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Original Research Article

A prospective, randomized, assessor blinded, active controlled, single center, phase IV clinical trial to compare the efficacy and safety of two different formulations of drotaverine in patients with spasmodic pain

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Abstract

Background: Spasmodic pain resulting from smooth muscle contraction is a common clinical concern in outpatient department (OPD) as well as in emergency setup. Drotaverine, a phosphodiesterase- 4 inhibitor, is widely used for its antispasmodic properties. A novel drotaverine 40 mg tablet formulation was developed with improved disintegration and dissolution profiles to achieve faster symptomatic relief.

Aim and Objective: The objective of this clinical trial was to evaluate and compare the efficacy and safety of two drotaverine tablet formulations in patients experiencing spasmodic pain.

Materials and Methods: This prospective, randomized, assessor-blinded, active-controlled, single-center phase IV clinical trial compared the efficacy and safety of advanced drotaverine 40 mg formulation (Indoco Remedies Ltd.) with the conventional formulation in patients aged 18–65 years experiencing acute spasmodic pain due to renal colic, gastrointestinal spasms, or primary dysmenorrhea.

Results: A total of 100 patients were randomized equally to receive either formulation, with pain intensity assessed using the Visual Analog Scale (VAS) over a 6-hour observation period. The primary endpoint, Sum of Pain Intensity Difference over 6 hours (SPID-6), showed no significant difference between the test and reference groups (-28.2 ± 2.3 vs. -26.9 ± 2.3; $p = 0.73$). However, the test formulation achieved significantly greater mean Pain Intensity Differences (mPID) at 15, 30, 45, and 60 minutes ($p < 0.05$), indicating faster onset of pain relief. At 6 hours, ≥50% pain relief was achieved in 98% (test) and 96% (reference) of patients. Perceived onset of action within 15 and 30 minutes was significantly higher in the test group (22% vs. 8% and 80% vs. 46%, respectively; $p < 0.05$). Both formulations were well tolerated, with mild adverse events such as nausea, fatigue, and dizziness reported in 7% of patients, and no serious adverse events or discontinuations.

Conclusion: While overall pain relief was comparable, the advanced drotaverine formulation provided a faster onset of action, offering a clinical advantage in managing acute spasmodic pain.

Keywords: Drotaverine, Advanced formulation, Rapid pain relief, Spasmodic pain

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1. Introduction

Pain is a multifaceted physiological sensation that can be categorized as either nociceptive or neuropathic.[1,2] Smooth muscle spasms are a frequent cause of abdominal discomfort.[3] Symptoms like abdominal pain, cramping, or general discomfort affect nearly half of the population. In primary care settings, approximately one in ten individuals report such issues. Common conditions including menstrual cramps, renal colic, biliary colic, and spasms in the genitourinary tract are often attributed to smooth muscle contractions.[4]

Antispasmodic agents work by relaxing smooth muscles or inhibiting excitatory neuromuscular signals.[5] They are a key therapeutic option for managing conditions involving smooth muscle spasms.[6-10] Drotaverine is an antispasmodic agent that acts by inhibiting phosphodiesterase-4 (PDE4) used for relieving symptoms in various gastrointestinal conditions, biliary dyskinesia, and also in managing dysmenorrhea, facilitating abortion, and aiding in labour augmentation.[11,12]

Clinical evidence supports the effectiveness of drotaverine in managing various types of spasmodic pain,

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offering consistent symptom relief in routine medical practice.[4,13] The fixed-dose combination (FDC) of drotaverine and other NSAID'S like mefenamic acid/ aceclofenac approved by the Central Drugs Standard Control Organisation (CDSCO) for use in adult patients experiencing muscle pain linked to spasms.[14] The combination offers prompt pain relief by leveraging drotaverine's antispasmodic effects along with the anti-inflammatory action of aceclofenac.[15]

