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Research Article

Adverse drug reactions and cost effectiveness of non-steroidal anti-inflammatory drugs, muscle relaxants, and neurotropic drugs in patients with low back pain

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ABSTRACT

Background: The objective was to evaluate the adverse drug reactions (ADRs) and cost effectiveness of different classes of drugs in therapy of low back pain.
Methods: A prospective observational study was carried out over a period of 12 months (November 2012 to November 2013) in which a total of 300 patients with low back pain were enrolled and divided equally into three groups – Group 1 (non-steroidal anti-inflammatory drugs [NSAIDs]), Group 2 (NSAIDs ± muscle relaxant), and Group 3 (NSAIDs ± muscle relaxant ± neurotropic drugs). Any ADR developed after the initiation of treatment at 3 weeks and 6 weeks was noted. Prescription cost per day was also calculated.
Results: There was a male predominance in the study population with a mean age of 39.76±9.40 years. A total of 262 ADRs were noted among which most were seen in Group 3 (119 ADRs). Gastritis was the most common ADR in Group 1. Drowsiness was the most common ADR in Group 2 (30%) and 3 (46%). Prescription cost per day was highest in Group 3 (30.28±11.24 Indian Rupee [INR]) followed by Group 2 (25.92±8.66 INR) and Group 1 (12.22±3.38 INR).
Conclusion: Patient on combination of three drugs (NSAIDs, muscle relaxants, and neurotropic agents) had maximum ADRs and their prescription cost per day was highest among the three groups.

Keywords: Adverse drug reactions, Cost effectiveness, Low back ache, Muscle relaxant, Neurotropic drugs, Non-steroidal anti-inflammatory drugs

INTRODUCTION

Low back pain is second most common cause and nonspecific mechanical low back pain is fifth most common cause of physician visits in the United States; accounting for approximately 2.8% of all physician visits.[1,2] The annual prevalence of low back pain in United States is 15-45% and costs over $100 billion to exchequer. This includes one-third direct cost and two-third indirect cost.[3,4] In modern society, about 80% of the population will experience back pain at some time during their life.[5] About 10% of the population in the United States suffer from chronic back pain and is one of the main reason for disability.[6] Almost 1% of the United States population is chronically disabled because of back pain.[4] In India, 60% of the population experience low back pain once in their entire life.[7,8]

The low back pain may be due to congenital anomalies of the lumbar spine, trauma: either minor trauma like sprain or strain or major trauma like fractures, intervertebral disk herniation, degenerative changes, and infection or inflammation in the spinal cord. Low back pain is classified as acute low back pain without radiculopathy, chronic low

back pain without radiculopathy and low back pain with radiculopathy. Acute low back pain without radiculopathy is defined as pain of less than 3 months duration. Non-steroidal anti-inflammatory drugs (NSAIDs) are first-line options for the treatment of acute low back pain. Skeletal muscle relaxants may be useful as well. Chronic low back pain without radiculopathy is defined as pain of more than 3 months duration. Treatment for chronic low back pain includes combination of NSAIDs and skeletal muscle relaxants plus exercise therapy which includes stretching exercises, aerobic exercises, and strengthening exercises. Low back pain with radiculopathy is defined as back pain with pain radiating down the leg depends on herniated disc with nerve root impingement. NSAIDs are appropriate for pain relief, although severe pain may require a short course of opioid analgesics or neurotropic agents like pregabalin or gabapentin. Patients who have progressive motor weakness or nerve root injury or cauda equina syndrome may require surgery.[4] There are various other approaches to relieve pain other than drug therapy like physiotherapy, acupuncture, lumbar support, yoga, etc., but drug therapy remains the mainstay for treatment of low back pain. Drug therapy causes symptomatic relief only; it does not cure the condition responsible for pain as pathophysiology of back pain is not clear.[9] However, the effectiveness of various drugs used in low back pain, their safety and cost involved is not fully explored.

Hence, this study was undertaken to assess adverse drug reactions (ADRs) of NSAIDs, muscle relaxants, and neurotropic drugs for low back pain and their cost effective analysis.

METHODS

A prospective observational study was carried out in the Department of Pharmacology, Kasturba Medical College and Department of Orthopedics, Kasturba Hospital, Manipal University, Manipal for a period of 12 months. Institutional Ethics Committee clearance was obtained before initiation of the study. A total of 300 patients with low back pain were enrolled in the study.

Subject selection criteria were as follows:
Inclusion Criteria

1. Patients (only outpatients) of both sex and who presented with low back pain
2. Patients whose magnetic resonance imaging suggests disc prolapse which could be managed by drugs.

