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EFFECT OF GUT MICROBIOME MODIFICATION ON POSTOPERATIVE PAIN

Anaesthesiology

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ABSTRACT

Management of postoperative pain is a huge clinical challenge because this affects the patient satisfaction, and surgical recovery. Research has shown that the gut microbiome plays a very important role in modulating systemic inflammation, and the immune response, as well as neural signalling pathways; all of which are responsible for pain perception. This study aims to evaluate the effect of gut microbiome modification on postoperative pain intensity. Following ethical committee approval and informed consent, eligible participants are randomised to two groups, namely Group C – which is a control group receiving placebo capsules and Group P – which is the group receiving probiotics. Participants in the probiotic group received two capsules of a commercially available multi-strain probiotic formulation twice daily (BD), beginning two days prior to surgery. Control Group (Group C) patients received two identical placebo capsules twice daily following the same schedule. All patients underwent standardized anaesthesia and surgery protocols. Their Postoperative pain intensity, was assessed using the Numerical rating scale (NRS) at regular time intervals of 6, 12, 24, hours postoperatively. Data was subjected to statistical analysis. It was found that there was a highly statistically significant difference among the groups in the postoperative NRS at 12 and 24 hours, with lesser pain in Group P (Probiotic group). There were no statistically significant differences among the groups in the requirement of postoperative analgesia. All patients tolerated the oral capsules (probiotics/placebo) well, with no cases of gastrointestinal intolerance. In conclusion, the findings of this study suggest that preoperative probiotic supplementation may serve as a promising adjunct in postoperative pain management in elective general surgical patients with ease of oral administration and excellent safety profile; which may help in enhanced patient recovery.

KEYWORDS

Probiotics, Postoperative Pain, Gut Microbiome, Pain Management, Gut-Brain Axis, Surgical Recovery

INTRODUCTION:

Management of postoperative pain is a huge clinical challenge because this affects the patient satisfaction, and surgical recovery. Many pharmacological interventions are used, but it may not be totally effective in all or can be limited by unwanted side effects. Research has shown that the gut microbiome plays a very important role in modulating systemic inflammation, and the immune response, as well as neural signalling pathways; all of which are responsible for pain perception and modulation[1]. It has been found that alterations in the gut microbiome composition through probiotic administration, influences inflammatory processes and decreases pain sensitivity[2]. This study aims to evaluate the effect of gut microbiome modification on postoperative pain in our population. This can provide insights in to effective pain management strategies.

AIM OF THE STUDY:

To evaluate the effect of preoperative probiotic supplementation on postoperative pain intensity in patients undergoing elective surgery.

OBJECTIVES OF THE STUDY:

Primary Objective: To evaluate the effect of preoperative probiotic supplementation on postoperative pain intensity at regular intervals

Secondary Objectives:

- To compare the total analgesic consumption in the first 48 hours after surgery between the groups.
- To note the occurrence of any adverse effects in the groups related to probiotic or placebo administration.

MATERIALS AND METHODS:

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of BHAARATH INSTITUTE OF HIGHER EDUCATION AND RESEARCH (BIHER), prior to the initiation of the trial.

All participants received a comprehensive patient information sheet, available in both local language Tamil and in English, detailing the study's objectives, procedures, risks, and benefits. Written informed consent was obtained from all participants or their legal representatives before enrollment. Participants were assured of their right to withdraw at any point without impacting their standard care. Confidentiality of all collected data was strictly maintained throughout the study.

This study was designed as a prospective, randomized, double-blind, placebo-controlled clinical trial. A convenience sampling of total 66 patients was taken.

Inclusion criteria included adult patients aged 18–60 years, ASA physical status I or II, and scheduled for elective, non-emergency surgery under spinal anesthesia, for surgeries namely open appendectomy, hydrocele, inguinal herniorrphy, hemorrhoids, and sphincterotomy.

Exclusion criteria included unwilling patients, a history of chronic pain, regular use of probiotics or antibiotics within the past 4 weeks, gastrointestinal disorders, immunosuppression, or known allergy to any of the components in the probiotic or placebo capsules.

The participants were divided in to two groups of 33 patients per group by BLOCK RANDOMISATION based on gender and type of surgery to ensure maintaining balance between both groups. The two groups were: Group C – which is a control group receiving placebo capsules and Group P – which is the group receiving probiotics. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes. Both participants and investigators involved in data collection and outcome assessment were blinded to group assignments throughout the study. All capsules were identical in appearance, taste, and packaging to ensure blinding.