Traditional antispasmodics, drotaverine formulations often face challenges like inconsistent release, slow onset of action in some patients that leads to delayed pain relief and can affect patient satisfaction. There is a growing need for rapid-onset, effective therapy especially in Anti-spasmodic segment. To satisfy this need, Indoco Remedies Ltd. has developed fast-release drotaverine, scientifically engineered for rapid disintegration and enhanced dissolution. Its quick therapeutic response may makes it highly valuable in urgent care settings, including OPD, emergency, and gynecological practice, where timely pain relief is crucial. By delivering prompt symptom control, it will improve patient compliance, satisfaction, and overall outcomes, particularly in acute pain scenarios. Its clinical utility extends across a range of conditions such as irritable bowel syndrome (IBS), dysmenorrhea, renal and biliary colic, as well as post-operative spasm, making it a versatile and impactful therapeutic option.

According to in vitro dissolution study data, our advanced drotaverine tablet formulation demonstrated faster and more complete dissolution compared to conventional drotaverine preparations. An in vivo scintigraphy study showed that the advanced drotaverine formulation disintegrates more quickly and completely than the conventional version, with full breakdown occurring in the stomach (data on file). This rapid gastric disintegration may help to improve its therapeutic effect. These advancements may enhance treatment efficacy in terms of rapid onset of action, offering clear advantages over conventional generic formulations in managing various medical conditions.

2. Aim and Objective

To confirm whether the advanced drotaverine formulation truly offers benefits compared with the conventional formulation in patients suffering from spasmodic pain, we conducted a Phase IV, prospective, randomized, assessor-blinded, and active-controlled single-center clinical trial.

3. Materials and Methods

3.1. Study design

This study was designed as a prospective, randomized, assessor-blinded, active-controlled, single-center phase IV clinical trial

3.2. Study population

The trial was conducted at a single center in India. Enrolled patients between aged 18 to 65 years of either gender with a confirmed diagnosis of acute spasmodic pain, including renal colic, gastrointestinal spasms, or acute primary dysmenorrhea. Eligible participants had a baseline pain intensity of at least 40 mm on the Visual Analog Scale (VAS), indicating moderate to severe pain requiring drotaverine treatment. A total of 100 patients were included in the study (**Table 1**). All 100 randomized patients completed the study as per protocol, and were thus included in the final analysis (**Figure 1**).

3.3. Dosing regimen

Participants in the study were randomly assigned to receive either the test formulation (advanced drotaverine 40 mg) or the reference formulation (conventional drotaverine 40 mg) at the study site. All eligible subjects were observed for a minimum of six hours following administration of the study drug to allow for continuous monitoring. No concomitant medications were administered during this six-hour observation period.

3.4. Treatment procedures

This study enrolled patients diagnosed with acute spasmodic pain such as renal colic, gastrointestinal spasms, or acute primary dysmenorrhea—who were deemed eligible for drotaverine treatment. Following screening, all participants were continuously monitored for at least six hours after receiving the study medication. Baseline evaluations were performed during Assessment 1 (Screening and Dosing). Follow-up assessments (Assessments 2 through 9) were carried out at 15, 30, 45, and 60 minutes, and then at 1.5, 2-, 3-, 4-, and 5-hours post-dose. The final assessment (Assessment 10) marked the end of the study. This two-arm trial required all participants to take the assigned study medication as instructed.

On Day 0, written informed consent was obtained from all patients prior to screening. Those with acute spasmodic pain were evaluated according to inclusion and exclusion criteria, with demographic details, medical history, vital signs, clinical examination findings, and concomitant diseases or medications documented. Female patients of childbearing potential underwent a urine pregnancy test. Eligible participants were randomized to receive either the test or reference product and instructed to avoid prohibited medications. Baseline pain intensity was assessed using the Visual Analog Scale (VAS), and any adverse events (AEs) were recorded.

During follow-up, VAS scores were documented at 15, 30, 45, and 60 minutes, and at 1.5, 2, 3, 4, and 5 hours post-dosing, along with AE monitoring. At 6 hours, vitals and clinical examination were repeated, the final VAS score was recorded, and any AEs during this period were noted.

