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A Concurrent Study on Management of Recurrent Biliary Colic and Comparison of Efficacy of Combination Drugs Used

Juvvadi Sharvani Rao[1], Varagandhi Susmitha[1], Mohammad Abdul Wahab Sufiyaan Osmani[1], Rampeesa Akhil[1], Gonepally Vaishnavi[1]
(Department of Pharmacy, Sree Chaitanya Institute of Pharmaceutical Science, India)
Corresponding Author:
Gonepally Vaishnavi
Assistant Professor, Department of Pharmacy Practice, Sree Chaitanya Institute of Pharmaceutical Sciences, Karimnagar, Telangana, India
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Abstract:
Background: Gallstones are hardened deposits of the digestive fluid bile, that can form within the gallbladder. Patients with symptomatic stones most often present with recurrent episodes of right-upper-quadrant or epigastric pain, probably related to the impaction of a stone in the cystic duct. They may experience intense pain in the upper-right side of the abdomen, often accompanied by nausea and vomiting represented as biliary colic. Oral NSAIDs, opioids and anti-spasmodics are available in managing biliary colic.
Materials and methods: This concurrent study was conducted over a period of 6 months to identify the analgesic efficacy of various combinations of drugs used for biliary colic in outpatients. A suitable data collection form was designed to collect required information and analyse the data which specifically included biliary colic questionnaire along with pain scale and adverse drug reaction questionnaire. A total of 300 patients were analysed in this study. Visual analogue scale scores were obtained from patients both before and after the use of drugs.
Results: NSAID and anti-spasmodics class of drugs were used as a first line in most patients and opioids are prescribed as second line in case of severe pain control among monotherapy. Various Combination of drugs were studied for analgesic efficacy. Drotaverine+ Mefenamic Acid and Tramadol + Paracetamol with highest difference in mean VAS scores before and after treatment were found to be effective and also safe combinations for outpatient management of biliary colic.
Conclusion: Pain management is a common necessity for symptomatic cholelithiasis patients. Combination drugs Drotaverine +Mefenamic acid and Tramadol +Paracetamol were mostly prescribed and are having a high difference in mean VAS scores with no ADR reportings. These combinations are safe, effective and could be suitable choice for outpatient management of biliary colic.
Keywords: Visual analogue scale; Biliary colic; Cholelithiasis.

I. INTRODUCTION

The gallbladder is a pear-shaped organ which is located in the right upper quadrant of the abdomen. It measures approximately 7 cm to 10 cm in length and 4 cm in width.[1] Gallstones are the hardened deposits of the digestive fluid bile, forming inside the gallbladder. They differ in dimension and shape. Gallstones appear when there is an imbalance in the chemical constituents of the bile that ensuing precipitation of one or extra of the components. Its prevalence is mainly excessive in the Scandinavian countries, Chile and amongst Native Americans. Gallstones are extra frequent in North America, Europe, and Australia, and are much less prevalent in Africa, India, China, Japan, Kashmir, and Egypt . [2] Gall stones are of three types there are 1) Cholesterol Stones, 2) Pigment Stones 3) Mixed Stones.[3] Predisposing factors for gallstones are 1) Cholesterol Stones [Demographic/genetic factors, Obesity, Weight loss, Female sex hormones, Increasing age, Gall bladder hypomotility, Clofibrate therapy, Decreased bile acid secretion, Decreased Phospholipid secretion] 2) Pigment stones [Demographic/genetic factors, Chronic hemolysis, Alcoholic cirrhosis, Pernicious anemia, Cystic fibrosis, Chronic biliary tract and parasite infection, ileal disease].[4] Most patients with gallstones have no symptoms are known as silent stones and may not require any treatment. Patients with symptomatic stones most frequently present with recurrent episodes of right- upper- quadrant ache or epigastric pain. Additionly patients

presents with some signs like Boas sign, Ortner's sign,[2] Murphy's sign,[5] Cullen's sign.[6] Initial labs to consider gallstones often encompass CBC, CMP, PT/PTT and LFT Ultrasound remains the first line and the high-quality imaging modality to diagnose gallstones. Additionally, tests such as ERCP/MRCP are sometimes beneficial when working up with jaundice and dilated CBD or suspected cholangitis, however are commonly obtained after an ultrasound.[7] Complications can occur in patients with or without symptoms and mostly include the following: Acute cholecystitis, Chronic cholecystitis, Choledocholithiasis, Acute cholangitis, Acute pancreatitis, Empyema in gallbladder, Obstructive jaundice, Choledochoduodenal fistula, Gall bladder perforation [8]. Management of gallstones depends on whether they are causing symptoms or not. Recurrent episodes of upper abdominal pain is the common indication of treatment of gallstones[2] Non operative therapies for Symptomatic Gallstones are 1) oral bile acid dissolution : Ursodeoxycholic acid at 8-10 mg per kg per day 2) Contact solvents:methyltert-butylether/n-propylacetate 3)Extracorporealshock – wave lithotripsy:Electrohydraulic/electromagnetic[9] and Surgical management include Laparoscopic Cholecystectomy.**[10]**For biliary colic management Analgesics,[11] Anti-inflammatory[12] and Anticholinergic[13] drugs are used. They are different types of pain scales are present for pain assessment here we have used visual analog pain scale for assessment of biliary colic pain in gall stone patients.[14]

II. Material And Methods

This concurrent comparative study was carried out on outpatient basis in Department of gastroenterology and liver at

- Dr. Kiran Kumar,SRR Gastro and Liver Hospitals, Karimnagar.
- Dr.RajuMulka,Abhinav Gastro and LiverCentre, Karimnagar from July 2020 to December 2020. A total 300 adult subjects (both male and females) of all age group are included inthis study.