Exclusion Criteria

1. Patient with congenital and developmental conditions like kyphoscoliosis, spina bifida occulta, tethered spinal cord syndrome
2. Any spinal infections like tuberculosis spine
3. Patients with spinal neoplasm, metastatic or primary bone tumors
4. Patients already presenting with significant neurological deficits.

Patient fulfilling the study criteria were enrolled after obtaining written informed consent.

They were divided into three different groups depending on the treatment they received. Patients who received only NSAIDs were recruited in Group 1. Patients who received only muscle relaxants like, thiocolchicoside, tizanidine, etc. or combinations of NSAIDs and muscle relaxants were recruited in Group 2. Group 3 included patients who received only neurotropic drugs like pregabalin, gabapentin, tramadol, etc., or combinations of NSAIDs and/or muscle relaxants and/or neurotropic drugs.

After taking the baseline demographic characteristics and recording the different drugs being prescribed the patients were followed up. The ADRs of patients in three groups were recorded in a suitably designed Central Drugs Standard Control Organization suspected ADR reporting form. Causality assessment was done using the WHO-UMC causality assessment system.[10] Cost analysis of prescribed drugs was done. Prescription cost per day was calculated by using details from patient's bills.

Statistical analysis

ADRs and cost were analyzed using a descriptive approach. Data were analyzed using SPSS software version 20.

RESULTS

A total of 300 patients with low back pain and put on study treatment were followed up for 6 weeks after treatment initiation. Of these, 172 patients were males showing a male preponderance (57.3%). Mean age of patients in study population was 39.76±9.40 years. Table 1 show that the majority of patients (54.33%) were in the age group of 21-40 years.

Of total 300 patients, 78.33% of patients received NSAIDs either alone or in combination, 73% of patients received muscle relaxants either alone or in combination and 36.33% of patients received neurotropic drugs either alone or in combination. As shown in Table 2, 43.33% received aceclofenac and paracetamol combination followed by thiocolchicoside (40.67% of patients). 60.67% of patients received proton pump inhibitors along with NSAIDs.

A total of 222 patients (74%) developed ADRs. Totally 262 ADRs were reported and divided according to treatment groups as shown in Table 3. Maximum number of ADRs were encountered by neurotropic drugs (119 ADRs) followed by 104 ADRs by muscle relaxants and 39 in NSAIDs group. Gastritis was most common ADR in NSAIDs group (24%). Drowsiness was most common ADR in muscle relaxant

group (30%) and neurotropic drugs group (46%). All ADRs were classified as "possible" according to WHO-UMC causality assessment system.

Table 1: Age wise distribution of study population.

Age group (in years)	Number of patients (%)
<20	1 (0.33)
21-40 (adult age group)	163 (54.33)
41-60 (middle age group)	130 (43.33)
>61	6 (2)

Table 2: Drug utilization pattern among study groups.

Drug group	Drug name	Number of patients (%)
NSAIDs	Aceclofenac+ paracetamol	130 (43.33)
	Diclofenac	105 (35)
Muscle Relaxant	Thiocolchicoside	122 (40.67)
	Tizanidine	97 (32.33)
Neurotropic agents	Pregabalin	83 (27.67)
	Tramadol	26 (8.67)
Others	Pantoprazole	98 (32.67)
	Rabeprazole	84 (28)

Table 3: ADR analysis.

Drug group	ADR	Number of ADR (%)
NSAIDs	Gastritis	24 (24)
	Vomiting	11 (11)
	Dizziness	03 (3)
	Headache	01 (1)
	Total	39
Muscle relaxants	Drowsiness	30 (30)
	Dry mouth	22 (22)
	Gastritis	18 (18)
	Fatigue	17 (17)
	Dizziness	12 (12)
	Vomiting	05 (5)
	Total	104
Neurotropic drugs	Drowsiness	46 (46)
	Fatigue	23 (23)
	Dizziness	19 (19)
	Vomiting	16 (16)
	Dry mouth	06 (6)
	Gastritis	04 (4)
	Constipation	02 (2)
	Pruritus	02 (2)
	Headache	01 (1)
	Total	119

ADR: Adverse drug reaction, NSAIDs: Non-steroidal anti-inflammatory drugs

Table 4 shows the cost of each prescribed drugs. Cost of illness that is prescription cost per day is mentioned in Table 5, which shows that per day prescription cost (30.28±11.24) was higher in neurotropic drugs group followed by muscle relaxant group.

