*ejpmr, 2024, 11(4), 103-117*

**SJIF Impact Factor 7.065**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

**Review Article**

**ISSN 2394-3211**

**EJPMR**

# EXPLORING THE COMBINED THERAPEUTIC POTENTIAL OF HYOSCINE BUTYLBROMIDE AND PARACETAMOL FOR RELIEF IN SPASMODIC CONDITIONS

**Nikhil Bangale[1]*, Aditi Gulhane[2], Auditi Narayan[3], B. S. Susheela Rani[4], Indrakumar Singh[5], Jayamala G.[6], K. Chandrika Kanne[7], K. Shilpi Reddy[7], Lata K.[8], Mani Kapur[9], Monica Saha[10], Narendra Malhotra[11], P. Madhavi[12], Rakhi Gupta[13], Shaveta Garg[14], Sheela V. Mane[15], Shipra Roy[16], Suneetha Gudipati[17], Sunita Chandra[18], Vidya V. Bhat[19] and Poonam Shah[1]**

[1]Head Medical Affairs, Bayer Consumer Health, Bayer House, Central Avenue, Hiranandani Estate, Thane (West), Maharashtra 400607 (India).
[2]Gulhane Nursing Home, Opposite Post office Nai Basti, Badnera, Amravati, Maharashtra 444701
[3]SGT Hospital, Budhera, Gurugram-Badli Road, Gurugram, Haryana-122505 (India).
[4]Manjushree Speciality Hospital, #22/70, St Johns Road, Landmark: Opposite to R.B.A.N.M.S Ground, Ulsoor, Bangalore, Karnataka-560042 (India).
[5]Shaibo Hospital, Khurai Sajor Leikai, near Chaithabi Leirak Road, Imphal, Manipur 795010 (India).
[6]Rainbow Hospital No B, 20, Rajaji St, Swarnapuri, Salem, Tamil Nadu 636016 (India).
[7]KIMS Cuddles, Survey No 55/EE, beside Union Bank, near RTA Office, Hanuman Nagar, Shilpa Hills, Kondapur, Hyderabad, Telangana 500084 (India).
[8]Lata Hospital, Nabi Complex, 79-15-15, Balaji Home St, Near Swathi Theatre, Bhavanipuram, Housing Board Colony, Vijayawada, Andhra Pradesh 520012 (India).
[9]The Healing Touch Maternity Center, 5/2, CTS No. 1012, Opp. "Sai Marigold, Rahatani Rd, Pimple Saudagar, Pimpri-Chinchwad, Maharashtra 411017 (India).
[10]ILS Hospital, 1, Mall Rd, near Nagerbazar Flyover, Golpark, Dum Dum, Kolkata, North Dumdum, West Bengal 700080 (India).
[11]Ujala Cygnus Rainbow Hospital, Sikandra, Agra, Uttar Pradesh 282007 (India).
[12]Mamata Nursing Home, #15-24-496, Remedy Hospital Ln, Kukatpally Housing Board Colony, Kukatpally, Hyderabad, Telangana 500072 (India).
[13]MI Heart & Women Health Care Clinic, C-36, Ground Floor, (Adjacent to C-Pocket Morket), Sarita Vihar, New Delhi -110076 (India).
[14]Cloudnine Hospital, Sector-5, Mansa Devi Complex, Swastik Vihar, Panchkula, Haryana 134109 (India).
[15]Anugraha Nursing Home, #2 Vinayaka circle, Palace Guttahalli Main road, Bangalore, Karnataka-560003 (India).
[16]Swasti Women's Hospital & Research Centre, V 19, Kankarbagh, Patna, Bihar-800020 (India).
[17]Medwise Hospital 288, 4th Street, K P H B Phase 1, Kukatpally, Hyderabad, Telangana 500072 (India).
[18]Morpheus Lucknow Fertility Center, 49, Guru Govind Singh Marg, Husainganj, Lucknow, Uttar Pradesh 226001 (India).
[19]Radha Krishna Hospital, No. 3/4, Sunrise Towers, Radhakrishna Multispeciality Hospital, J P Road, 30th Cross, Girinagar, Bangalore, Karnataka – 560085 (India).

***Corresponding Author: Dr. Nikhil Bangale**

Head Medical Affairs, Bayer Consumer Health, Bayer House, Central Avenue, Hiranandani Estate, Thane (West), Maharashtra 400607 (India).

**Article Received on 20/02/2024** **Article Revised on 11/03/2024** **Article Accepted on 01/04/2024**

## ABSTRACT

Menstruation, a fundamental aspect of women's reproductive health, often introduces discomfort, with dysmenorrhea affecting about 81% – 93% of women, alongside other distressing symptoms such as abdominal cramps, headache, back pain, body aches, and fatigue, impacting nearly 3 out of 4 women. This poses significant challenges to daily routines and activities, profoundly affecting quality of life. While over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain management, they often provide only partial relief, necessitating a holistic approach to address pain and discomfort, as well as distressing menstrual symptoms, without severe adverse events.

**KEYWORDS:** Spasmodic conditions, menstrual pain, distressing symptoms, hyoscine butylbromide, paracetamol, safety, quality of life.

**INTODUCTION**

Paracetamol offers significant safety advantages over traditional NSAIDs like mefenamic acid, which carry higher risks of gastrointestinal bleeding, heartburn, nausea, and gastric ulcers, alongside recent alerts regarding DRESS syndrome. Similarly, while dicyclomine effectively manages spasmodic pain, it is associated with an increased incidence of dry mouth, blurred vision, and constipation compared to hyoscine butylbromide (HBB) derived from natural source. The minimal systemic side effects and absence of central effects of HBB ensure safer clinical usage. Additionally, the minimal anti-inflammatory activity of paracetamol offers superior gastrointestinal safety compared to mefenamic acid and dicyclomine combination, rendering HBB+paracetamol a safer alternative, enhancing tolerability and compliance in patients with spasmodic pain conditions.

The combination of HBB and paracetamol has emerged as a potent pharmacotherapeutic option over decades, with a faster onset and longer duration of action. Its versatility extends beyond dysmenorrhea and related symptoms, effectively addressing a broad spectrum of spasmodic conditions, including specific or non-specific abdominal pain with or without cramping, colicky pain, irritable bowel syndrome, and post-operative spasmodic pain. Additionally, it is effective in managing urinary tract infections, polycystic ovary disease, pelvic inflammatory disease, endometriosis, fibroids, and ovarian cysts, thus widening its adaptability and clinical utility, establishing it as a valuable addition to children (>10 years) and women across all age groups and settings. Backed by strong clinical evidence and favourable safety, the combination of HBB+paracetamol is established as a clinically effective and well-tolerated treatment for menstrual pain, its related symptoms, and a range of spasmodic conditions. Embracing this combination heralds a path towards better women's health, where efficient symptom relief leads to an overall enhancement in quality of life amidst the challenges posed by menstruation.

**INTRODUCTION**

Abdominal pain is a complex and multifaceted symptom that can arise from a variety of underlying conditions. Among the diverse spectrum of abdominal pain disorders, spasmodic conditions stand out for their characteristic muscle contractions within the abdomen, often leading to sharp, intermittent pain and discomfort.[1-3] These conditions encompass a broad range of disorders affecting different regions of the gastrointestinal (GI) tract, including the stomach, intestines, and uterus.[1-3]

Spasmodic conditions are characterised by involuntary, rhythmic contractions of smooth muscle fibres within the abdominal organs, leading to episodes of pain and discomfort.[2,3] These contractions can be triggered by various factors, including physiological processes such as menstruation or digestion, as well as pathological conditions such as irritable bowel syndrome (IBS), dysmenorrhea, urinary tract infections, polycystic ovary disease, pelvic inflammatory disease, endometriosis, fibroids, and ovarian cysts.

Primary dysmenorrhea (PD), characterized by spasmodic and painful cramps in the lower abdomen, is a highly prevalent issue among females, affecting both young girls and adults. It typically occurs shortly before or at the onset of menstruation and is not linked to any pelvic pathology.[4] The pain is sharp, intermittent, and spasmodic, categorised as mild, moderate, or severe based on its interference with daily activities.[5] The pain associated with dysmenorrhea usually begins 1 to 2 days before the onset of menstruation or shortly after it begins, lasting for approximately 8 to 72 hours, potentially disrupting daily functioning, leading to absenteeism from school or work, and affecting social engagements.[4,6]

Dysmenorrhea should be distinguished from premenstrual syndrome (PMS), which shares similar symptoms but resolves shortly after menstruation begins.[7,8] Dysmenorrhoea focuses on pain accompanying menses, while PMS primarily involves emotional or psychological symptoms.[7,8] Clinical evidences have highlighted an alarming prevalence rate of dysmenorrhea projected to be as high as 80.9 – 92.5% in women of reproductive age[9-12] whereas four in ten women (40%) experience symptoms of PMS, with 5–8% of these individuals enduring severe PMS as underscored by the Royal College of Obstetricians and Gynaecologists (RCOG).[13,14]

***Common symptoms experienced with spasmodic Dysmenorrhea and Pain intensity during menstruation***

Dysmenorrhea, apart from causing pelvic pain is also accompanied by a wide array of distressing physical symptoms such as malaise, fatigue (85%), nausea and vomiting (89%), diarrhoea (60%), back pain (60%), and headache (45%) that may pose a substantial impact on the quality of life of women.[4,8,15] Several studies (Table 1) have identified a heightened prevalence of these symptoms especially abdominal pain, back pain, tiredness/fatigue, and headache among Indian women as well as worldwide.