Probiotic Group (Group P) participants received two capsules of a commercially available multi-strain probiotic formulation twice daily (BD), beginning two days prior to surgery. The probiotic was carefully selected from reputable brands - Healthy Hey's® and Himalayan Probiotic® . Control Group (Group C) participants received two identical placebo capsules twice daily following the same schedule.

On the day of surgery, all patients underwent standardized spinal anesthesia with 3.5ml of levobupivacaine heavy 0.5% and surgical protocols were appropriate to their procedure. The patients received no other analgesia intraoperatively.

Primary Outcome measured was Postoperative pain intensity, which was assessed using the Numerical rating scale (NRS) at regular time intervals of 6, 12, 24, hours postoperatively.

Secondary Outcomes Measured Were

- Requirement of additional post operative analgesia in the first 48 hours after surgery.
- Occurrence of any adverse effects related to probiotic or placebo intake, such as gastrointestinal symptoms (e.g., bloating, flatus, nausea, vomiting, constipation etc).

Postoperative analgesic administration was according to the pre-approved protocol for both study groups. All patients received standard non-opioid analgesia, primarily paracetamol 1g administered twice daily (BD), as part of routine postoperative care. If pain persists, they will receive Inj. Tramadol 50mg IV bd. If pain persists even then, opioid Inj. Morphine 0.1mg/kg IV bd will be given.

Statistical Analysis

Statistical analysis was performed by STATA 11 software using the non-parametric Mann- Whitney test for comparisons between two groups, and one – way ANOVA with Bonferroni's post – hoc test for multiple comparisons. Paired and unpaired t tests, chi square tests were used as required. The data were presented as the mean ± standard deviation (SD) in all analysis, and p value of < 0.05 was taken to indicate statistical significance.

Table 1: Comparison Of Demographic Data

	Group C	Group P	"p" value	Interpretation of "p" value
Age in years	43.1 ± 11.2	42.3 ± 10.5	0.7656	Not significant
Males	16	17	0.8064	Not significant
Females	17	16	0.8064	Not significant
BMI	24.9 ± 2.6	24.7 ± 2.3	0.7417	Not significant

All p-values < 0.05 indicate statistically significant difference.

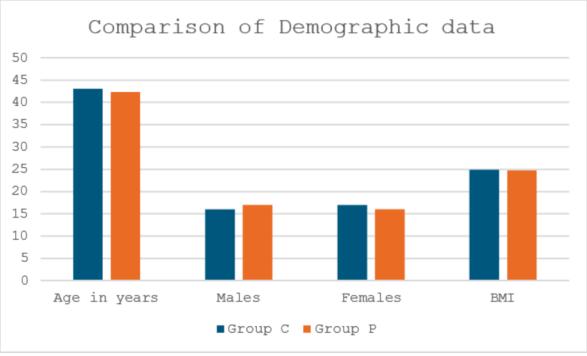
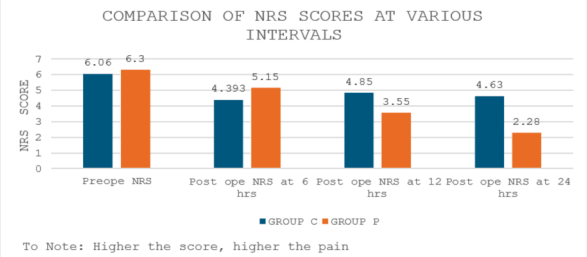


Table 2: Comparison Of NRS Scores At Various Intervals & Additional Post Operative Analgesia Requirement

	Group C	Group P	"P" value	Interpretation of "p" value
Preope NRS	6.06	6.3	0.595	Not significant
Post ope NRS at 6 hrs	4.393	5.15	0.0981	Not significant
Post ope NRS at 12 hrs	4.85	3.55	0.0001	Highly significant
Post ope NRS at 24 hrs	4.63	2.28	0.0001	Highly significant
Additional Post operative requirement of Tramadol	15 (45.45 %)	9 (27.27 %)	0.1276	Not significant
Additional Post operative requirement of Morphine	0	0		

All p-values < 0.05 indicate statistically significant difference.



RESULTS:

All participants completed the 48-hour postoperative follow-up. There were no losses to follow-up, or protocol deviations.

