototype opioid medication that has become the cornerstone for effective, safe, and economical management of persistent severe pain, especially in cancer patients. Opioid-induced Constipation (OIC)is defined as "a change in bowel habits within seven days of initiating opioid therapy that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, sense of incomplete rectal evacuation, or harder stool consistency"[1,2]. It is the most frequent and persistent side effect seen in patients receiving opioid analgesics. Oral formulation of morphine sulphate is the most commonly used opioid. OIC has a reported prevalence of 81 per cent, depending on the tool used for evaluation[3].

In a survey among cancer patients on morphine as analgesic, 61.7 per cent reported a degree of constipation that they considered problematic[4].There is a marked inter-patient variation in the degree of distress and the duration of OIC [5]. OIC can be difficult to treat and can escalate to obstipation, spurious diarrhea, or narcotic bowel syndrome (paradoxical increase in abdominal pain associated with increasing doses of opioids). Failure to address OIC can impact compliance to the prescribed opioid, the analgesia achieved, and can directly reduce quality of life (QoL) of patients.

Bisacodyl is the most common stimulant laxative used to prevent and treat OIC. The common side effects of this drug, especially in doses more than 10mg are diarrhea, abdominal cramps, anorexia, and nausea/vomiting. Radiographic changes of colonic redundancy and dilation of colon, with loss of haustral markings have been noted with chronic use of stimulant laxatives i.e. > 3 times per week for > 1 year6.

Ayurveda, the indigenous system of medicine, has a holistic approach to health and illness[7]. Optimisation of digestive health is a core principle of ayurvedic approach[8]. Icchabhedirasa, is an established herbo-mineral Ayurvedic formulation that is commonly used for modifying digestive functions[9]. Table 1 lists the ingredients of both Bisacodyl and Icchabhedirasa.

## Aim

This study aims to compare the efficacy of Icchabhedirasa, an Ayurvedic formulation with that of Bisacodyl, a stimulant laxative used in Modern medicine in addressing the OIC among cancer patients using morphine as the analgesic.

### Primary objective:

1. To study the efficacy of Icchabhedirasa, in preventing and treating OIC among cancer patients in palliative care setting, using oral morphine sulphate, and compare it with the standard stimulant laxative, bisacodyl.

### Secondary objectives:

1. To compare the incidence of OIC in the study population
2. To record the average effective dose of each drug studied for treating OIC.
3. To compare incidence of nausea, vomiting, and abdominal cramps when using the two medications.
4. To compare changes in appetite and the sense of wellbeing, when using the two medications.

## Materials and Methods

Study was conducted on opioid naïve cancer patients, who required oral morphine sulphate as analgesic for their moderate to severe pain. Randomization was achieved by assigning patient-participants into two groups in 1:1 ratio through odd and even number method. The study was double blinded by formulating both drugs into identical capsules for blind data collection. Patients registered under the Institute of Palliative Care Thrissur, were selected for the study, based on the inclusion (≥ 18 years old, using oral morphine sulphate (OMS) for their cancer pain relief); and

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exclusion criteria (pre-existing colo-rectal pathologies). Patients were recruited for the study from January 2022 to December 2023. Both inpatients and outpatients were included. Their doshaprakruthi was documented and they were allocated randomly to the two study groups, (odd numbered files to Group-1 and even numbered files to group-2). Group-1 received Bisacodyl, and group-2 received Icchabhedirasa. Bowel functions were monitored using the validated clinician-administered tool 'Bowel Function Index (BFI). BFI requires patients to rate their evacuation experience of the preceding seven days using a numerical analogue scale (NAS) of 0 – 100, where 0 represents freedom from the symptom and 100 represents maximum difficulty or the most severe symptom. The three variables rated using NAS are i) ease of defaecation; ii) feeling of incomplete bowel evacuation; and iii) personal judgement of constipation. BFI was monitored every three days during first week and on the last day of the second week. Evidence suggests using 0 – 28.8 as the reference rangefor non-constipated patients with chronic pain[10].

At step 1, all patients had their baseline BFI recorded and on the same day, the oral morphine and prescribed laxative were initiated. Patients from both groups received the one capsule of the assigned medication at bedtime for two days. If the bowel evacuation was unsatisfactory on day three, the dose was modified to one capsule twice daily (afternoon and bedtime) as step-2. On continued monitoring, if the bowel function was dis-satisfactory on day five, step-2 regimen was maintained, with addition of 15 ml syrup of a stool softener (liquid paraffin-3.75ml with milk of magnesia-11.25ml), twice a day (afternoon and bedtime). If bowel functions remained unrelieved with this regime on day seven, rectal measures such as rectal examination followed by digital evacuation and suppository were employed.