DISCUSSION

Low back pain is one of the common health problems in our society that causes disability, work absenteeism, and utilization of health care resources. Present study suggests that most of the patients (54.33%) with low back pain belong to age group of 21-40 years. Higher incidence of low back pain in the young and middle age group (21-40 years) as seen in the present study could be due to higher activity level and exposure to various stress.[11] Earlier studies also found that the incidence of low back pain was common in patients with age more than 40 years.[12,13]

In the present study, there was a male predominance (57.3%) as men are commonly involved in various strenuous activities in their daily life. Previous studies conducted in Australia,[12] England,[13] and Germany,[14] however reported that the incidence of low back pain was higher in females as compared to males. Reason for a high incidence of low back pain in males in this study could be due to cultural or economic reasons and also the fact that males seek medical advice more frequently than females in India.

Table 4: Cost of individual drugs.

Drug group	Drug (brand name)	Drug (generic name)	Cost per tablet (INR)
NSAIDs	Aceclo plus	Aceclofenac+ paracetamol	3.38
	Voveran	Diclofenac	3.75
Muscle relaxants	Myoril	Thiocolchicoside	11.8
	Sirdalaud	Tizanidine	15.58
Neurotropic drugs	Pregaba	Pregabalin	5.82
	Ultracet	Tramadol	8.2
Additional drugs	Pan-40	Pantoprazole	7.34
	Kyrab	Rabeprazole	7.18

NSAIDs: Non-steroidal anti-inflammatory drugs, INR: International normalized ratio

Table 5: Cost of illness.

Group	Cost (INR)/day (mean±SD)
NSAIDs	12.22±3.38
Muscle relaxants	25.92±8.66
Neurotropic drugs	30.28±11.24

NSAIDs: Non-steroidal anti-inflammatory drugs, INR: International normalized ratio, SD: Standard deviation

About 74% of patients developed ADRs and most of the ADRs were seen in neurotropic group (31.33%), followed by muscle relaxant group (29.66%) and NSAIDs group (13%) In NSAIDs group, the most common ADRs were related to gastrointestinal system, which included gastritis (24%) and vomiting (11%). Three patients developed dizziness and one patient developed headache. Consistent with our finding, a study conducted by Laine in California also found that upper gastrointestinal side effects occurred most commonly in NSAID users.[15] Despite ethnic variability, incidence of gastrointestinal side effects with NSAIDs in the present study was comparable to the above mentioned study.

In the muscle relaxant group, drowsiness (30%) was the most common ADR followed by dry mouth (22%), gastritis (18%), and fatigue (17%). Consistent with our finding, Saper et al. found that drowsiness (47%) was the most common side effect with muscle relaxants like tizanidine followed by dizziness (24%) and dry mouth (19%).[16]

In the neurotropic group, drowsiness (46%) was the most common ADR followed by fatigue (23%) and dizziness (19%). Consistent with above findings, Rosenstock et al. also found that neurotropic drugs like pregabalin had higher incidence of somnolence and dizziness like side effects.[17] Similarly, Langley et al. reported that dizziness, somnolence, vomiting, constipation, and headache were commonly seen with tramadol.[18]

All ADRs were mild to moderate in severity and did not require withdrawal of treatment. According to WHO-UMS causality assessment system, all these ADRs were classified as "possible" because all ADRs occurred with a reasonable time sequence to administration of the drugs, but could also be explained by other concomitant disease or drugs.[10]

For cost analysis, prescription cost per day was calculated which included the cost of prescribed drugs. Hence, our study found that prescription cost per day was highest in neurotropic group (30.28±11.24 international normalized ratio [INR]) followed by muscle relaxant group (25.92±8.66 INR) and NSAIDs group (12.22±3.38 INR). Prescription cost was higher in neurotropic group as most of the patients in this group received combination therapy of NSAIDs, muscle relaxant, and neurotropic drugs. While in case of NSAIDs group, most of the patients received NSAIDs alone or with gastro-protective agents.

The major limitation of this study is shorter duration of study period. All patients were followed for only 6 weeks. Low back pain is a chronic condition which recurs in most of the patients. Hence, patients have to be followed for a longer period of time to evaluate the efficacy of drugs over a long period and ability to prevent reoccurrence of back pain.

CONCLUSION

Most of the drugs used for low back pain have a symptomatic benefit. Therefore, possible adverse effects expected should be weighed while deciding to prescribe the drugs. Furthermore, long-term effects of the above mentioned combination for this chronic and distressing health problem needs to be explored.

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