3.5. Laboratory investigations

Urine Pregnancy Test (UPT) was done at before randomization for females of childbearing age, as per the investigator's discretion. The detailed demographic & baseline characteristics of the patients enrolled in the study are shown in **Table 2**.

3.6. Outcomes

3.6.1. Efficacy outcome

1. Primary endpoint: The primary endpoint was the sum of Pain Intensity Difference over 6 hours (SPID-6) in the two arms from baseline to 6 hours, using the VAS.
2. Secondary endpoints: The secondary endpoints assessed were the mean pain intensity difference (mPID) at multiple time points up to 6 hours post-dose using the VAS, the proportion of patients achieving at least 50% pain relief or total pain relief (TOTPAR) at 6 hours, the distribution of perceived onset of pain relief across predefined time intervals (<15 minutes, 16–30 minutes, 31–60 minutes, and >60 minutes), and the proportion of patients withdrawn due to lack of response who required rescue medication.

For the efficacy analysis, the modified Intention to treat (mITT) and Per Protocol (PP) populations were found to be equal, with 50 patients in each arm. As both populations were identical, a single unified analysis was conducted

3.6.2. Safety outcome

The safety endpoints were adverse events and serious adverse events reported during the study. All the subjects who have used at least a single dose of the study drug were considered for the safety analysis.