Study Design: This study was a concurrent observational study
Study Location: This was a tertiary care hospital based study done in Department of gastroenterology and liver at Dr. Kiran Kumar,SRR Gastro and Liver Hospitals,Karimnagar and Dr.RajuMulka,Abhinav Gastro and Liver Centre,Karimnagar.

Study Duration: July 2020 to December 2020(6 months).
Sample size: 300 patients.
Subjects & selection method: The study population was drawn from consecutive cholelithiasis patients who presented to Dr. Kiran Kumar, SRR Gastro and Liver Hospitals, Karimnagar. Dr.Raju Mulka, Abhinav Gastro and Liver Centre, Karimnagar with biliary colic and were prescribed with pain killers and underwent surgery if gall stone was greater than or equal to 10 mm in size from July 2020 to December 2020.

Inclusion criteria:

1. Patients diagnosed with cholelithiasis following ultrasound abdomen confirmation.
2. Patients of all ages.
3. Out patients of male and female genders.

Exclusion criteria:

1. Patients who are unable to provide information of drugs and doses been used.
2. All inpatients diagnosed with cholelithiasis.

Procedure methodology
Sources of data:

- ❖ Through the review of case records of outpatients.
- Drug class being used (NSAID/opioid/anti-spasmodic).
- Route and frequency of administration.
- Diagnostic tests and laboratory data (ultrasound abdomen, liver function tests).
- Pain assessment.
- Associated complications.
- ❖ Through direct communication with patients and patient caretakers.
- ❖ Interacting with medical staff and health care professionals.

Data collection and assessment of study results
A suitable data collection form was designed to collect required information and analyse the data. The data collection form included the information related to patient demographics such as age, weight and gender along with the complaints of visiting, past medical history and social history, diagnostic information such as liver function tests and ultrasound abdomen, biliary colic questionnaire along with pain scale,complete management plan and ADR questionnaire.

An observational analysis was done on prescribing patterns of NSAID's, opioid's and anti-spasmodics, their associated pain management in biliary colic attacks and complications associated with cholelithiasis.
Outpatients those who visit the gastroenterology and liver department are reviewed on daily basis. Those patients who reach the inclusion criteria are included in to the study. All the required information is collected through review from patient records, laboratory data and direct communication with patients and patient care takers.

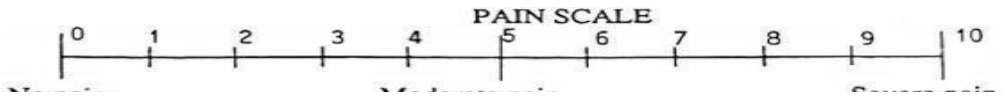
Statistical analysis

The data was analysed based on the information collected in case sheets

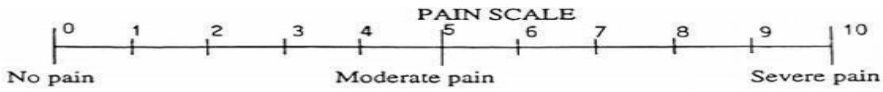
1. Abnormalities in liver function tests and ultrasound abdomen.
2. Drug class being used.
3. Development of complications.
4. Biliary colic questionnaire.
5. Pain assessment scale.
6. ADR questionnaire.

Biliary colic questionnaire:

- How long have you been experiencing pain from your Gallstones? (Specify weeks/months/years)
- Do you take pain killers for any other medical conditions other than gallstones?
- Drug ---------- Dose ---------- Duration ----------
- What other symptoms do you suffer other than pain during an attack? ----------
- On the scale below rate the severity of gallstone pain before analgesic use



- What pain killer do you take for your gallstone pain? ----------
- What dosage and frequency? ----------
- Mark on the scale below how effective this pain killer is at relieving your pain



Adr questionnaire:

1. Have you had experienced any reactions/symptoms after the initiation of treatment plan?
2. If yes, describe the symptoms?
3. Have any of the symptoms you have described gone away after stopping the analgesic ?

III. Result

This study ―An Observational Study on Outpatient Management of Biliary Colicwas conducted in ABHINAV and SRR HOSPITALS. A total number of 300 patients who were diagnosed with gallstones were included in the study.
Table no 1 shows the study population which was divided into various groups based on age and gender. In our study, it was observed that male patients (59.33%) suffering from cholelithiasis were higher than female patients (40.66%). Out of the 300 patients, 178 were male and remaining 122 patients were female. It was observed that most of the patients were maximum in the age group of41- 60 (males 28% and females 18%), followed by 21-40 (males 15.33% and female 9.33%) and then in age group of 61-80 (males 10% and females 8%) and 0-20 (males 4% and females 4%).