**Table 1: Common symptoms associated with menstrual pain.**

| | | |
|---|---|---|
| Nagar *et al.*[16] | • An investigational analysis in Indian school going girls<br>• N=100<br>• Age: 12-18 years | • 97% reported pain in lower abdomen<br>• 89% reported back pain<br>• 82% reported |

| | | |
|---|---|---|
| | | weakness/tiredness<br>• 55% reported bodyache<br>• 44% reported pain in thighs/legs 31% reported headache |
| Agarwal *et al.*[11] | • An exploratory survey in Indian adolescent college going girls (12th grade)<br>• N=970<br>• Age: 15-20 years | Persistent symptoms observed for continuously 3 days of menstruation<br>• Dysmenorrhea in 72%<br>• Tiredness and lethargy in 57.4% girls, and, Headache in 28% |
| Dhar *et al.*[17] | • An epidemiological survey across 7 educational institutes (including schools, colleges, and universities) in young Indian women<br>• N=799<br>• Age: 10-29 years | One third women (>33%) reported frequent headache and tiredness/dizziness as predominant symptoms |
| Schoep *et al.*[18] | • A nationwide, cross-sectional survey on general Dutch women population<br>• N= 42,879<br>• Age (mean): 28.7 years | • >85% women reported dysmenorrhea<br>• Fatigue: 71%<br>• Back pain: 59.2%<br>• Headache: 56.2%, and, Perimenstrual psychological complaints: 77.3% |
| Gebeyehu *et al.*[10] | • An institution-based cross-sectional study in female students<br>• N=389<br>• Age (mean): 21 years | Most frequently experienced dysmenorrhea symptoms:<br>• Abdominal spasm: 70.4%<br>• Back pain: 70%<br>• Fatigue and weakness: 64% |
| Smith *et al.*[19] | • A large cross-sectional survey on Nurses from Japan<br>• N=958<br>• Age (mean): 33 years | • Around 83% women had experienced at least one episode of low back pain in the previous 12-months<br>• 76.2% women experienced abdominal pain<br>• 30% reported fatigue and, 23% experienced headache |
| Pedlar *et al.*[20] | • An online survey from the STRAVA membership database of women who exercise on regular basis<br>• N= 6,812<br>• Age (mean): 38.3 years | The influence of menstrual cycle on sports participation and exercise performance, is an underexplored area.<br>The most prevalent symptoms were:<br>• Tiredness/fatigue in 86.2%<br>• Stomach cramps in 84.2%<br>• Mood changes/anxiety in 91% |
| Gambaudauro *et al.*[21] | • A cross sectional survey in school girls from Sweden of 7th-8th grade<br>• N=1100<br>• Age: 13-15 years | About 93.2% reported experiencing menstrual symptoms (malaise, headache, tiredness, nausea/ vomiting), with 81.3% grappling with at least one moderate symptom and 31.3% facing severe symptoms |
| Alkhati *et al.*[22] | • A cross-sectional study on female students in a University from 45 countries<br>• N=345<br>• Age (mean): 26.59 years | Most frequently reported symptoms<br>• Abdominal cramps: 17.68%<br>• Irritation: 15%<br>• Fatigue and abdominal pain: 12.46%<br>• Headaches: 10% |

***Unveiling the impact of symptoms related to menstrual pain on quality of life***

A cross-sectional survey by Durairaj *et al*., among Indian college girls aged 17 – 25 years reported fatigue/lack of energy as the most common premenstrual symptom, with anger prevalent in moderate to severe PMS. An impairment of college efficiency or productivity was observed in 83% of students with moderate to severe PMS. Notably, a significant 86% of affected students did not perceive their symptoms as abnormal, and only a minority sought physician consultation. PMS adversely affects academic performance, emotional well-being, and behaviour and these findings emphasise the importance of implementing strategies for timely recognition and management of PMS.[23]

Omidvar *et al*. revealed that about 57% Indian girls aged between 11 – 28 years experienced tiredness and 40% experienced low back pain upon menstruation. Females experiencing mild pain on average were absent for one and a half days per month, while those who experienced moderate and severe forms of dysmenorrhea were absent for 2.1±1.2 and 2.5±1.3 days, respectively. Additionally, results showed that 69.7% of subjects were moderately affected, and 7.6% of both dysmenorrheic and non-dysmenorrheic individuals reported a clear inhibition of their activities. Despite their suffering, only 14.2% of patients sought medical advice, with 83.2% relying on non-pharmacological methods.[24]

Armour *et al*. investigated the potential influence of menstrual pain and related symptoms on academic performance and other school-related activities in a systematic review and meta-analysis of 38 studies, encompassing 21,573 young women between the age group of 13-23 years based in school, university or higher education. The academic impact was significant, with 20.1% reporting absenteeism from school or university due to dysmenorrhea (N = 19, n = 11,226, 95% CI 14.9–26.7), and 40.9% reporting a negative effect on classroom performance or concentration (N= 10, n = 5126, 95% CI 28.3–54.9).[25]

According to Itani *et al*. and Unsal *et al*., primary dysmenorrhea poses significant challenges in educational settings. Absenteeism rates in girls aged 17 – 30 years due to this condition vary notably, ranging between 14% and 51%. This absenteeism translates into a substantial loss of educational hours, estimated at 600 million hours per year, with an associated annual economic loss of $2 billion. Moreover, the impact extends beyond absenteeism, as class attendance shows a considerable decrease, ranging from 29% to 50%.[4,26]

Gebeyehu *et al*., reported that 63% respondents with an average age of 21 years reported facing social withdrawal, and 51.4% noted a decrease in academic performance and about 64% relied on home remedies as the primary management option.[10]

These findings underscore the profound effects of primary dysmenorrhea on academic participation and performance, highlighting the need for effective management strategies to mitigate its impact on education.

Dysmenorrhea presents a recurring challenge necessitating long-term medication. Though NSAIDs provide symptomatic relief, they do not have long lasting benefits. This necessitates, exploring treatment beyond the conventional route. An alternative therapy should target both the neuronal and uterine components of dysmenorrhea without affecting the cycle dynamics. Clinical evidences in the past have highlighted that drugs from a natural source offer a promising regimen, boasting proven efficacy in dysmenorrhea with a superior safety index compared to traditional NSAIDs.

**Management**

***Hyoscine butylbromide: Background, Recommendations, Pharmacodynamics, and Pharmacokinetics***

Hyoscine, a tropane alkaloid obtained from a natural source, (leaves of the Solanaceae plant species), undergoes a process to yield hyoscine butylbromide (HBB). It is also known as butylscopolaminebromide or N-butylscopolamonium. It acts as an anticholinergic agent that blocks the effects of acetylcholine, the endogenous muscarinic receptor agonist.[27] HBB is a widely utilised antispasmodic medication that was first introduced as a pharmaceutical drug in Europe in 1952 and is now registered in over 80 countries, including India, available in various forms (oral formulations, an intravenous solution, and suppositories).[27,28]

***Recommendations***

It is recommended as an antispasmodic in the World Gastroenterology Organization Global and the American College of Gastroenterology guidelines, indicated for alleviating gastrointestinal (GI) and genito-urinary spasms, along with relief from symptoms (Spasms and Cramps) associated with irritable bowel syndrome (IBS).[28]

**HBB exhibits key pharmacological mechanisms, including[27,29]**

i. Obstructing the action of acetylcholine at parasympathetic sites found in both smooth muscle and secretory glands.
ii. Reduced motility within the gastrointestinal and urogenital tracts offers a targeted and effective approach in managing spasmodic conditions.
iii. A parasympathetic ganglion-blocking effect

For therapeutic use, the recommended starting dose for adults experiencing abdominal pain due to cramping is two tablets 3 times daily. The total daily dose should not exceed 6 tablets.

The tablets should not be chewed but swallowed whole with a sufficient amount of water.