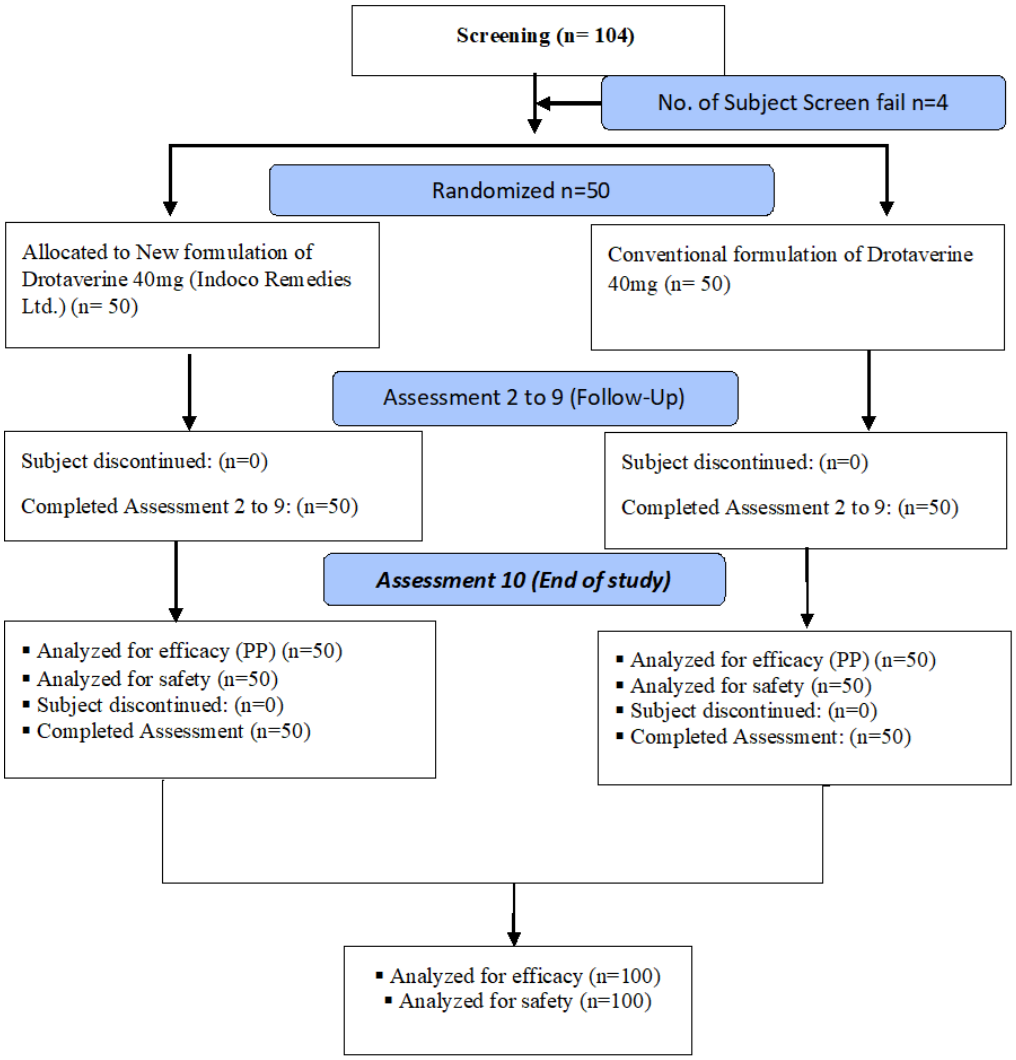

Figure 1: Flow of patients in the study

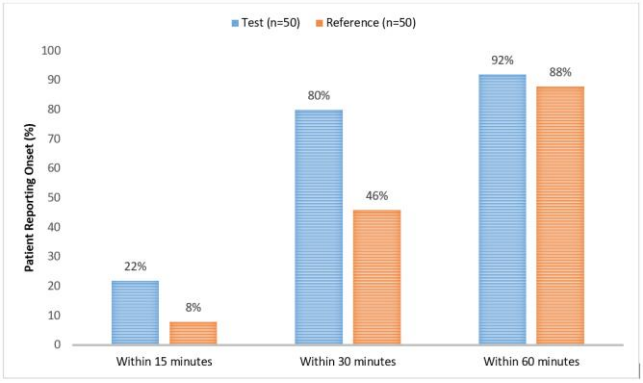

Figure 2: Patient-reported onset of action following administration of test and reference formulations within 15, patient-reported onset of action: Test vs. Reference at 15, 30 and 60 minutes

4. Results

4.1. Primary efficacy endpoint

4.1.1. Sum of pain intensity difference over 6 hours (SPID-6) in the two arms from baseline to 6 hours, using the VAS.

The SPID-6 (Sum of pain intensity differences over 6 hours) values were comparable between the Test and Reference groups. The Test group demonstrated a mean SPID-6 of -28.2 ± 2.3, while the Reference group showed a mean of -26.9 ± 2.3. These negative values indicate a reduction in pain intensity over the 6-hour observation period, with greater negative values reflecting greater pain relief. Although both formulations were effective in reducing pain, the difference between the groups was minimal and not statistically significant ($p = 0.73$) (**Table 3**).

4.2. Secondary Efficacy Endpoints

4.2.1. Mean Pain Intensity Difference (mPID) measured at 15, 30, 45, 60 minutes, and at 1.5,2, 3-, 4-, 5-, and 6-hours post-dose from baseline in the two arms, using the VAS.

Significant differences in pain reduction were observed at 15, 30, 45, and 60 minutes post-dosing, with the Test group demonstrating greater relief compared to the Reference group ($p < 0.05$).

From 1.5 hours onward, no statistically significant differences were observed between the Test and Reference groups ($p > 0.05$). While the Test group exhibited more rapid pain relief in the initial phase, both groups achieved comparable levels of pain reduction during the later time points (3 to 6 hours)(**Table 4**).

4.2.2. Percentage of patients achieving ≥ 50% pain relief or Total Pain Relief (TOTPAR) at 6 hours post-dose from baseline in the two arms based on VAS.