Table no 1: Showsage and gender wise distribution of patients

AGE	NO. OF PATIENT	FREQUENCY
0-20		
MALE	12	4
FEMALE	12	4
21-40		
MALE	46	15.33

FEMALE	28	9.33
41-60		
MALE	84	28
FEMALE	54	18
61-80		
MALE	30	10
FEMALE	24	8
> 81 & ABOVE		
MALE	6	2
FEMALE	4	1.33

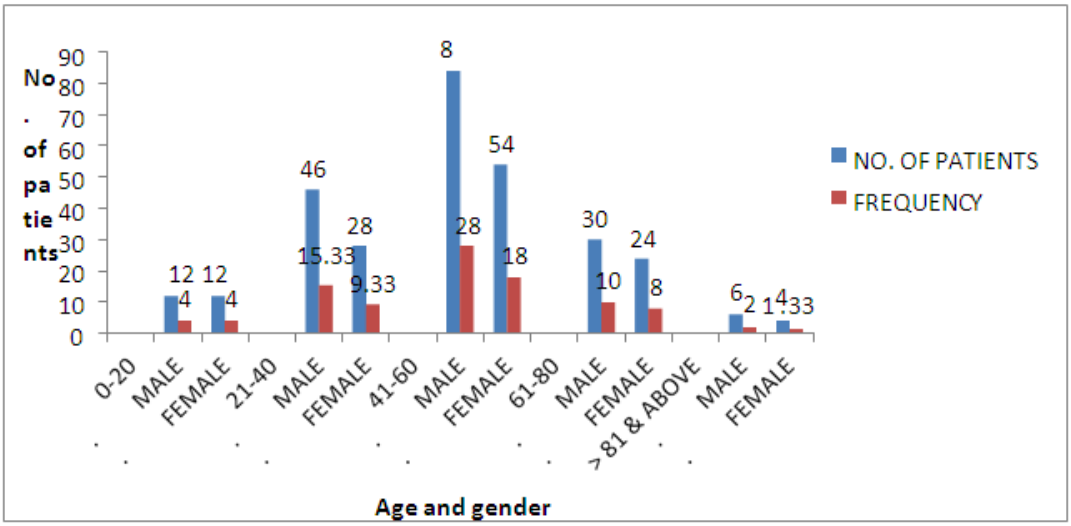


Table no 2 shows patients based on symptomatology, patients were divided as asymptomatic(14.66%) and symptomatic(85.33%). Biliary colic was the predominant symptom among symptomatic with 100% frequency. 48.43% of patients were seen with nausea/vomiting, followed by fever with 26.56% and jaundice with11.71%.

Table no 2 : Shows distribution of patients based on symptoms

SYMPTOMATOLOGY	NO. OFPATIENTS	FREQUENCY
ASYMPTOMATIC	44	14.66
SYMPTOMATIC	256	85.33
BILIARY COLIC		
NAUSEA/VOMITING	256	100
FEVER	124	48.43
JAUNDICE	68	26.56
	30	11.71

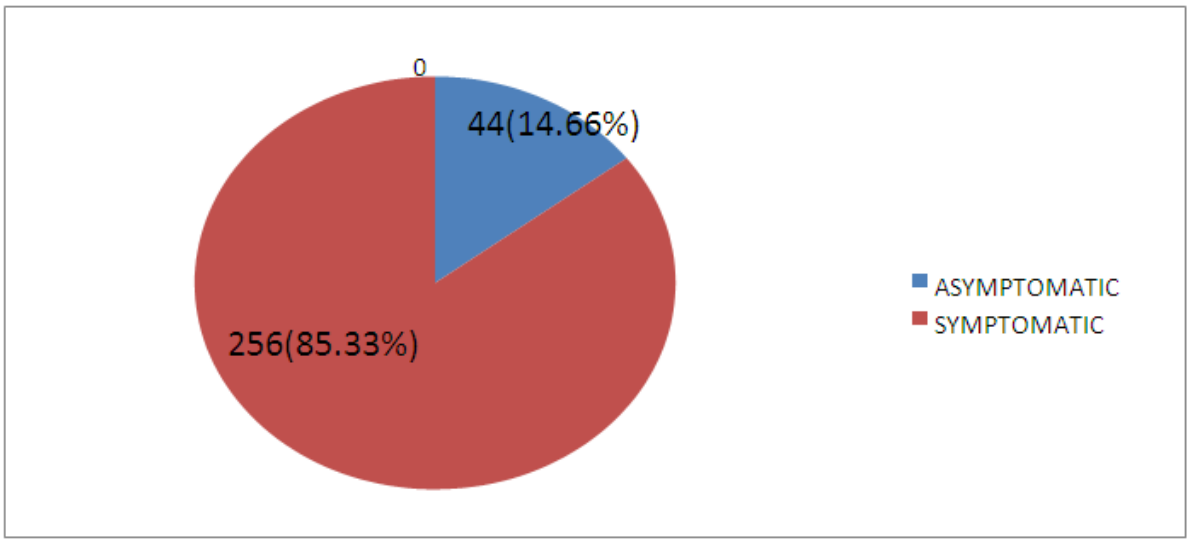


Table no 3 shows the signs commonly observed in the study population, it was observed that number of patients with Murphy‘s sign were maximum (25.33%) followed by Cullen‘s sign (10.66%), Boa‘s sign(8%) and Ortner‘s sign(2.66%).