Few other subjective parameters were recorded during the study period; such as nausea / vomiting and abdominal cramps and rated using a Likert scale of 0 -3; where 0 = symptom is always present, 1 = frequently present, 2 = only when taking food, and 3 = absence of symptoms.

Impact on appetite was recorded on a scale of 0-3; where 0 = no appetite, 1 = reduced appetite, 2 = normal appetite, and 3 = good appetite. The feeling of sense of wellbeing was noted on a scale of 0-3; where 0 = very bad, 1 = bad, 2 = can't say whether good or bad and 3 = feeling better.

The study continued to monitor bowel functions up to and including Day 14.

### Statistical Analysis

The statistical analysis of the collected data was done by using the statistical software SPSS version 21.0. As BFI was measured five time periods namely before treatment, 3rd day after treatment, 5th day after treatment, 7th day after treatment and 2nd week after treatment, comparison of BFI between period within each study group was done by using Friedman Test followed by Wilcoxon signed rank test for pairwise comparison. Comparison of BFI between groups for each time period was done by using Mann Whitney U test. Scores related to nausea, abdominal cramps, appetite and sense of well-being were also compared between different time period by using Friedman's Test. Z- test for two independent proportions was used for comparing proportion in two study groups. $P < 0.05$ was considered statistically significant.

## Results

Of the 72 patients recruited, six patients from Group 1 and five patients from Group 2 died before completing the follow up period. Three patients of Group 1 and four patients from Group 2 were excluded due to poor compliance. Morphine was withdrawn for two patients in Group 1 and one patient in Group 2; and these patients too were excluded. One patient of Group 2 developed allergic reactions, with generalised itching and redness, and was also excluded from study.

A total of 50 Patient-participants (n=25 in each group), fulfilled all the study criteria. The mean age was 60 (± 7.68) years in Group 1 and 60.12 (± 12.80) years in Group 2. The male to female ratio was 22:3 in Group-1 and 13:12 in Group-2. The predominant dosha-prakruthi of participants was vatha kabha with 52% in group 1, and 44% group 2 [Table 2]. One patient from Group 1 and two patients from Group 2 were on medications likely to contribute to constipation (iron supplements, tricyclic anti-depressants). Also, allergic reactions were noted in one patient on Icchabhedirasa.

The comparison of BFI measures during the study period for both groups are depicted in Table 3. The improvement in the BFI from baseline and across the study period in both the groups was significant, with a p-value <0.001. Although BFI showed a comparable reduction from baseline to 2nd weeks in both groups (p-value > 0.05) across the study period, Pairwise comparison showed statistically significant reduction from 7 days onwards in group I and 5 days onwards in Group 2, which sustained until the final recording at 2nd week. Comparison of mean values indicate that the rate of improvement in BFI was higher in group 2.

The number of patients that required increased dosage to twice per day were 15 in Group-1 and 13 in Group-2. Additional stool-softener was required in 13 patients (52 %) in Group-1 and 11 patients (44 %) in Group-2.

Nine patients needed rectal measures in Group-1 in comparison to 6 in Group-2 (Table 4).

No significant difference was noted in nausea, abdominal cramps, and in the sense of wellbeing amongst participants in both groups (Table 5). However the median score of appetite during the study period showed a significant improvement (P=0.012) from the 5th day onwards in Group 2 (Table 6)

## Discussion

Constipation is a common and distressing side effect of opioids such as Morphine, which are widely used for controlling cancer-pain. This adverse effect impairs quality of life of patients and can contribute to analgesic treatment failure. Stimulant laxative bisacodyl, is standard drug used commonly in Indian palliative care settings, to prevent and treat OIC.

Ayurveda being an ancient system of medicine, is well received in India. Due to its special focus on activating the digestive system and regularising bowel activity, there are several herb-based medicines in its therapeutic armamentarium that are aimed to activate the digestive system and regularises bowel activity. Icchabhedirasa is an age old ayurveda medication used in disease conditions requiring virechana, ('purging' or laxative) and hence selected for the study. The demographic profile of patient in terms of age, cancer-diagnosis and baseline bowel-functions, and dosha-prakrithi was comparable (Table 2). The number of females in Group 1 were lower (3/25) than in Group 2 (12/25). This finding makes the effectiveness of icchabhedirasa all the more significant, as women are known to have higher incidence of constipation symptoms [11].