At 6 hours post-dose, 98% of patients in the Test group (49 out of 50) and 96% in the Reference group (48 out of 50) experienced ≥50% pain relief. Both formulations demonstrated high efficacy in relieving pain, with a slight advantage observed in the Test group. However, the difference was minimal, suggesting that both versions of drotaverine were similarly effective within the 6-hour evaluation period (**Table 5).**

4.2.3. Percentage of patients perceived onset of pain relief in less than 15 minutes, between 16-30 minutes, 31 to 60 minutes, more than 60 minutes post-dose from baseline in the two arms

When evaluated at 15 minutes, 22% of patients (11 out of 50) In the Test group reported a perceived onset of action, whereas only 8% (4 out of 50) in the Reference group reported the same. Conversely, 78% of patients in the Test group and 92% in the Reference group did not perceive a distinct onset of action.

A chi-square test yielded a p-value of <0.05, indicating a statistically significant difference between the two groups. A higher proportion of patients in the Test group reported perceiving the onset of action compared to those in the Reference group (**Table 6**, **Figure 2**)

When evaluated at 30 minutes, 80% (40 out of 50) patients who received the test formulation, reported a perceived onset of action, compared to 46% (23 out of 50) in the reference group. In contrast, 20% (10 patients) in the test group and 54% (27 patients) in the reference group did not report any onset of action. This difference was statistically significant ($p < 0.05$), indicating that the test formulation was more likely to produce a noticeable onset of action within 30 minutes (**Table 6**).

When evaluated at 60 minutes, 92% (46 patients out of 50) who received the test formulation, reported a perceived onset of action, compared to 88% (44 patients) in the reference group. Conversely, 8% (4 patients) in the test group and 12% (6 patients) in the reference group did not report an onset of action. The difference between the two groups was not statistically significant ($p = 0.50$), indicating no meaningful difference in the perceived onset of action within 60 minutes (**Table 6**, **Figure 2**). The proportion of patients withdrawn and given rescue medication in lack of response to the treatment were none.

4.3. Safety outcome

4.3.1. Adverse events (AE)

All adverse events (AEs) documented in the Case Report Forms (CRFs) were included in the AE listings. A total of 35 AEs were reported among 35 patients, representing 7.0% of the study population. Of these, 33 events were classified as mild (Grade 1), while two were of moderate severity. All AEs resolved completely, either with or without medical intervention. No clinically significant changes were observed in vital signs, systemic examinations, or laboratory parameters at the end of the study compared to baseline (**Table 7**).

4.3.2. Serious adverse events (SAEs), unexpected adverse events, and discontinuation of the study due to adverse events

No SAE, unexpected adverse events were reported in any patient in this study. None of the patients discontinued the study due to AEs.

4.3.3. Severity and association of adverse events reported in the study

The grades of severity and the association of the AEs reported in the study are detailed in the **Table 8**.

Table 1: Patient disposition during the study

Parameter	Test	Reference
No. of patient's assessment 1 (randomization & dosing):	50	50
No. of patient's assessment 2-9	50	50
No. of patient's assessment 10	50	50
No. of patients analyzed for Safety	50	50

Table 2: Demographic and baseline characteristics of the enrolled patients.

Parameters		Test(n=50)	Reference (n=50)
Age (years)*	18 – 40	3 (6%)	4 (8%)
	40 – 60	45 (90%)	44 (88%)
	> 60	2 (4%)	2 (4%)
Gender*	Male	34 (68%)	32 (64%)
	Female	16 (32%)	18 (36%)
Indication*	Acute renal colic	20 (40%)	19 (38%)
	Acute gastrointestinal spasms	26 (52%)	27 (54%)
	Acute primary dysmenorrhea	4 (8%)	4 (8%)
Baseline VAS score# (P=0.34)~		7.74 ± 1.08	7.52 ± 1.22

*Data presented as n (%)
#Data presented as mean ± SD
~P-value calculated by unpaired t-test.