Table no 3 :showsdistribution of patients based on signs observed

SIGNS	NO. OF PATIENT	FREQUENCY
MURPHY‘S SIGN	76	25.33
BOA‘S SIGN	24	8
ORTNER‘S SIGN	8	2.66
CULLEN‘S SIGN	32	10.66

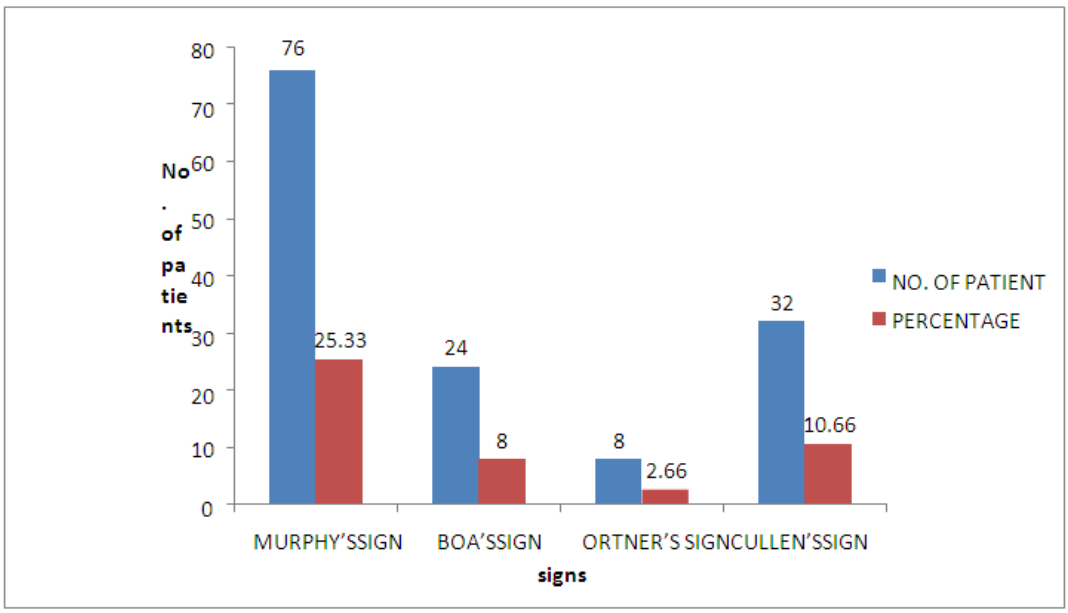


Table no 4 shows the initial pain assessment scores of patients, out of 300 patients, maximum number of patients for Initial pain assessment according to Visual Analogue Scale (VAS) were with score 4 i.e 18.66% followed by score 7 with 15%, score 3 with 14.66%, score 2 with 12%, score 6 with 9.33%, score 1 with 6.66%,score 5 with 5.66% and 8 with 3.33%.

Table no 4 :showsdistribution of patients according to initial pain assessment

VAS SCORE	NO. OF PATIENTS	FREQUENCY
0	44	14.66
1	20	6.66
2	36	12
3	44	14.66
4	56	18.66
5	17	5.66
6	28	9.33
7	45	15
8	10	3.33
9	0	0
10	0	0