It may also be used for children over 10 years old if required, but it should not be exceeded for more than 3 days without doctor's consultation.[30] A maximum oral dose limitation of 100 mg/day has been established.[27]

HBB, since its discovery, has undergone continuous safety scrutiny throughout its enduring presence. The safety profile of the drug has been meticulously monitored, with three comprehensive Periodic Safety Update Reports (PSURs) submitted to health authorities since 1992. Over the subsequent span of years, an extensive dataset has emerged, encompassing approximately 1.6 million patient-years of exposure or 194 million treatment episodes (with an average treatment duration of 3 days) involving HBB across the globe, including India.[27]

HBB, exhibits limited absorption, about 8%, and bioavailability <1%. It does not cross the blood brain barrier, thus, the incidence of central nervous system and anticholinergic side effects is much lower compared to systemically available smooth-muscle relaxants like Cimetropium bromide, dicyclomine (dicycloverine), mebeverine, pinaverium bromide, octylonium bromide/otilonium bromide and trimebutine.[27-29]

***Clinical evidence***

Tytgat *et al*.[27] and Corsetti *et al*.[28] evaluated data from ten placebo-controlled studies that examined the efficacy of HBB in treating a wide array of abdominal pain (specific/non-specific colicky) associated with or without cramping, acute abdominal pain from various origins, pain from the ulcus ventriculi, pain associated with IBS, and discomfort. These studies encompassed 3699 patients, with 911 receiving oral or rectal HBB.[27,28] The remaining patients were administered paracetamol, placebo, or a combination of HBB with other drugs. Patient populations included individuals with irritable bowel syndrome (IBS) and those with functional abdominal pain and discomfort. Treatment durations across all placebo-controlled trials varied from a single dose study to a 3-month regimen. [27,28] The maximum daily dose of HBB ranged from 20mg to 200mg for 10 days. Despite a significant placebo effect, HBB demonstrated statistically superior efficacy to placebo on at least one efficacy variable in all trials. In these trials, the HBB dose ranged between 30 and 60 mg/day, with treatment durations of 4 weeks, 4 days, and 3 weeks, respectively.[27,28] The clinical efficacy of HBB over the wide spectrum of spasmodic conditions is highlighted in Table 2.

**Table 2: Clinical evidence on the efficacy of HBB across an array of spasmodic conditions.**

| Author | Study details | Outcomes |
|---|---|---|
| **Spasmodic dysmenorrhea** | | |
| Kemp *et al*.[31] | N=17<br>Aspirin 300 mg, hyoscine 40 mg. and placebo | • Both hyoscine and aspirin were found to be significantly more effective and provided satisfactory relief vs. placebo<br>• No side-effects were reported with both treatments |
| **Recurrent abdominal Pain and Cramping** | | |
| Lacy *et al*.[32] | N=175<br>Hyoscine 20–100 mg (N=88) vs. PBO (N=87)<br>Duration: 2 separate episodes of APC during 4-wk period | • Pain intensity decreased within 30 minutes (45 for HBB vs 60 min for placebo) earlier with HBB and sustained for 2 hours with a ≤2-point improvement in NPRS (~30% pain relief) with HBB<br>• 35% patients reported that they were more satisfied with symptom improvement when taking HBB vs. placebo (23%) |
| Lissner *et al*.[33] | HBB (10 mg, N=415), placebo (N=414) | • Abdominal pain intensity assessed on 100-mm VAS, decreased significantly with hyoscine significantly vs. placebo (mean change from baseline: 2.3 mm vs 1.9 mm; P <0.0001)<br>• Significant decrease observed in pain frequency based on verbal rating scale; 0 [not at all] to 3 [≥5 times]) for hyoscine vs. placebo: 0.7/d vs 0.5/d; P <0.0001 |
| **Alleviating Spasms and Cramps in non-specific colicky pain and IBS** | | |
| Americo *et al*.[34] | N=14 | • HBB decreased the mechanical motility index (MI) by 50.9%, while for electrical MI the reduction was 36.5%<br>• The anti-muscarinic effects of HBB result in the relaxation of GI smooth muscles, alleviating spasms and cramps in abdominal pain of non-specific origin |

| | | |
|---|---|---|
| **Gastric or intestinal spasm-like pain** | | |
| Ge *et al*.[35] | **N=302** | • Within 30 minutes of HBB administration, pain intensity decreased<br>• After 3 hours the pain intensity reduced to ~59%.<br>• After 3 days, approximately 55% reduction in peak pain intensity was noted<br>• No occurrence of serious AEs with HBB |
| **Biliary colic** | | |
| Kumar *et al*.[36] | **N=72** | • Complete pain relief was achieved in 69.4% patients within four hours post ingestion of HBB |
| **Renal colic** | | |
| Samuels *et al*.[29] | 6 studies<br>N=755<br>HBB+morphine and indomethacin vs. placebo vs. NSAIDs vs. other antispasmodics | • HBB plus opoid combination showed 90% effectiveness in relieving pain within 30 minutes after administration.<br>• HBB combination with analgesics consistently showed consistent significant pain relief. |
| **Post-operative pain** | | |
| Esmaeili *et al*.[37] | **N=70** | • 60% (42) had reduction in pain, 50 pain<br>• 71% (50) patients had reduction in tenderness<br>• 55% (39) patients had reduction in rebound tenderness<br>• Lower incidence of adverse events (n=4) |

***Paracetamol*: Background, Recommendations and edge over other NSAIDs**

Globally, paracetamol stands as the foremost commonly used over-the-counter analgesic and is the preferred first-line choice for individuals experiencing mild-to-moderate acute pain for its well-tolerated nature.[38] According to the WHO pain relief ladder and various international guidelines, paracetamol is recommended as the first-line treatment for mild to moderate pain due to its favorable safety profile. It is considered safer than NSAIDs in terms of adverse effects on the GI, CV, renal, and hepatic systems compared to other pain medications.[39] A study by Chatterjee *et al*. conducted on the Indian population using NSAIDs revealed a point prevalence of 30.08% for GI complications, 42.77% for cardiac complications, and 27.88% for renal complications.[40] Additionally, an analysis of 51 clinical trials revealed that 18% of women experience minimal or no relief of menstrual pain with NSAIDs. This lack of pain relief indicates the involvement of multiple pathological mechanisms contributing to treatment unresponsiveness.[41] Clarifying these mechanisms stands is a crucial requirement in gynaecological research.[41] Current understanding suggests that while traditional NSAIDs (Ibuprofen, naproxen, ketoprofen, indomethacin, diclofenac, and mefenamic acid) inhibit COX enzyme activity, paracetamol selectively inhibits the peroxidase activity of COX at low peroxide levels.[42] This peroxide-dependent inhibition allows paracetamol to predominantly target the central nervous system without exerting significant peripheral anti-inflammatory effects.[42] Thus, acetaminophen induces analgesia via direct action on the brain, and helps in alleviating headache, body pain, and other symptoms related to menstrual discomfort.[12,43,44]

NSAIDs, while effective in pain management, bear a distinct risk profile concerning the GI tract. A comprehensive study comparing paracetamol and ketoprofen, an NSAID, demonstrated the propensity of the latter to induce gastroduodenal lesions, including gastric ulcers. Traditional NSAIDs (Mefenamic acid, ibuprofen, diclofenac, aspirin at recommended doses) may also lead to bothersome symptoms (heartburn, nausea, vomiting, diarrhoea, dizziness, and in severe cases, gastric/peptic ulcer and perforation) and may need to be prescribed with mucosal protective agents or proton pump inhibitors.[42] Also, the traditional NSAIDs may also lead to elevated liver enzymes, thrombocytopenia, hypotension, hypersensitivity reactions, acid reflux, discomfort or edema. The potential benefits of paracetamol over NSAIDs are highlighted in Table 3.[39,43,45,46]

**Table 3: The potential benefits of paracetamol over NSAIDs.**

| Parameter | Paracetamol | NSAIDs |
|---|---|---|
| Administration | With/without food, minimal effect on bioavailability | With food, better bioavailability |
| Safe for use in GI, CV, hepatic disease (3-4g/day) and renal complications (3 g/day) | Yes | No |

| | | |
|---|---|---|
| Adverse effects | Rare | Related to GI, hepatic, CV, neurological, hematological, renal, anaphylactic |
| Bleeding risk | Low compared to traditional NSAIDs | High, should be avoided after surgery to avoid bleeding risk |
| Concomitant PPIs/ gastroprotective agents | No | Yes, to minimize GI complications, but for a shorter duration |
| Hepatotoxicity | ~50% lower | High |
| CV, cardiovascular; GI, gastrointestinal, PPIs, proton pump inhibitors | | |

**Rationale for Combining Spasmolytic Agents and Analgesics in Abdominal Pain and Cramps: A Comprehensive approach for enhanced relief**