The current study outcomes suggest that the laxative efficacy of Icchabhedirasa for managing OIC is comparable to bisacodyl, the stimulant laxative used commonly in palliative care settings. Both groups showed significant improvement in bowel functions over the study period with monitored dose titration (Table 3) (Figure 1). By day 3, fifteen patients from Group-1 and thirteen patients from group-2 required doubling of dose; with 20 mg of bisacodyl and 500 mg of Icchabhedirasa. Nine patients in Group-1 (36 %) and 6 patients in Group-2 (24 %) required rectal measures during the study period. Results indicate that 35 of the 50 (70%) patient participants (16 from group 1, and 19 from group 2) had satisfactory bowel movement by the end of 1st week which improved even further by 2nd week, with a satisfactory average BFI (Table 3), suggesting the need for close monitoring and early upward titration of drugs to prevent and treat OIC.

The side-effect profile of the study drug icchabhedirasa, such as nausea and abdominal cramps was comparable to bisacodyl, being negligible. The sense of wellbeing was also comparable. However, the improvement in appetite when using 500 mg icchabhedirasa (p=0.012) was significantly higher than bisacodyl. This is an important advantage over bisacodyl, when treating constipation in palliative care patients, who struggle with poor appetite. Allergic reaction was noted in one patient on Icchabhedirasa, for which other causes could not be ruled-out. More data will clarify the relevance of this observation.

As OIC involves blockage of peripherally acting μ-opioid receptors, there is an emerging body of research on the effectiveness of PAMORAs (peripherally acting μ-opioid receptor antagonists) as second-line medications. Methylnaltrexone is available as subcutaneous injection, and naldemedine and naloxegol are available as oral formulations. Their cost (Rs 300 rupees for a 25 mg tablet of naloxegol, and Rs 3500/vial of methylnaltrexone), and their limited availability affect usage. In its non-capsulated form icchabhedirasa is affordable and accessible. In comparison, the average weekly cost of 20 mg bisacodyl is Rs 41 and the same for 500 mg icchabhedirasa is Rs 30.

### Strengths and Limitations of the study

The integration of competencies with researchers representing allopathic and ayurvedic approach allowed for methodological diligence. Encapsulated drug formulation to ensure double-blinding and randomisation of the drug usage during the study is an important example of the same. Recording of dosha-prakruthi added the unique ayurvedic dimension to the demographic profile of the patient-population.

As the study was conducted in palliative patients with advanced cancer, several other factors may have affected the bowel movements. For example, the daily functional status and dietary details of participants were not recorded during the study period. Also, hospitalisation by itself is known to impact bowel functions.

## Conclusion

In this study on 50 patients, laxative action of the ayurveda formulation Icchabhedirasa was comparable to the standard stimulant bisacodyl, to prevent and manage OIC. At a titrated average dose of two tablets of 250 mg per day, it can be an effective, economical and safe alternative for preventing and managing OIC, without significant side effects and an additional improvement in appetite. Future studies using Icchabhedirasa that include baseline performance status, diet and activities of patients, along with BFI and side-effect profile, monitored over a longer period would be helpful to establish its routine use in preventing and treating OIC in palliative care population.

### Declaration of patient consent

The authors certify that they have obtained appropriate consent in all patients.


### Financial support and sponsorship

Veda Ayurveda Kozhikode, Kerala provided the study drug Icchabhedirasa in powder form free of cost for the study. It is made in to capsular form of 250 mg capsules from Sitaram Ayurveda Pvt. ltd, Thrissur.

### Acknowledgment

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### Declaration of Conflicts of interest

There are no conflicts of interest to declare.

**Table1: List of ingredients of Bisacodyl and Icchabhedirasa**

| **Bisacodyl[1]** | | | | |
|---|---|---|---|---|
| **Parent compound** | | **Other ingredients** | | |
| Triphenylmethane | | Lactose, maize starch, cellulose acetate phthalate, diethyl phthalate, sucrose, povidone, magnesium stearate, pregelatinized maize starch, talc, E171 (titanium dioxide) and E104 (quinoline yellow). | | |
| **Icchabhedirasa[2]** | | | | |
| Ingredients | Scientific name | Family | Parts used | Quantity in parts |
| Shunti | Zingiber officinale | zingiberacea | Dried rhizome | 1 |
| Maricha | Piper nigrum | Piperaceae | fruit | 1 |
| Suddhaparada | hydrargyrum | | | 1 |
| Suddhagandaka | Sulphur | | | 1 |
| Suddhatankana | Borax | | | 1 |
| Suddhajayapala | Croton triglium | euphorbiaceae | seed | 3 |
| Jala | Water | | | qs |

1 Bisacodyl 5 mg tablets were powdered and made into capsules of 10 mg each to be taken orally as prescribed for the study.
2 Icchabhedirasa in powder form was purchased from aryavaidyakalpasala", Pune, through Veda Ayurveda, Kozhikode, then made into capsules of 250 mg from Sitaram Ayurveda Pvt.ltd, Thrissur. This was to be taken orally as prescribed for the study.