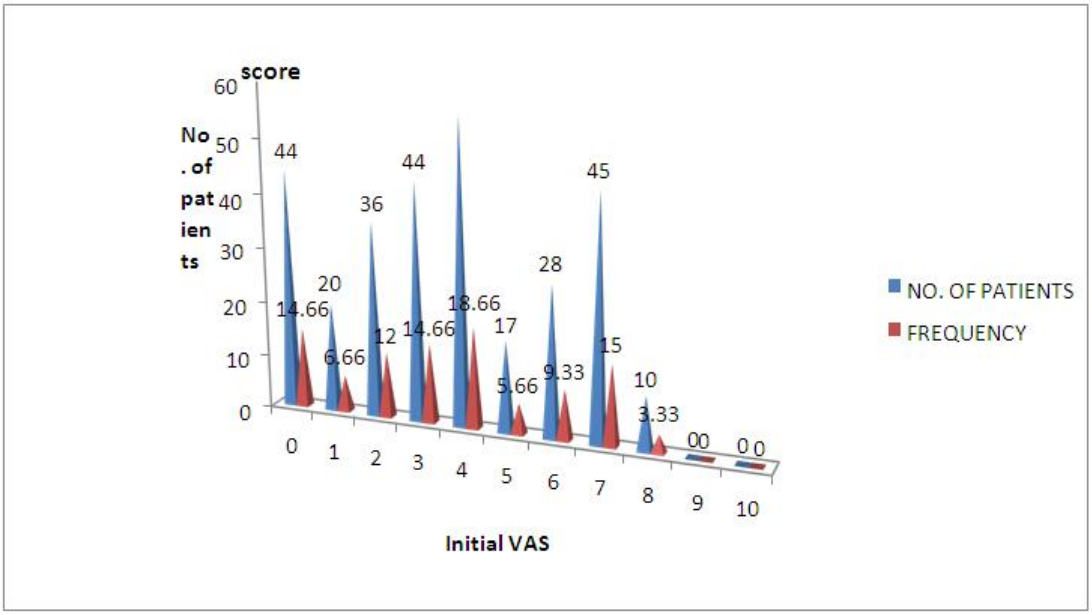


Table no 5 shows complications observed in patients, it was observed that acute cholecystitis (30%) was most commonly seen complications following choledocholithiasis (16%), obstructive jaundice (10%), acute pancreatitis (5.33%), chronic pancreatitis (5.33%), acute cholangitis(2%), chronic cholecystitis(1.3%) and gall stone ileus(0.6%).

Table no 5 : shows distribution of patients according to complications observed

COMPLICATIONS	NO. OF PATIENTS	FREQUENCY
ACUTE CHOLECYSTITIS	90	30
CHRONICCHOLECYSTITIS	4	1.3
ACUTE PANCREATITIS	14	5.33
CHRONIC PANCREATITIS	14	5.33
ACUTE CHOLANGITIS	6	2
OBSTRUCTIVE JAUNDICE	30	10
GALL STONE ILEUS	2	0.6
GALL BLADDER CANCER	0	0
CHOLEDOCHOLITHIASIS	48	16

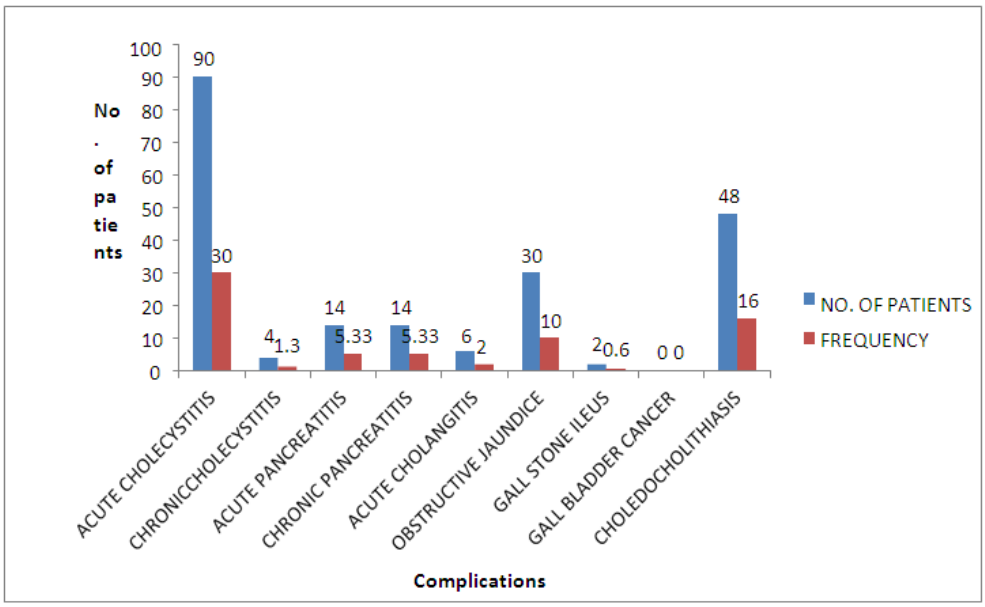


Table no 6 shows the class of drugs used to relieve pain, it was observed that maximum number of patients were with combination drugs (65.6%) compared to monotherapy (34.37%). In monotherapy most commonly used class of drugs were NSAIDs(14.06%) followed by antispasmodics (12.5%) and then opioids (7.81%)

Table no 6 :showsdistribution of patients according to the class of drugs used to relieve pain

CLASS OF DRUGS	NO. OF PATIENTS	FREQUENCY
NSAIDS	36	14.06
OPIODS	20	7.81
ANTISPASMODICS	32	12.5
COMBINATION DRUGS	168	65.6