The American College of Obstetricians and Gynecologists, The Royal College of Obstetricians and Gynecologists, The Society of Obstetricians and Gynaecologists of Canada and The Indian Academy of Pediatrics Standard Treatment guidelines, emphasize on the management of dysmenorrhea and related symptoms with conventional treatment.[13,14,28]

The amalgamation of spasmolytic agents, exemplified by HBB, with analgesics like paracetamol in addressing abdominal pain and cramps is underpinned by a multitude of compelling rationales.

a. **Comprehensive symptom relief:** Spasmolytic agents, like HBB, target the underlying muscle spasms, providing relief from the core cause whereas, analgesics, such as paracetamol, act on pain receptors to alleviate the perception of pain, ensuring more comprehensive relief from both muscle-related discomfort and pain sensation.

b. **Synergistic effect:** The combination of a spasmolytic and an analgesic can result in a synergistic effect, by targeting different aspects of the pain pathway, these agents provide more effective and faster relief and a longer duration of action than either drug alone.

c. **Avoidance/Reduced adverse effects:** Combining lower doses of spasmolytic agents and analgesics may achieve the desired therapeutic effect with a reduced risk of adverse effects commonly associated with higher individual doses of each drug. The absence of severe adverse events and the high satisfaction rates among users underscore the overall positive safety experience.

d. **Broader applicability:** The combination therapy may have broader applicability across various indications associated with abdominal pain and bloating with discomfort, recurrent crampy abdominal pain, abdominal pain in infections, irritable bowel syndrome, renal colic, gastrointestinal and urogenital spasms, urinary tract infections, polycystic ovary disease, pelvic inflammatory disease, endometriosis, fibroids, and ovarian cysts may benefit from the dual mechanism of action provided by spasmolytics and analgesics.

e. **Patient compliance:** Combining spasmolytic agents with analgesics can simplify treatment regimens, potentially improving patient compliance leading to better adherence to the prescribed therapy that addresses both muscle spasms and pain.

f. **Customization of treatment:** The combination allows for flexibility in tailoring the treatment based on the predominant symptoms such as back pain, headache, abdominal pain and cramps, and individual patient needs.

g. **Patient-tailored safety:** Clinicians can adapt the treatment regimen based on individual patient needs and responses, ensuring a personalised approach that enhances safety.

The rationale for combining a spasmolytic agent like HBB with analgesics such as paracetamol lies in achieving a more holistic and synergistic approach to relieve abdominal pain and cramps, while minimising adverse effects and improving overall treatment outcomes.

**The Dynamic Duo: HBB and Paracetamol Pharmacotherapy in Spasmodic Pain Conditions**

In the 1980s, a fixed dose combination of HBB 10 mg and paracetamol 500 mg was globally introduced for clinical use. This combination was approved by CDSCO in 2005 for the management of spasmodic pain and became available in India in May 2007.[47,48]

***Dysmenorrhea***

A prospective randomised double-blind crossover study by Santos *et al*. on dysmenorrhea included 125 patients with primary dysmenorrhea. The patients underwent three treatment phases comparing HBB and paracetamol with lysine clonixinate plus propinox and a placebo. The fixed-dose schedule involved taking 1 tablet every 6 hours, starting 3 days before menses and continuing for 5 days. On day 5, both active treatments significantly reduced pain intensity compared to the placebo. Patients' diaries showed progressively lower pain intensities from day 1 with all three treatments and higher analgesic efficacy. No changes in menstrual bleeding or adverse effects were observed.[49]

Beuno *et al.*, performed an investigational analysis to assess the safety and efficacy of a combination of a spasmolytic-analgesic (lysine clonixinate 125 mg and HBB 10 mg) over three consecutive menstrual cycles in 30 women experiencing uterine dysfunction due to primary or secondary dysmenorrhea during a menstrual cycle observation period. The combination alleviated dysmenorrhea as well as the most commonly associated manifestations including headache, abdominal pain, general pain, nausea, and vomiting.[50]

***Dysmenorrhea, Gastrointestinal and Genitourinary Spasms, and IBS in the Indian Setting: SPICE Study[48]***

Rathod *et al.* conducted a post-marketing study involving 481 physicians (gynaecologists, surgeons, consulting physicians, and general practitioners) to assess the efficacy of HBB+paracetamol (10mg+500mg) in 2080 patients (66% were females, mean age: 33.54 years) with 37.7% experiencing dysmenorrhea, 24.3% suffering from GI-biliary colic, 12.2% reporting pain and spasm associated with IBS, 9.5% with acute gastroenteritis-related pain and spasm, and 16.3% having other causes.

The baseline mean pain intensity score was 78.12 (± 20.41) mm, which decreased significantly to 9.41 mm (± 11.09; mean) after 7 days of treatment. Notably, on the first day of treatment alone, there was a significant reduction of 14.2% in the mean pain intensity score from baseline. At the end of day 4, a substantial decline of 65.7% was observed in pain intensity and 87.8% at the end of the 7$^{th}$ day from baseline. Daily assessment of the mean pain intensity score throughout the study is depicted in Figure 1.

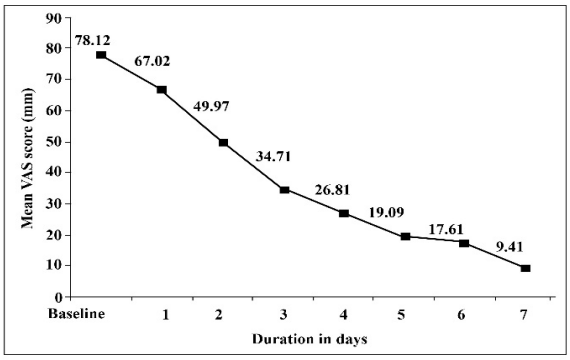


**Figure 1: Pain intensity score (mean) as assessed on a daily basis; *P<0.05*.**

A considerable relief from pain, as assessed on a 5-point scale, showed that at the end of day 1, 39.7% of cases reported 'a lot' to 'complete' pain relief, increasing to 59.6% by the end of day 5. Notably, 90.1% of patients experienced ‘good to excellent’ resolution of pain, 8.9% had some resolution of pain, and only 1% did not show any pain relief at the end of the treatment (Figure 2).

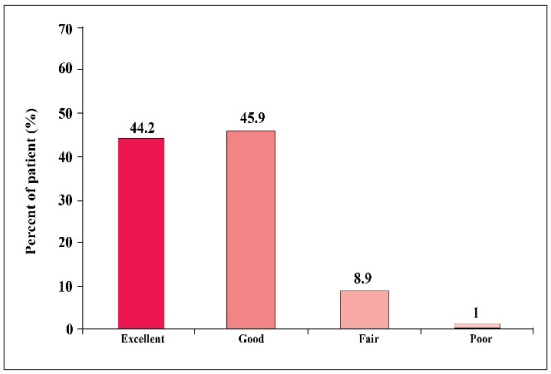


**Figure 2: Overall assessment of efficacy with HBB+Paracetamol combination.**

About 5.7% of patients reported adverse events of which 2.6% had GI side events, followed by central nervous system side events were 1.8%, and other adverse events were 1.3%. The intensity of adverse events was mild in most cases and resolved during the treatment. No 'serious' adverse events were reported, that led to discontinuation from the study.

***Recurrent crampy abdominal pain***

Lissner *et al.*[33] conducted a study to assess the efficacy and tolerability of HBB, paracetamol, and their

combination in patients experiencing recurrent, crampy abdominal pain. 1,113 patients with a VAS pain score of ≥3 cm in the preceding 2 days and adherence to medication were randomly assigned to receive HBB (10 mg), paracetamol (500 mg), HBB+paracetamol (10mg+500mg), or placebo, three times daily for 3 weeks. Pain intensity and frequency significantly decreased in VAS (mean) by 2.3 cm, 2.4 cm, and 2.4 cm for HBB, paracetamol, and the combination, respectively, compared to 1.9 cm for the placebo group ($p$ <0.0001 for all comparisons). After 3 weeks, approximately 15% more patients in the combination group achieved a global efficacy score of 'good' or 'excellent' compared to placebo (Figure 3).