**Table 2: Demographic characteristics of study group [mean ± SD or n (percentage)]**

| **Characteristics** | **Group 1 (n=25) (group treated with bisacodyl)** | **Group 2(n=25) (group treated with icchabhedirasa)** |
|---|---|---|
| Age | 60 (± 7.68) | 60.12 (± 12.80) |
| **Gender** | | |
| Male | 22 (88.0) | 13 (52.0) |
| Female | 3 (12.0) | 12 (48.0) |
| **Prakruthi** | | |
| Vatha | 4 (16.0) | 5 (20.0) |
| Pitha | 1 (4.0) | |
| Kabha | 1 (4.0) | 4 (16.0) |
| Vatha Pitha | 2 (8.0) | 2 (8.0) |
| Vatha Kabha | 13 (52.0) | 11 (44.0) |
| Pitha Kapha | 4 (16.0) | 3 (12.0) |

**Table 3: Comparison of Bowel Function Index - BFI (Mean ± SD) across the study period between Bisacodyl (group-1) and Icchabhedirasa (group-2) for opioid induced constipation.**

| Characteristics | Group 1 (n=25) (group treated with bisacodyl) | Group2 (n= 25) (group treated with icchabhedirasa) | P-value |
|---|---|---|---|
| Baseline Average BFI | 52.00a ± 24.96 | 66.53a ± 25.4 | 0.028 |
| Average BFI -Day 3 | 42.00a ± 27.50 | 49.60ab ± 31.16 | 0.354 |
| Average BFI - Day 5 | 36.40ab ± 31.44 | 36.26b ± 34.78 | 0.992 |
| Average BFI - Day 7 | 27.20bc ± 26.44 | 22.93c ± 28.45 | 0.486 |
| Average BFI at the End of 2 weeks | 20.93c ± 20.94 | 14.00c ± 19.46 | 0.246 |
| P-value | <0.001 | <0.001 | |

*** Significant at 0.01 level; ns non-significant Means having different letter as super script differ significantly within a column.*

**Table 4: Comparison of other characteristics between study groups**

| Characteristics | Group 1 (n=25) (group treated with bisacodyl) | Group2 (n= 25) (group treated with icchabhedirasa) | P-value |
|---|---|---|---|
| Number of patients that required transition to step 2 double dosing | 15 | 13 | $0.568^{ns}$ |
| Number of patients that needed additional stool softener | 13 | 11 | $0.570^{ns}$ |
| Number of patients that needed rectal measures | 9 | 6 | $0.350^{ns}$ |

*ns non-significant*

**Table 5: Comparative outcomes between study groups**

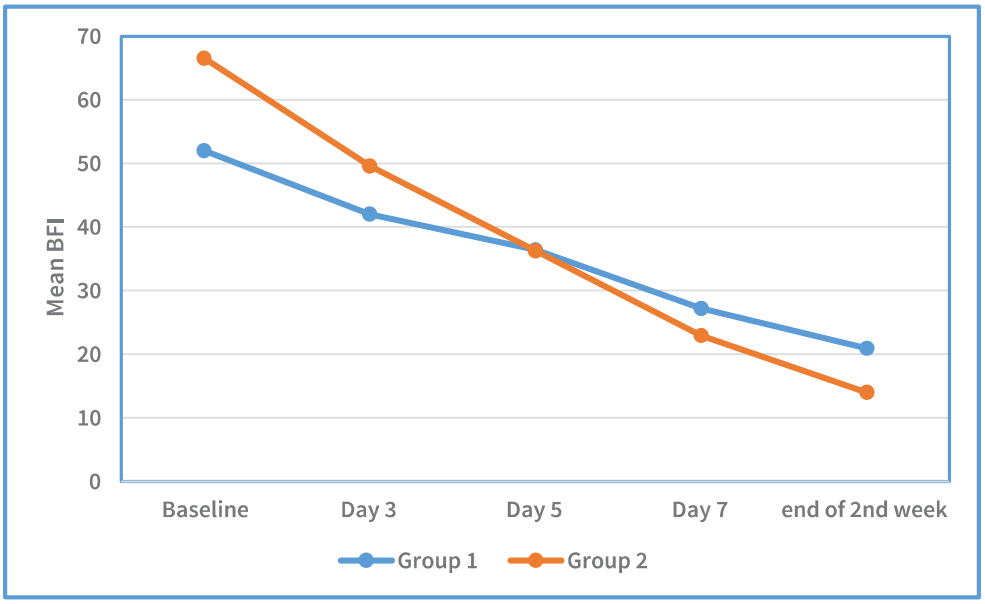
| Parameter studied | P value Group 1 (Group treated with bisacodyl) | P value Group2 (Group treated with icchabhedirasa) | Significance of P Value (Comparison of values over the study period) - |
|---|---|---|---|
| Nausea | $0.763^{ns}$ | $0.265^{ns}$ | not significant in both groups |
| Stomach ache | $0.512^{ns}$ | $0.310^{ns}$ | not significant in both groups |
| Appetite | $0.432^{ns}$ | 0.012* | significant in group 2 only |
| Sense of well being | $0.619^{ns}$ | $0.125^{ns}$ | Improvement was not significant in both groups |