1. There were no statistically significant differences among the groups in the demographics or type of surgeries the participants were subjected to.
2. There were no statistically significant differences among the groups in the preoperative NRS or the postoperative NRS at 6 hours.
3. There was a highly statistically significant difference among the groups in the postoperative NRS at 12 and 24 hours, with lesser pain in Group P (Probiotic group).
4. There were no statistically significant differences among the groups in the requirement of postoperative analgesia, though the actual number of patients requiring such was lesser in probiotic Group P.
5. No adverse events or postoperative complications were reported in either the probiotic or placebo groups. All patients tolerated the oral capsules (probiotics/placebo) well, with no cases of gastrointestinal intolerance, such as nausea, vomiting, abdominal discomfort, or diarrhoea.

DISCUSSION:

Post operative pain management is crucial for a good surgical outcome. Conventional pain management strategies with NSAIDs, opioids, and regional anaesthesia are often accompanied by side effects and efficacy may vary[3]. Research is directed towards other adjunct pharmacological approaches to enhance pain control and decrease the reliance on conventional analgesics. One emerging area of research is on the gut microbiome, which is said to have a role in modulating pain and inflammation[4].

Dysbiosis, which is an imbalance in microbial populations has been linked to heightened pain sensitivity and is seen in conditions such as irritable bowel syndrome, fibromyalgia, and postoperative recovery[5]. Probiotics, are defined[6] as "live microorganisms that confer health benefits when administered in adequate amounts, offer a promising means of modulating the gut microbiome".

Hence, this randomized controlled trial aimed to assess the effect of preoperative probiotic supplementation on postoperative pain levels among patients undergoing elective general surgery under spinal anaesthesia. Since pain varies with the type of surgery and gender among many factors; by block randomisation; we ensured equal number of same type of surgeries in either group, namely Inguinal Hernioplasty 10, Hydrocele 7, Haemorrhoid 6, Open Appendicectomy 5 and Sphincterotomy 5; and balanced the gender distribution in each of the groups.

In our study, probiotics were administered for two days prior to surgery. The high-dose probiotic supplementation (200 billion CFU/day) used in our trial is sufficient for gut recolonization. Research has shown that gut microbes are regularly purged, double in number within one hour and within 24–48 h of a dietary intervention rapid changes occur in the gut microbiome[7]. The findings in our study showed that there was a highly statistically significant difference among the groups in the postoperative pain scores (NRS) at 12 and 24 hours, with lesser pain in Probiotic Group P. This is similar to the research findings by Masaud etal[8]. And Jorgensen etal[9].

The reasons for the pain reduction on probiotic administration are said to be due to various causes, acting via the gut-brain axis. The gut microbiota exerts effects on host immunity, metabolic function, and neural pathways[10]. They alter inflammatory responses, nociceptive processing, and pain sensitivity[11]. Research has shown that certain probiotic strains reduce pro- inflammatory cytokines, enhance gut barrier integrity, and modulate neuro immune signalling, particularly in the context of surgical trauma[12].

Certain strains of Lactobacillus and Bifidobacterium have demonstrated anti-inflammatory effects, improved intestinal barrier integrity, and the ability to modulate gut-brain communication[13]. In our study, we gave capsules from reputable brands - Healthy Hey's® and Himalayan Probiotic® - both of which contain clinically studied strains, such as Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus casei, Lactobacillus casei Shirota and Bifidobacterium lactis.Another mechanism of action for pain reduction by gut microbiome is to activate quorum sensing (QS), which is a cell-density–dependent microbial communication system[14]. They interfere

with QS pathways by a process known as quorum quenching which leads to reduced virulence factor expression and biofilm formation in pathogenic bacteria[15]. All these mechanisms offer a plausible explanation for the observed trend towards lower postoperative pain scores in the probiotic group.

In our study, there were no statistically significant differences among the groups in the requirement of postoperative analgesia, though the actual number of patients requiring such analgesia was lesser in probiotic Group P. No adverse events or complications were reported in either the probiotic or placebo groups. In the doses we administered, all patients tolerated the oral capsules (probiotics/placebo) well, with no cases of gastrointestinal intolerance, such as nausea, vomiting, abdominal discomfort, or diarrhoea.

However, limitations in our study must be acknowledged and this being that; Pain perception is inherently subjective, and psychological factors associated with pain perception were not assessed. Further research can be done in this field of probiotic administration as an adjunct to post operative pain management, in larger populations, evaluating probiotic use in different types of surgeries / anaesthesia techniques and in investigating various molecular pathways linked to pain modulation.

CONCLUSION:

The findings of this study suggest that preoperative probiotic supplementation may serve as a promising adjunct in postoperative pain management in elective general surgical patients with ease of oral administration and excellent safety profile; which may help in enhanced recovery.

Conflict Of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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This research received no external funding. All study-related expenses, including probiotic supplementation, materials, and data management, were personally borne by the investigators.

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