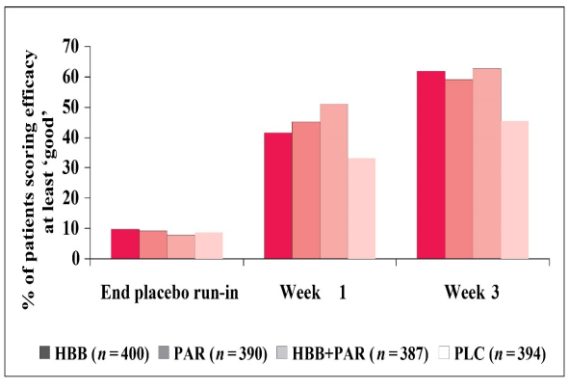


**Figure 3: Global assessment of efficacy after placebo run-in and after 1 and 3 weeks of active treatment.**

The study concluded that HBB, paracetamol, and their combination were superior to placebo for pain intensity, daily pain frequency, and global efficacy score, with a 23% greater improvement over placebo. None of the patients reported dry mouth with HBB, possibly due to the poor absorption and low bioavailability (<1%) and its action exerted from the luminal side of the gut wall.[33]

**HBB and Paracetamol: An Ideal Spasmolytic-Analgesic with Unmatched Safety**

***The Safety Assurance of HBB over Dicyclomine and Others in Spasmodic Pain***

Clinical studies on HBB have shown significant improvement in various GI symptoms in a larger proportion of patients compared to placebo, accompanied by fewer or milder adverse events.[28,51,52] Clinical evidences on alternative spasmolytic agents such as dicyclomine, has demonstrated its efficacy in improving GI symptoms in patients with IBS, albeit with a notably higher rate of adverse events observed in 69% of patients within the treatment span of 10 –14 days, whereas with hyoscine the rate of adverse events were low (<15%) and mild in nature which were observed in the treatment span of 4 weeks to 3 months.[53] These evidences signal the potential safety concerns associated with dicyclomine despite its effectiveness[54] in the management of spasmodic pain. Furthermore, compared to droatverine, oral hyoscine significantly increased the rectal threshold for discomfort/pain, indicating its superior efficacy in alleviating visceral pain.[53] Overall, these findings suggest that hyoscine, a natural resource, not only effectively improves symptoms and manages spasmodic pain in patients but also possesses a more favourable safety profile compared to dicyclomine.

***The Superior GI Safety of Paracetamol over Mefenamic acid***

Among the NSAIDS, mefenamic acid is associated with a higher incidence of GI bleeding risk, may also lead to heartburn, nausea, vomiting, diarrhoea, gastric/peptic ulcer, and perforation in some cases, primarily due to their inhibition of prostaglandin production in the gastric mucosa.[42] In patients at elevated risk of GI problems, it may need to be prescribed alongside mucosal protective agents or proton pump inhibitors.[42] Also, recently the Indian Pharmacopoeia Commission (IPC) issued alerts and emphasised the potential risks associated with the use of mefenamic acid. The issued warning by IPC highlighted the adverse reactions such as skin lesions, edema, and respiratory difficulties and the risk of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome linked to mefenamic acid. With harmful side effects affecting one in every 5000 to 10000 individuals, the alert emphasises the critical role of healthcare providers in ensuring the appropriate use of this combination of mefenamic acid and dicyclomine.[56]

Considering the evidence surrounding GI and CV safety, paracetamol emerges as one of the safest analgesic available due to its negligible impact on peripheral COX activity,[42] documented safety profile, and use in populations vulnerable to GI complications, collectively positioning itself as the preferred choice over mefenamic acid in clinical practice.[55,56]

***Safety of HBB and paracetamol combination over Mefenamic acid-dicyclomine***

Combining HBB with paracetamol offers several advantages over other combinations of spasmolytics + analgesics/NSAIDs such as dicyclomine and mefenamic

acid for management of spasms, pain, cramps, GI discomfort and related symptoms such as headache and fatigue (Figure 4).

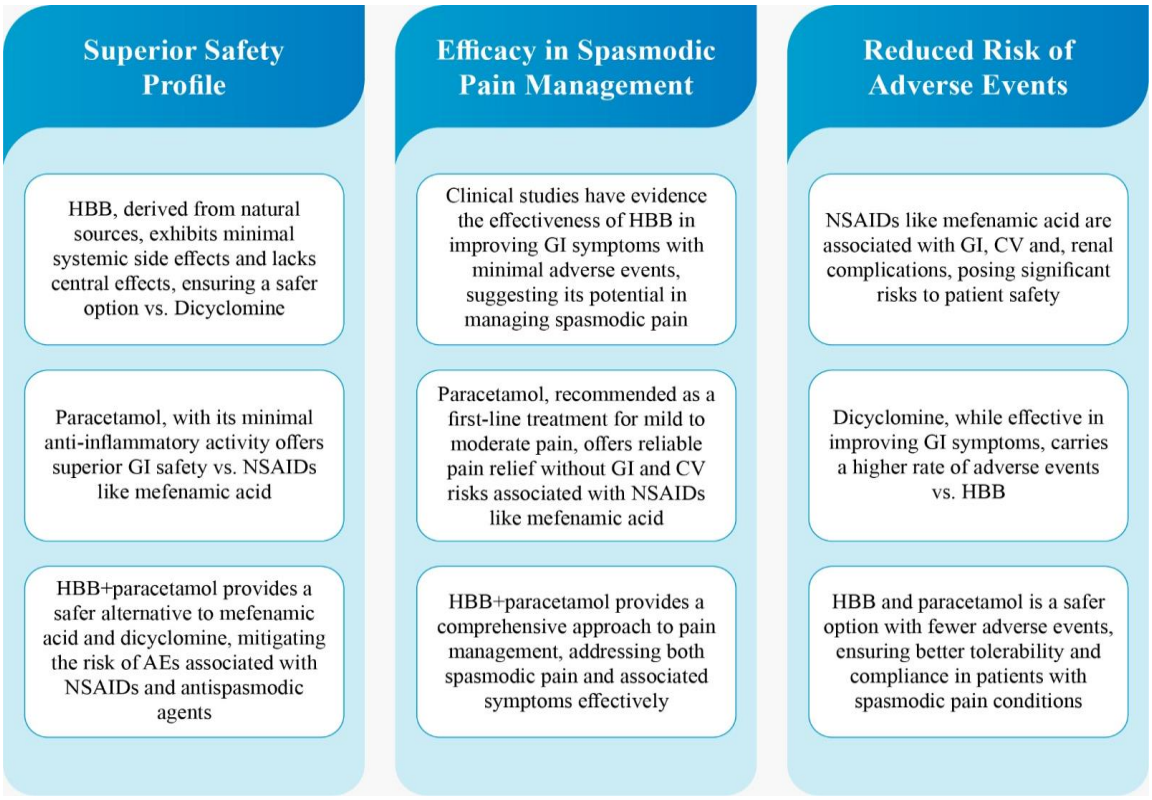


**Figure 4: Potential advantages of combining HBB+paracetamol over other combinations.**

***Exploring the Versatile Applications of HBB and Paracetamol Combination in Spasmodic Pain Management***

The combination therapy of hyoscine and paracetamol showcases a broad spectrum of applicability in pain management across various clinical scenarios. Post-procedural pain, although typically self-limiting, often necessitates medication, with options like paracetamol, HBB and NSAIDs proving effective.[57] The Royal College of Obstetricians and Gynaecologists also recommends HBB for alleviating pain in specialised procedures like uterine artery embolisation.[58] Ryu *et al.* highlighted that administration of HBB effectively reduces both the severity of catheter-related bladder discomfort (CRBD) and the need for rescue analgesics without any adverse effects.[59] Gabhane *et al.*[60] highlighted that the combination of antispasmodics and analgesics can be utilised for diverse indications including abdominal/stomach pain, dysmenorrhea, abdominal pain with GI disorder, pain in para-umbilical region, bowel irregularity, peptic ulcer, gastritis/gastric pain, renal colic, biliary colic, and intestinal/ abdominal colic, and active phase of labour.[33,60] In the realm of pelvic pain management, Souza *et al*. indicated that prior medication with HBB combined with an analgesic agent effectively decreased pain levels, particularly in patients undergoing outpatient hysteroscopy.[61] Esmailie *et al.* corroborated the efficacy of hyoscine in post-surgical pain management, particularly in appendicitis cases, where it significantly reduces pain, tenderness, and rebound tenderness.[37] Collectively, these findings underscore the broad applicability and efficacy of HBB and paracetamol combination in addressing diverse pain management needs across clinical settings.