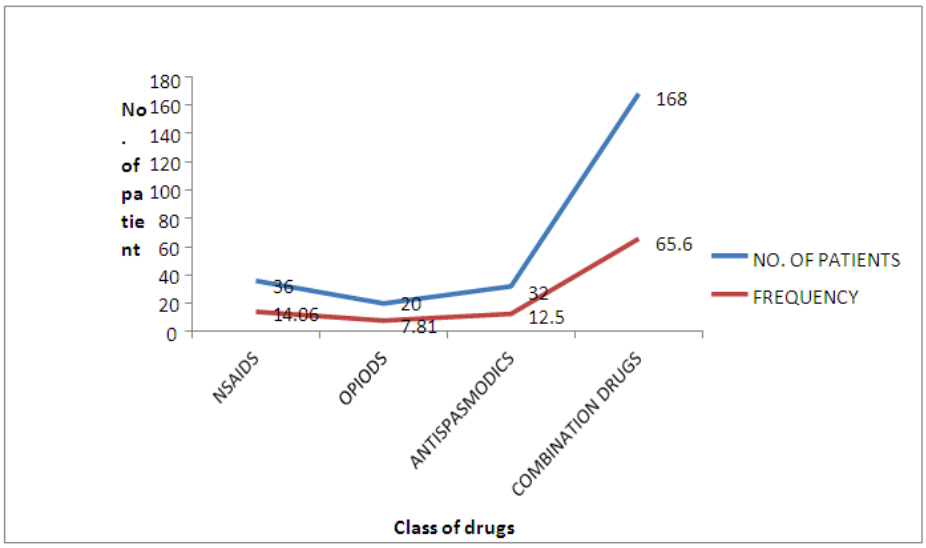


Table no 7 shows the distribution of patients in monotherapy drugs, it was observed that maximum number of patients were prescribed with ketorolac. Among 88,22 patients were prescribed with ketorolac with frequency of 7.33%, followed by tramadol with 18 patients(6%), 10 patients with drotaverine (3.33%), 8 patients with mebeverine (2.66%), 18 patients were prescribed with paracetamol, diclofenac&hyoscine butyl

bromidein equal ratios with equal frequency of each 2%, 4 patients with baclofen (1.33%). ibuprofen, pentazocine, clidinium and flavoxate were prescribed in equal ratios with 0.66% each.

Table no 7 :showsdistribution of patients based on monotherapy drugs used

DRUGS	NO. OF PATIENTS	FREQUENCY
PARACETAMOL	6	2.34
DICLOFENAC	6	2.34
KETOROLAC	22	8.59
IBUPROFEN	2	0.78
TRAMADOL	18	7.03
PENTAZOCINE	2	0.78
DROTAVERINE	10	3.90
MEBEVERINE	8	3.12
HYOSCINEBUTYL BROMIDE	6	2.34
BACLOFEN	4	1.56
CLIDINIUM	2	0.78
FLAVOXATE	2	0.78

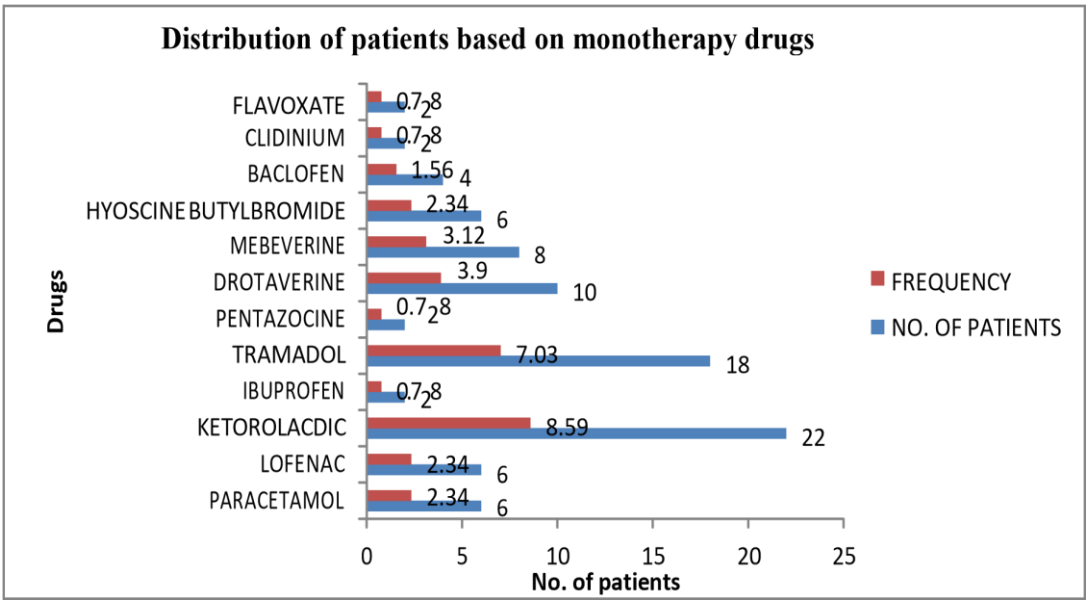


Table no 8 shows the distribution of patients based on combination drugs used,it was observed that 58 patients were prescribed with Drotaverine+ Mefenamic Acid(22.65%) followed by 41 patients with Tramadol+Paracetamol(16.01%),19 patients with Hyoscine butyl bromide+Mefenamic Acid(7.42%),15 patients with Dicyclomine+Mefenamic acid(5.85%),Diclofenac+ParacetamolandDrotaverine+Aceclofenac in 11 each patients(4.29%),8 patients with Camylofin+Diclofenac(3.12%) and 5 patients withAceclofenac+Paracetamol(1.95%).