*ns non-significant*

**Table 6: Appetite during the study period in two study groups (when recorded on a scale of 0-3; where 0 = no appetite, 1 = reduced appetite, 2 = normal appetite, and 3 = good appetite)**

| Group | Before treatment | 3rd day | 5th day | First Week | 2nd week |
|---|---|---|---|---|---|
| 1 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| 2 | 1.0 | 1.0 | 2.0 | 2.0 | 2.0 |

**Fig. 1. Change in Bowel Function Index (BFI) during the study period when comparing Bisacodyl (group-1) and Icchabhedirasa (group-2) for opioid induced constipation.**





References:

1. Müller-Lissner S, Bassotti G, Coffin B, Drewes AM, Breivik H, Eisenberg E, Emmanuel A, Laroche F, Meissner W, Morlion B. Opioid-Induced Constipation and Bowel Dysfunction: A Clinical Guideline. Pain Med. 2017 Oct 1;18(10):1837-1863. doi: 10.1093/pm/pnw255. PMID: 28034973; PMCID: PMC5914368.
2. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil. 2014 Oct;26(10):1386-95. doi: 10.1111/nmo.12417. Epub 2014 Aug 28. PMID: 25164154; PMCID: PMC4358801.
3. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med. 2009 Jan;10(1):35-42. doi: 10.1111/j.1526-4637.2008.00495.x. Epub 2008 Aug 18. PMID: 18721170.
4. Abramowitz L, Béziaud N, Labreze L, Giardina V, Caussé C, Chuberre B, Allaert FA, Perrot S. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain: DYONISOS study. J Med Econ. 2013 Dec;16(12):1423-33. doi: 10.3111/13696998.2013.851082. Epub 2013 Oct 25. PMID: 24102123.
5. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. Gastroenterol Res Pract. 2014;2014:141737. doi: 10.1155/2014/141737. Epub 2014 May 5. PMID: 24883055; PMCID: PMC4027019.
6. Joo JS, Ehrenpreis ED, Gonzalez L, Kaye M, Breno S, Wexner SD, Zaitman D, Secrest K. Alterations in colonic anatomy induced by chronic stimulant laxatives: the cathartic colon revisited. J Clin Gastroenterol. 1998 Jun;26(4):283-6. doi: 10.1097/00004836-199806000-00014. PMID: 9649012.
7. Vaidya Jadavji Trikamji Acharya, Sushruta, Sushruta Samhita, Sutra Sthana, Dosha - Dhatu - Mala Kshaya Vriddhi Vijnaniya Adhyaya, 15/41,8th ed. Varanasi: Chaukhamba Orientalia; 2005.page 75.
8. Sharma PV, Charakasamhita vol 1, reprint edition, 2011, choukhambha orientalia Varanasi,India (jaikrishna ayurveda series no 36 : charaka samhitha chikitsa sthana 15/4; page 249.
9. Sri Sharma Sadananda. Rasa Tarangini. Edited by Pandit Kashinatha Shastri, 11th Edition. Varanasi: Motilal Banarasidas Publication; 1979. 24th Taranga, Verses 321- 328, page706.
10. The Journal of International Medical Research;2011; 39: 41 – 50
11. Verkuijl, S.J., Meinds, R.J., Trzpis, M. et al. The influence of demographic characteristics on constipation symptoms: a detailed overview. BMC Gastroenterol 20, 168 (2020). https://doi.org/10.1186/s12876-020-01306-y