***Abdominal Pain and Cramps***

Pain, bloating, GI cramps, and flatulence related to functional GI disorders, frequently cause discomfort. Sultanoglu *et al.*, investigated the efficacy of HBB and paracetamol in 281 cases with abdominal pain and cramps associated with functional GI disorders. Both HBB and paracetamol demonstrated a reduction in pain and cramps after 30 minutes of administration. Throughout the course of treatment, the occurrence of adverse effects (Discomfort, hypersensitivity, hypotension, elevated liver enzymes, thrombocytopenia) commonly observed with traditional NSAIDs was rare with HBB+paracetamol combination, underscoring the effectiveness and safe utilisation of HBB+paracetamol combination.[62]

Storr *et al.* conducted a pharmacy-based patient survey on 1686 users to compare HBB alone, HBB+paracetamol, and peppermint oil. The HBB+paracetamol group showed significant reduction in the intensity of GI cramps and pain by 73.4% vs. 68.8% for HBB and 62.2% for peppermint oil. Among users who received HBB+paracetamol combination, more than

93% reported symptom relief within 60 mins of the first dose (vs. 20.1% on peppermint oil). Notably, over 50% of individuals on HBB+paracetamol experienced relief within the first 6–30 minutes compared to monotherapy. These data suggests that the combination of HBB and paracetamol may result in an onset of action that is 2 times faster or more accelerated than single-drug interventions. These variations could be attributed to the diverse symptoms being addressed and the pharmacokinetic distinctions of HBB+paracetamol combination where HBB acts swiftly on muscarinic receptors in the GI tract, ensuring a faster onset within 60 minutes, and a longer duration of action. Addition of paracetamol further potentiates the action of HBB in relieving GI cramps and pain. Conversely, the menthol component in peppermint oil, encapsulated for stomach resistance, achieves peak plasma concentrations about 5 hours post-oral administration. For the global effectiveness rating, 96.4% users of HBB plus Paracetamol were satisfied or very satisfied with the effectiveness of the treatment. Global tolerability was ranked as good or very good by 97.1% users of HBB plus Paracetamol. In the global rating of satisfaction with treatment, 96.1% of users were very satisfied or satisfied with HBB plus Paracetamol. HBB plus Paracetamol users experienced a reduction in the intensity of GI cramps and pain of more than 50%. The degree of impairment of work/daily chores, leisure activities, and sleep was reduced by more than 50% with HBB plus paracetamol.[63]

Corsetti *et al*., evaluated the efficacy of HBB+paracetamol combination in four studies. One study demonstrated that 93% (14/15) patients showed faster relief in abdominal pain, while only one patient in the placebo group experienced decreased pain.[28] Additionally, the responders (81%) were higher for the antispasmodic-analgesic combination compared to placebo (64%). The incidence of adverse events was infrequent or mild in nature, further highlighting the safety profile of HBB+ paracetamol (Schafer and Ewe 1990).[51]

***Spasmodic disorders of the GI, Biliary, and Urinary tracts***

Gregorio *et al*., evaluated the efficacy of HBB alone and in combination with an analgesic in alleviating pain associated with smooth-muscle spasmodic disorders of the GI, biliary, and urinary tract. Among the 818 subjects enrolled in the trial, a subset received HBB orally (60 mg/day) or rectally (20 mg/day), while another subset received a combination of HBB + analgesic. Analysis revealed that 81.5% of patients in the HBB+analgesic group experienced significantly greater reductions in pain intensity compared to 62% of subjects treated with HBB alone.[64]

***Acute renal colic pain***

Combination of HBB and an analgesic agent is used to relieve severe colic pain quickly and effectively in the renal, hepatobiliary, or gastrointestinal tract.[65] Janczura *et al*. evaluated the efficacy of HBB-analgesic combination versus monotherapy in patients who experienced acute renal colic. After 1 hour, the HBB+analgesic combination showed that 87.5% of patients showed better efficacy in the HBB+analgesic group vs. monotherapy. A similar study showed that HBB+analgesic combination therapy showed relief in pain after 30 mins post-ingestion compared to analgesic monotherapy.[65]

**Self-Care Tips for managing pain during menstruation[66-74]**

Period pain can sometimes be severe enough to interfere with day-to-day activities. Exercise increases blood flow through the body and releases "feel-good hormones" called endorphins. Exercising and adapting to a routine may help in relieving period pain.

***Exercise Routine:***

a. Embrace Aerobic Exercises and Relaxation Therapies:
- Engage in aerobic activities like brisk walking, running, cycling, and swimming for at least 30 minutes most days to alleviate fatigue and depression.
- Relaxation techniques: Breathing exercises, meditation, and yoga to reduce stress.

b. Explore Massage Therapy:
- Beneficial for relaxation and managing symptoms.

c. Sleep Hygiene:
- Establish Regular Sleeping Habits
- Maintain consistent waking up and sleeping times every day, including weekends, to minimize moodiness and fatigue.

Exercises that you can try to relieve your period pain

1. Cobra Pose or Bhujangasana: This pose will help tone up your reproductive organs, stretch your abdomen, increase the flexibility of your spine, and strengthen your back.
2. Cow-cat pose or Marjaryasana-bitilasana: Involves the muscles of your abdomen. The breathing movements in this pose will gently stretch your back.
3. Fish Pose or Matsyasana: Improves flexibility of your spine and increase blood flow to your abdomen.
4. Anulom-vilom: This breathing exercise helps relax your muscles, and increases your pain tolerance.
5. Bow pose or Dhanurasana: This asana will increase blood flow to your womb, and will stretch your chest and back muscles.

***Additional tips***

1. Use a heating pad or warm water bottle on the abdomen for soothing relief.
2. Keep a menstrual chart to identify patterns and changes across cycles.
3. Avoiding foods that contain caffeine.
4. Avoiding smoking cigarettes and drinking alcohol.

5. Massaging your lower back and abdomen.
6. Ensure consistency in the chosen management strategies for pre-menstrual changes.
7. Practice deep breathing, warm baths, or listening to calming music for relaxation.
8. Consider pain relief medications like paracetamol and hyoscine combination, to help alleviate period pain.
9. Alternative therapies such as acupuncture and acupressure, consuming anti-inflammatory foods (leafy green vegetables, ginger and nuts, green tea). https://my.clevelandclinic.org/health/diseases/4148-dysmenorrhea
10. Natural ingredients like shatavari and ashoka may improve hormonal imbalance, regulating the menstrual cycle, reducing the adverse menstrual symptoms and revitalizing the female reproductive system.

Adhering to these personalized self-care strategies can significantly enhance your well-being and effectively manage bothersome menstrual symptoms at onset. If you have specific concerns or need further guidance, don't hesitate to reach out.

## CONCLUSION

Menstruation, a natural facet of reproductive health for women, often brings with it a range of discomforts, including dysmenorrhea which is projected to have a very high prevalence in women ranging from 81% – 93%, abdominal cramps, headache, back pain, bodyaches, and fatigue affecting nearly 3 out of 4 women. The physical discomfort associated with these symptoms can pose challenges to women in their daily routine and activities, significantly impacting their quality of life. While many women opt for over-the-counter NSAIDs to manage pain and related conditions, majority of them experience only partial relief. This calls the need of a holistic approach that addresses the pain and discomfort along with the distressing menstrual symptoms without any severe adverse events.

Paracetamol demonstrates significant safety advantages over traditional NSAIDs like mefenamic acid which poses a higher risk of GI bleeding, heartburn, nausea, and gastric ulcers and recent alerts issued by the regulatory bodies related to DRESS syndrome. Similarly, while dicyclomine is effective in managing spasmodic pain, it is associated with a higher incidence of dry mouth, blurred vision, and constipation compared to HBB obtained from a natural resource. The combination of HBB and paracetamol stands out for its superior safety profile when compared to the mefenamic acid and dicyclomine combination. HBB, derived from natural sources, offers minimal systemic side effects and lacks central effects, ensuring safer usage in clinical settings. Additionally, paracetamol shows minimal anti-inflammatory activity providing superior gastrointestinal safety compared to NSAIDs like mefenamic acid. This combination thus presents a safer alternative, mitigating the risk of adverse events associated with traditional NSAIDs and antispasmodic agents, ultimately ensuring better tolerability, and compliance among patients with spasmodic pain conditions.

The combination of HBB and paracetamol has garnered attention as a potent pharmacotherapeutic option for decades with a faster onset and longer duration of action, particularly in the management of dysmenorrhea along with painful menstrual symptoms including low back pain, cramps, headache, and fatigue. The versatility of HBB+paracetamol extends its application beyond dysmenorrhea, addressing a broad spectrum of spasmodic conditions associated with specific/non-specific abdominal pain with/without cramping, specific/non-specific colicky pain, IBS and post-operative spasmodic pain, urinary tract infections, polycystic ovary disease, pelvic inflammatory disease, endometriosis, fibroids, and ovarian cysts. This adaptability broadens its utility in various clinical scenarios, reinforcing its position as a valuable addition to the armamentarium of children older than 10 years and women's healthcare across all groups (school/high school, university students, higher education, as well as working women).

This robust clinical evidence, coupled with the favourable safety profile, makes HBB+paracetamol a clinically proven and well tolerated option for addressing menstrual pain and commonly associated symptoms as well as other spasmodic conditions. In embracing HBB with paracetamol, we embark on a journey towards a new era of women's health, where effective symptom management translates into a better overall quality of life for women navigating the intricacies of menstruation.