TRA - Tramadol 37.5 mg
PCM - Paracetamol 325mg
ACE - Aceclofenac 100 mg

DRO - Drotaverine 80 mg
DICLO - Diclofenac 50 mg
DICY - Dicyclomine 10mg
HYO - Hyoscine butyl bromide 10 mg
CAMY - Camylofin 50mg

Table no 8 :showsthe distribution of patients based on combination of drugs used

COMBINATION DRUGS	NO. OF PATIENTS	FREQUENCY
TRA + PCM	41	16.01
ACE + PCM	5	1.95
DRO + MEFE	58	22.65
DICLO + PCM	11	4.29
DICY +MEFE	15	5.85
HYO + MEFE	19	7.42
CAMY + DICLO	8	3.12
DRO+ACE	11	4.29

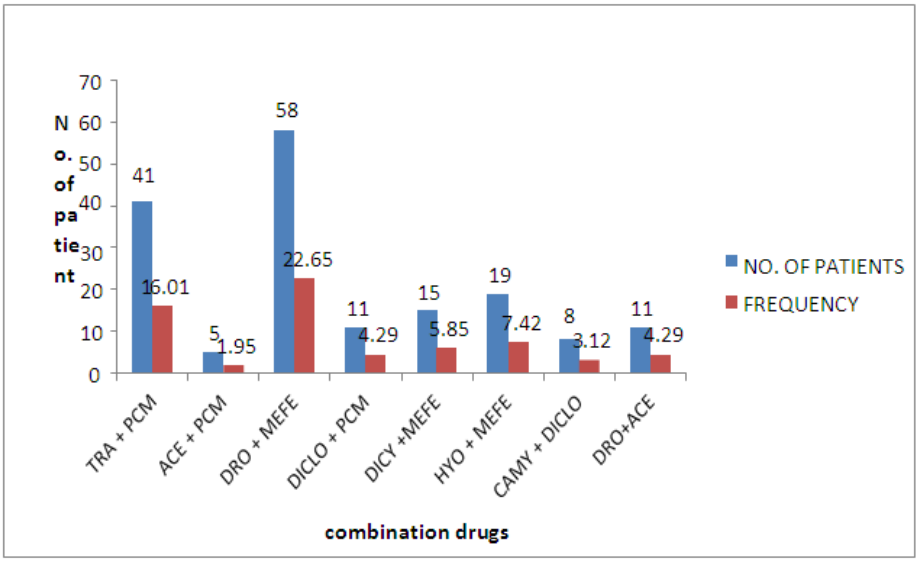


Table no 9 shows the frequency of class of drugs used, within the monotherapy, NSAIDs were mostly prescribed twice daily with 61.11% followed by thrice daily (22.22%) and once daily (16.66%).Opioids were mostly prescribed twice daily with 50% followed by thrice daily (30%) and once daily (20%).Anti-spasmodics were mostly prescribed twice daily with 50% followed by once daily (31.25%) and thrice daily (18.75%).

Table no 9 :showsdistribution of patients based on frequency of class of drugs used