Table 3: Assessment of post-dose efficacy of test and reference formulations using SPID-6 from baseline

Parameters	Test (n=50)	Reference (n=50)	P-value#
SPID-6*	-28.2 ± 2.3	-26.9 ± 2.3	0.73

*Data presented as mean ± SD
#P-value calculated by unpaired t-test.
SPID-6: Sum of pain intensity difference over 6 hours using the visual analog scale (VAS).

Table 4: Efficacy evaluation of test and reference formulations based on post-dose mPID from baseline

Parameters		Test (n=50)	Reference (n=50)	P-value#
mPID*	15mins	1.14 ± 0.40	0.94 ± 0.31	<0.05
	30mins	2.7 ± 0.65	2.24 ± 0.66	<0.05
	45mins	3.54 ± 0.76	3.06 ± 1.04	<0.05
	60mins	3.86 ± 0.83	3.44 ± 1.09	0.03
	1.5 hours	4.42 ± 1.09	4.08 ± 1.14	0.13
	2 hours	4.84 ± 1.17	4.56 ± 1.18	0.23
	3 hours	5.06 ± 1.11	4.86 ± 1.32	0.41
	4 hours	5.44 ± 1.09	5.28 ± 1.28	0.50
	5 hours	5.62 ± 1.16	5.54 ± 1.33	0.74
	6 hours	5.88 ± 1.19	5.74 ± 1.43	0.59

*****Data presented as mean ± SD
#P-value calculated by unpaired t-test.
mPID: mean Pain Intensity Difference at various post-dose time intervals from baseline

Table 5: Efficacy evaluation of test and reference formulations based on TOTPAR from baseline

Parameters	Test (n=50)	Reference (n=50)
TOTPAR or ≥50% pain relief *	49 (98%)	48 (96%)

*Data presented as n (%)
TOTPAR: Total Pain Relief at post-dose 6 hours from baseline

Table 6: Patient-reported onset of action following administration of test and reference formulations within 15, 30 and 60 minutes.

Time after administration	Perceived onset of action	Test (n=50)*	Reference (n=50)*	P-value#
Within 15 minutes	Yes	11 (22%)	4 (8%)	<0.05
	No	39 (78%)	46 (92%)	
Within 30 minutes	Yes	40 (80%)	23 (46%)	<0.05
	No	10 (20%)	27 (54%)	
Within 60 minutes	Yes	46 (92%)	44 (88%)	0.5
	No	4 (8%)	6 (12%)	
*Data presented as n (%). #P-value calculated by chi-square test.				

Table 7: Adverse events reported in the study

Adverse event term	Test (n=50)*	Reference (n=50)*
Nausea	3 (6%)	4 (8%)
Fatigue	2 (4%)	3 (6%)
Dizziness	1 (2%)	1 (2%)
Data presented as n(%); % calculated from No. of patients analyzed for safety		

Table 8: Severity and association of adverse events reported in study

Sr. No.	Adverse event	No. of events	Severity		Association	
			Test (50) *	Reference (50) *	Test (50) *	Reference (50) *
1	Nausea	7	Mild 3 (6%)	Mild 4 (8%)	Not-Related 3 (6%)	Not-Related 4 (8%)
2	Fatigue	5	Mild 2 (4%)	Mild 3 (6%)	Not-Related 2 (4%)	Not-Related 3 (6%)
3	Dizziness	2	Mild 1 (2%)	Mild 1 (2%)	Not-Related 1 (2%)	Not-Related 1 (2%)
*Data presented as n; % of events % calculated from No. of AEs reported						

5. Discussion

The primary objective of this Phase IV clinical trial was to evaluate and compare the efficacy and safety of two drotaverine 40 mg formulations in the treatment of acute spasmodic pain. The study compared advanced formulation of drotaverine (manufactured by Indoco Remedies Ltd.) referred to as the test product with the conventional formulation, serving as the reference product.

Efficacy analysis of the primary endpoint, the sum of pain intensity difference over 6 hours (SPID-6), revealed no statistically significant difference between the test and reference groups ($p = 0.73$). These findings indicate that both formulations offered comparable levels of pain relief at the 6-hour assessment point.