## ACKNOWLEDGEMENT

Manuscript and editorial support by Ms. Stuti Jain, Sr. Medical Writer, Insignia Communication Pvt Ltd, Mumbai. Dr. Nikhil Bangale contributed by reviewing the final draft of the manuscript and offering expert opinions.

## REFERENCES

1. Cartwright SL, Knudson MP. Evaluation of acute abdominal pain in adults. *American family physician*, 2008; 1, 77(7): 971-8.
2. Sherman R. Abdominal Pain. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. Boston: Butterworth, 1990; 3: 86. Available from: https://www.ncbi.nlm.nih.gov/books/NBK412/
3. Stern LZ, Bernick C. Muscle Cramps. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 53. Available from: https://www.ncbi.nlm.nih.gov/books/NBK376/
4. Itani R, Soubra L, Karout S, Rahme D, Karout L, Khojah HM. Primary dysmenorrhea:

pathophysiology, diagnosis, and treatment updates. *Korean journal of family medicine*, 2022; 43(2): 101.
5. Hailemeskel S, Demissie A, Assefa N. Primary dysmenorrhea magnitude, associated risk factors, and its effect on academic performance: evidence from female university students in Ethiopia. *International journal of women's health*, 2016; 19: 489-96.
6. Nagy H, Carlson K, Khan MAB. Dysmenorrhea. [Updated 2023 Nov 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560834/
7. Bezuidenhout S, Mahlaba KJ, Nxumalo G, Meyer JC, Chukwu BO. Dysmenorrhoea: an overview. *SA Pharmaceutical Journal*, 2018; 1, 85(4): 19-25.
8. Negriff S, Dorn LD, Hillman JB, Huang B. The measurement of menstrual symptoms: factor structure of the menstrual symptom questionnaire in adolescent girls. *Journal of health psychology*, 2009; 14(7): 899-908.
9. Guo JL, Lee TC, Lin FH, Hsu HP, Huang CM. Medical care-seeking patterns among women with menstrual syndromes-related diagnoses: a longitudinal population-based study. *European Journal of Medical Research*, 2022; 15, 27(1): 250.
10. Gebeyehu MB, Mekuria AB, Tefera YG, Andarge DA, Debay YB, Bejiga GS, Gebresillassie BM. Prevalence, impact, and management practice of dysmenorrhea among University of Gondar Students, Northwestern Ethiopia: a cross-sectional study. *International journal of reproductive medicine*, 2017; 14, 2017.
11. Agarwal AK, Agarwal A. A study of dysmenorrhea during menstruation in adolescent girls. *Indian journal of community medicine*, 2010; 1, 35(1): 159-64.
12. Preeti Kumari, Smriti Gohri, Rustam Iqbal. A review article on analgesic and anti-inflammatory treatments in menstrual cramps. *World Journal of Pharmaceutical and Medical Research*, 2023; 9(9): 62-66.
13. Abay H, Kaplan S. Current approaches in premenstrual syndrome management. *Bezmialem Sci*, 2019; 1, 7(2): 150-6.
14. Frackiewicz EJ, Shiovitz TM. Evaluation and management of premenstrual syndrome and premenstrual dysphoric disorder. *Journal of the American Pharmaceutical Association*, 1996, 2001; 1, 41(3): 437-47.
15. Auld B, Sinha P. Dysmenorrhoea: Features and current treatment options. *Prescriber*, 2006; 5, 17(13): 33-40.
16. Nagar S, Aimol KR. Knowledge of adolescent girls regarding menstruation in tribal areas of Meghalaya. *Studies of Tribes and Tribals*, 2010; 1, 8(1): 27-30.
17. Dhar S, Mondal KK, Bhattacharjee P. Influence of lifestyle factors with the outcome of menstrual disorders among adolescents and young women in West Bengal, India. *Scientific Reports*, 2023; 1, 13(1): 12476.
18. Schoep ME, Nieboer TE, van der Zanden M, Braat DD, Nap AW. The impact of menstrual symptoms on everyday life: a survey among 42,879 women. *American journal of obstetrics and gynecology*, 2019; 1, 220(6): 569-e1.
19. Smith DR, Mihashi M, Adachi Y, Shouyama Y, Mouri F, Ishibashi N, Ishitake T. Menstrual disorders and their influence on low back pain among Japanese nurses. *Industrial health*, 2009; 47(3): 301-12.
20. Pedlar C, Bruinvels G, Goldsmith E, Blagrove RC, Simpkin AJ, Lewis NA, Morton K, Suppiah A, Rogers JP, Ackerman KE, Newell J. The prevalence and frequency of menstrual cycle symptoms are associated with women's availability to train and compete: A study of 6,812 exercising women recruited using the STRAVA™ exercise app. *British Journal of Sports Medicine*, 2020; 16.
21. Gambadauro P, Hadlaczky G, Wasserman D, Carli V. Menstrual symptoms and subjective well-being among postmenarchal adolescents. *AJOG Global Reports*, 2024; 1, 4(1): 100304.
22. Alkhatib A, Zhou Q, Bajinka O, Pakwan Suwal R, Wiley J, Li X. Prevalence of menstrual symptoms change and influencing factors among international female students studying in china during acculturation period. *BMC Women's Health*, 2022; 25, 22(1): 311.
23. Durairaj A, Ramamurthi R. Prevalence, pattern and predictors of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) among college girls. *New Indian J OBGYN*, 2019; 5(2): 93-8.
24. Omidvar S, Bakouei F, Amiri FN, Begum K. Primary dysmenorrhea and menstrual symptoms in Indian female students: prevalence, impact and management. *Global journal of health science*, 2016; 8(8): 135.
25. Armour M, Parry K, Manohar N, Holmes K, Ferfolja T, Curry C, MacMillan F, Smith CA. The prevalence and academic impact of dysmenorrhea in 21,573 young women: a systematic review and meta-analysis. *Journal of women's health*, 2019; 1, 28(8): 1161-71.
26. Unsal A, Ayranci U, Tozun M, Arslan G, Calik E. Prevalence of dysmenorrhea and its effect on quality of life among a group of female university students. *Upsala journal of medical sciences*, 2010; 1, 115(2): 138-45.
27. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs*, 2007; 67: 1343-57.
28. Corsetti M, Forestier S, Jiménez M. Hyoscine butylbromide mode of action on bowel motility: From pharmacology to clinical practice. *Neurogastroenterology & Motility*, 2023; 35(4): e14451.

29. Samuels LA. Pharmacotherapy update: Hyoscine butylbromide in the treatment of abdominal spasms. Clinical Medicine. *Therapeutics*, 2009; 1: CMT-S1134.
30. BUSCOGAST PLUS PI. Available at https://www.sanofi.in/dam/jcr:6a128e81-b0ed-4060-90c9-476e82d65de4/Buscogast%20Plus%20API_Aug%202021.pdf Accessed on February 2024.
31. Kemp JH. 'Buscopan'in spasmodic dysmenorrhoea. *Current medical research and opinion*, 1972; 1, 1(1): 19-25.
32. Lacy BE, study group, Wang F, Bhowal S, Schaefer E. On-demand hyoscine butylbromide for the treatment of self-reported functional cramping abdominal pain. *Scandinavian Journal of Gastroenterology*, 2013; 1, 48(8): 926-35.
33. Mueller-Lissner S, Tytgat GN, Paulo LG, Quigley EM, Bubeck J, Peil H, Schaefer E. Placebo-and paracetamol-controlled study on the efficacy and tolerability of hyoscine butylbromide in the treatment of patients with recurrent crampy abdominal pain. *Alimentary pharmacology & therapeutics*, 2006; 23(12): 1741-8.
34. Americo MF, Miranda JR, Cora LA, Romeiro FG. Electrical and mechanical effects of hyoscine butylbromide on the human stomach: a non-invasive approach. *Physiological measurement*, 2009; 12, 30(4): 363.
35. Ge Z, Yuan Y, Zhang S, Hou X, Wang J, Cai J, Shi R, Li Y, Wang B, Ji F, Richter E. Efficacy and tolerability of two oral hyoscine butylbromide formulations in Chinese patients with recurrent episodes of self-reported gastric or intestinal spasm-like pain. *International journal of clinical pharmacology and therapeutics*, 2011; 1, 49(3): 198-205.
36. Kumar A, Deed JS, Bhasin B, Kumar A, Thomas S. Comparison of the effect of diclofenac with hyoscine-N-butylbromide in the symptomatic treatment of acute biliary colic. *ANZ journal of surgery*, 2004; 74(7): 573-6.
37. Esmaeili A, Salimi V, Karimi NM, Hajimaghsoudi M, Vakili M, Zarepur E. The Effect of Hyoscine on Pain, Tenderness, and Rebound Tenderness in Patients with Appendicitis: Quasi-Interventional Study. *Bulletin of Emergency & Trauma*, 2018; 6(4): 300.
38. Mallet C, Desmeules J, Pegahi R, Eschalier A. An updated review on the metabolite (AM404)-mediated central mechanism of action of paracetamol (acetaminophen): experimental evidence and potential clinical impact. *Journal of Pain Research*, 2023; 31: 1081-94.
39. Agam Vora, S V Kulkarni, Anand Meenawat, Pradeep Ganguly, Srinivas Murty, Raghu Satyanarayan, Mangesh Tiwaskar. NSAIDs Safety in Pain and Fever Management. *Journal of the Association of Physicians of India*, 2023: 10.5005/japi-11001-0216.
40. Chatterjee S, Dureja GP, Kadhe G, Mane A, Phansalkar AA, Sawant S, Kapatkar V. Cross-sectional study for prevalence of non-steroidal anti-inflammatory drug-induced gastrointestinal, cardiac and renal complications in India: interim report. *Gastroenterology research*, 2015; 8(3-4): 216.
41. Oladosu FA, Tu FF, Hellman KM. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. *American journal of obstetrics and gynecology*, 2018; 1, 218(4): 390-400.
42. Kim SJ, Seo JT. Selection of analgesics for the management of acute and postoperative dental pain: a mini-review. *Journal of Periodontal & Implant Science*, 2020; 50(2): 68.
43. Gerriets V, Anderson J, Patel P, Nappe TM. Acetaminophen. 2024 Jan 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024 Jan–. PMID: 29493991.
44. Ohashi N, Kohno T. Analgesic effect of acetaminophen: a review of known and novel mechanisms of action. *Frontiers in pharmacology*, 2020; 30, 11: 580289.
45. Mefenamic acid PI. Moore RA, Derry S, Wiffen PJ, Straube S. Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs–a systematic review. *British journal of clinical pharmacology*, 2015; 80(3): 381-8.
46. CDSCO. FIXED DOSE COMBINATIONS APPROVED BY DCG (I) SINCE, 2019; 1961: 28. Available at https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadApprovalNewDrugs/dciApprovedfdc.pdf Accessed on February, 2024.
47. Rathod R, Misra D. Spice: An indian experience With Buscopan plus in Spasm and pain. *Indian Journal Of Clinical Practice*, 2008; 19(5).
48. De los Santos AR, Zmijanovich R, Martí ML, Di Girolamo G. Antispasmodic/analgesic associations in primary dysmenorrhea double-blind crossover placebo-controlled clinical trial. *International journal of clinical pharmacology research*, 2001; 1, 21(1): 21-9.
49. JA HB, de la Jara Diaz J. Analgesic-antispasmodic effect and safety of lysine clonixinate and L-hyoscinbutylbromide in the treatment of dysmenorrhea. *Ginecologia y Obstetricia de Mexico*, 1998; 1, 66: 35-9.
50. Schäfer E, Ewe K. Behandlung des Colon irritabile. Wirksamkeit und Verträglichkeit von Buscopan plus, Buscopan, Paracetamol und Plazebo bei ambulanten Patienten mit Colon irritabile [The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patients with irritable colon]. *Fortschr Med*, 1990; 30, 108(25): 488-92. German. PMID: 2210587.
51. Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine

butylbromide, and ispaghula husk. *Br Med J*, 1979; 10, 1(6160): 376-8.
52. Brenner DM, Lacy BE. Antispasmodics for chronic abdominal pain: analysis of North American treatment options. *Official journal of the American College of Gastroenterology| ACG*, 2021; 1, 116(8): 1587-600.
53. Page JG, Dirnberger GM. Treatment of the irritable bowel syndrome with Bentyl®(dicyclomine hydrochloride). *Journal of Clinical Gastroenterology*, 1981; 1, 3(2): 153-6.
54. Monthly Drug Safety Alert. November, 2023; 30. Available at https://www.ipc.gov.in/images/Drug_Safety_Alert_November_2023.pdf Accessed on February, 2024.
55. IPC issues warning against reactions of painkiller drug Mefenamic Acid; know possible side-effects here. Available at IPC issues warning against reactions of painkiller drug Mefenamic Acid; know possible side-effects here (dnaindia.com) Accessed on February, 2024.
56. Recker F, Thudium M, Strunk H, Tonguc T, Dohmen S, Luechters G, Bette B, Welz S, Salam B, Wilhelm K, Egger EK. Multidisciplinary management to optimize outcome of ultrasound-guided high-intensity focused ultrasound (HIFU) in patients with uterine fibroids. *Scientific Reports*, 2021; 23, 11(1): 22768.
57. Clinical recommendations on the use of uterine artery embolization in the management of fibroids. RCOG 2013. Available at https://www.rcog.org.uk/media/gw3f4wzc/23-12-2013_rcog_rcr_uae.pdf Accessed on February 2024.
58. Ryu JH, Hwang JW, Lee JW, Seo JH, Park HP, Oh AY, Jeon YT, Do SH. Efficacy of butylscopolamine for the treatment of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *British journal of anaesthesia*, 2013; 1, 111(6): 932-7.
59. Gabhane M, Braganza L. Preference trends for antispasmodics among Indian healthcare professionals: Results of a cross sectional survey. *The Indian Practitioner*, 2015; 1: 32-7.
60. Souza CA, Genro VK, Tarrasconi DV, Oppermann ML, Cunha Filho JS. Diclofenac versus a combination of hyoscine and diclofenac for outpatient hysteroscopy: A placebo controlled randomized clinical trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2020; 1, 247: 1-5.
61. Sultanoğlu H, Safi Y, Demirel ME, Demir MC, Altinsoy HB, Boğan M, Gümüşboğa H. Comparison of paracetamol and hyoscine-N-butylbromide in the treatment of abdominal pain and cramps due to acute gastroenteritis. *IMC J Med Sci*, 2022; 16(1): 009.
62. Storr M, Weigmann H, Landes S, Michel MC. Self-Medication for the Treatment of Abdominal Cramps and Pain—A Real-Life Comparison of Three Frequently Used Preparations. *Journal of Clinical Medicine*, 2022; 28, 11(21): 6361.
63. De Gregorio, M., Damiani, S. and Gatta, G. Antalgic Properties of Proxazole: Double Blind Study in Visceral Algoplastic Conditions. *Panminerva Medica*, 1969; 11: 436.
64. Janczura M, Kobus-Moryson M, Sip S, Żarowski M, Wareńczak A, Cielecka-Piontek J. Fixed-dose combination of NSAIDs and spasmolytic agents in the treatment of different types of pain—A practical review. *Journal of clinical medicine*, 2021; 15, 10(14): 3118.
65. Premenstual Syndrome (PMS). ACOG> Available at https://www.acog.org/womens-health/faqs/premenstrual-syndrome Accessed on February, 2024.
66. Malik R, Bhat MD. The management of Premenstrual syndrome: A review. Bangladesh *Journal of Medical Science*, 2018; 17(1): 16.
67. Dysmenorrhea and Endometriosis in the Adolescent. Available at https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/12/dysmenorrhea-and-endometriosis-in-the-adolescent Accessed on February, 2024.
68. Kaur R, Kaur K, Kaur R. Menstrual hygiene, management, and waste disposal: practices and challenges faced by girls/women of developing countries. *Journal of environmental and public health*, 2018; 20: 2018.
69. Rakhshaee Z. Effect of three yoga poses (cobra, cat and fish poses) in women with primary dysmenorrhea: a randomized clinical trial. *Journal of pediatric and adolescent gynecology,* 2011; 1, 24(4): 192-6.
70. Prabhu S, Nagrale S, Shyam A, Sancheti P. Effect of yogasanas on menstrual cramps in young adult females with primary dysmenorrhea. *Int J Physiother Res*, 2019; 11, 7(4): 3129-34.
71. Menstrual cramps. Available at https://www.mayoclinic.org/diseases-conditions/menstrual-cramps/symptoms-causes/syc-20374938 Accessed on February, 2024.
72. Pandey AK, Gupta A, Tiwari M, Prasad S, Pandey AN, Yadav PK, Sharma A, Sahu K, Asrafuzzaman S, Vengayil DT, Shrivastav TG. Impact of stress on female reproductive health disorders: Possible beneficial effects of shatavari (Asparagus racemosus). *Biomedicine & Pharmacotherapy*, 2018; 1, 103: 46-9.
73. Yadava L. Potential Use of Saraca Asoca in the Management of Artavadushti wsr to Menstrual Disorders in Modern Era. *Int J Ayur Pharma Research*, 2021; 9: 69.