A more detailed analysis of the mean pain intensity difference (mPID) at individual time points post-dose revealed statistically significant differences during the early phase of treatment. At 15, 30, 45, and 60 minutes, the test formulation demonstrated a significantly greater mPID compared to the reference formulation, suggesting that the test product provided faster pain relief in the initial hours following administration. For instance, at the 15-minute mark, the mean reduction in pain was notably higher in the test group, with a p-value of <0.05. These findings support the hypothesis that the advanced formulation may offer a quicker onset of action.

The Total Pain Relief (TOTPAR) analysis further confirmed the effectiveness of both formulations, with 98% of patients in the test group and 96% in the reference group experiencing at least a 50% reduction in pain at 6 hours post-dose. While the overall extent of pain relief was comparable between the groups, the quicker onset observed with the test formulation may offer a clinical advantage particularly for patients requiring rapid relief from acute spasmodic pain.

A notable difference was observed in the perceived onset of action between the two formulations. At 15 minutes, 22% of patients in the test group reported experiencing relief, compared to only 8% in the reference group. By 30 minutes, these figures increased to 80% and 46%, respectively—indicating a significantly faster onset with the test formulation. These results are particularly relevant in clinical settings where rapid symptom relief is crucial, such as in cases of renal colic or gastrointestinal spasms.

Although both formulations were effective overall, the faster onset associated with the advanced formulation offers a clear clinical advantage, making it a potentially preferred choice in situations requiring prompt intervention.

Both formulations exhibited comparable safety profiles. The most frequently reported adverse events were mild in nature, including nausea, fatigue, and dizziness. While the reference group showed a slightly higher incidence of nausea and fatigue, these differences were minimal and not clinically significant. Importantly, no serious adverse events occurred, and no patients discontinued the study due to adverse effects. These findings confirm that both drotaverine formulations were well tolerated, with safety outcomes aligning with the known profile of the drug.

The absence of serious adverse events (SAEs) in this study further reinforces the safety of both formulations in the treatment of acute spasmodic pain. This finding offers reassurance that both the test and reference products can be safely used in the intended patient population without presenting significant safety concerns.

6. Conclusion

This prospective, randomized clinical trial evaluated the efficacy and safety of advanced formulation of drotaverine 40 mg (Indoco Remedies Ltd.) compared to the conventional formulation in patients with spasmodic pain. The findings revealed no statistically significant difference in overall pain relief, as measured by SPID-6, or in general efficacy between the two groups. However, the advanced formulation offered a clear advantage in terms of faster onset of action. Patients receiving the test formulation experienced significantly greater mean Pain Intensity Differences (mPID) during the first 60 minutes post-administration, particularly at the 15-, 30-, 45-, and 60-minute intervals, indicating more rapid pain relief.

7. Clinical Implications

In today's fast-paced healthcare environment, patients expect quick results. Fast-release advanced drotaverine tablet formulation aligns perfectly with those expectations enhancing treatment satisfaction, reducing the need for secondary interventions, and increasing patient confidence in their care.

8. Abbreviations

PDE-4-phosphodiesterase 4, AE-adverse event, CRF-case report form, GI-gastrointestinal, mPID-mean pain intensity difference, PP-per protocol, SAE- serious adverse event, SPID-6-sum of pain intensity difference over 6 hours, TOTPAR- total pain relief, UPT-urine pregnancy test, VAS-visual analog scale, mITT-modified intention to treat.

9. Ethical Statement

This work was conducted according to the declaration of Helsinki and approved by the Institutional Ethics Committee. Written informed consent was obtained from the volunteers at the time of their enrolment in the study.

10. Source of Funding

Sponsorship for this study and its publication, was funded by Indoco Remedies Limited, India.

11. Conflict of Interest

All authors are the employees of Indoco Remedies Limited, a pharmaceutical company in India involved in the development and sponsorship of the products evaluated in this study.

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