THERAPY	NO. OF PATIENTS	FREQUENCY
NSAIDS OD	6	16.66
BD	22	61.11
TID	8	22.22
OPIOIDS OD	4	20
BD	10	50
TID	6	30

ANTISPASMODICS OD	10	31.25
BD	16	50
TID	6	18.75

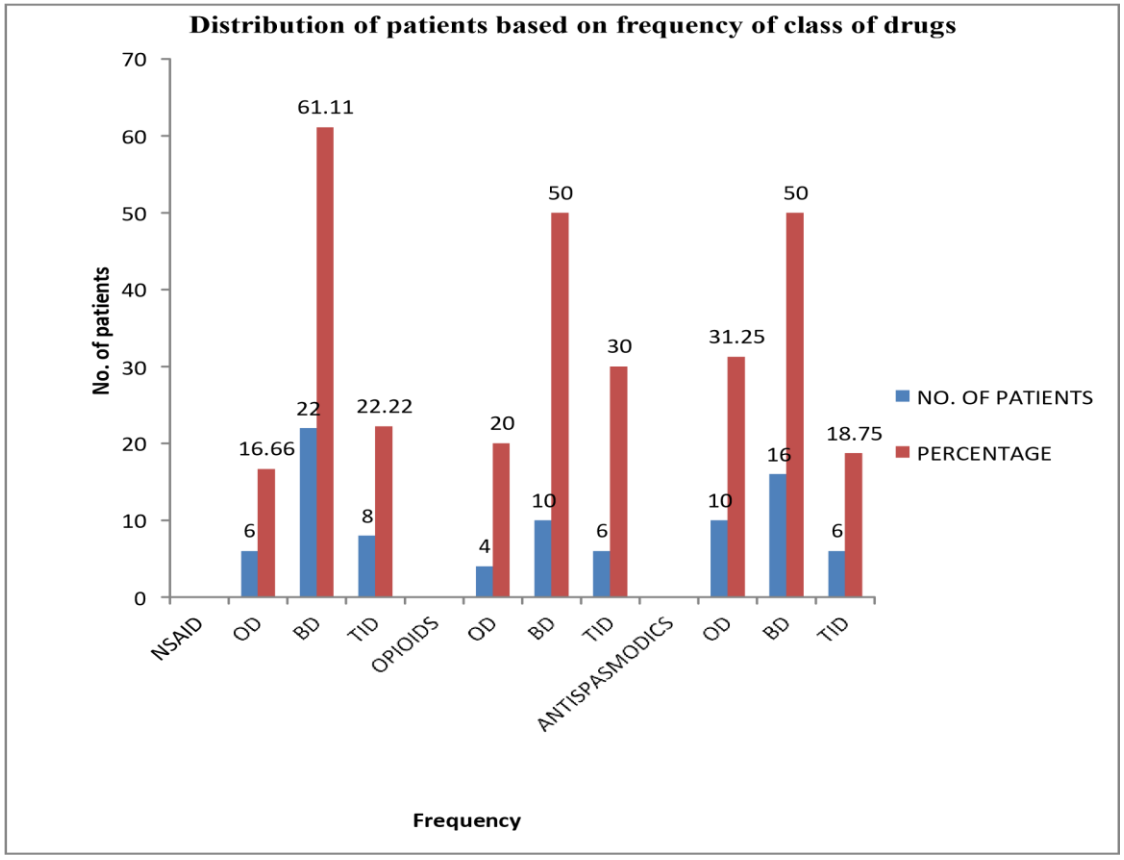


Table no 10 shows frequency in which combinations are used, it was observed that most of the orally available combination drugs were prescribed twice daily except Tramadol + Paracetamol which is mostly given once daily with 13.09%.

Table no 10 :showsdistribution of patients based on frequency of combination drugs used

DRUGS	NO. OF PATIENTS	FREQUENCY
TRA + PCM OD	29	70.73
BD	8	19.51
TID	4	9.75
ACE + PCM OD	1	20
BD	3	60
TID	1	20
DRO + MEFE OD	23	39.65
BD	33	56.89
TID	2	3.44
DICLO + PCM OD	0	0

□BD	10	90.90
□TID	1	9.09
DICY + MEFE □OD	2	13.33
□BD	12	80
□TID	1	6.66
HYO + MEFE □OD	1	5.26
□BD	12	63.15
□TID	6	31.57
CAMY + DICLO □OD	1	12.5
□BD	6	75
□TID	1	12.5
DRO + ACE □OD	2	18.18
□BD	9	81.81
□TID	0	0

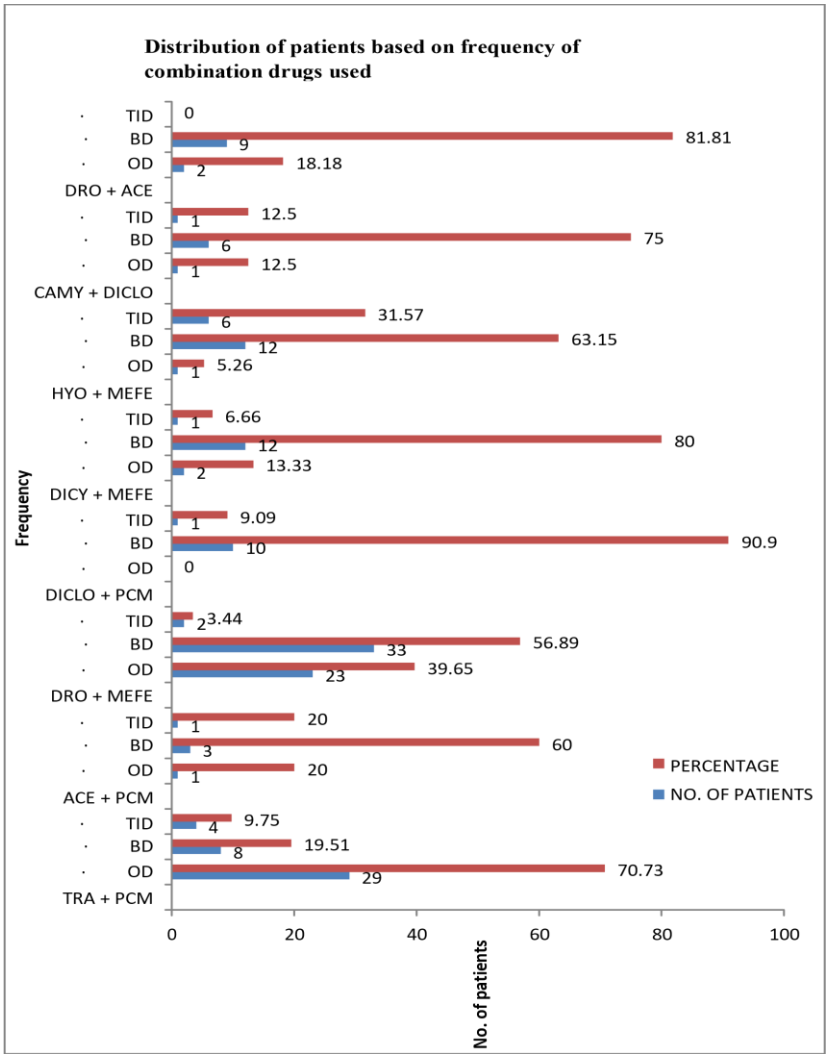
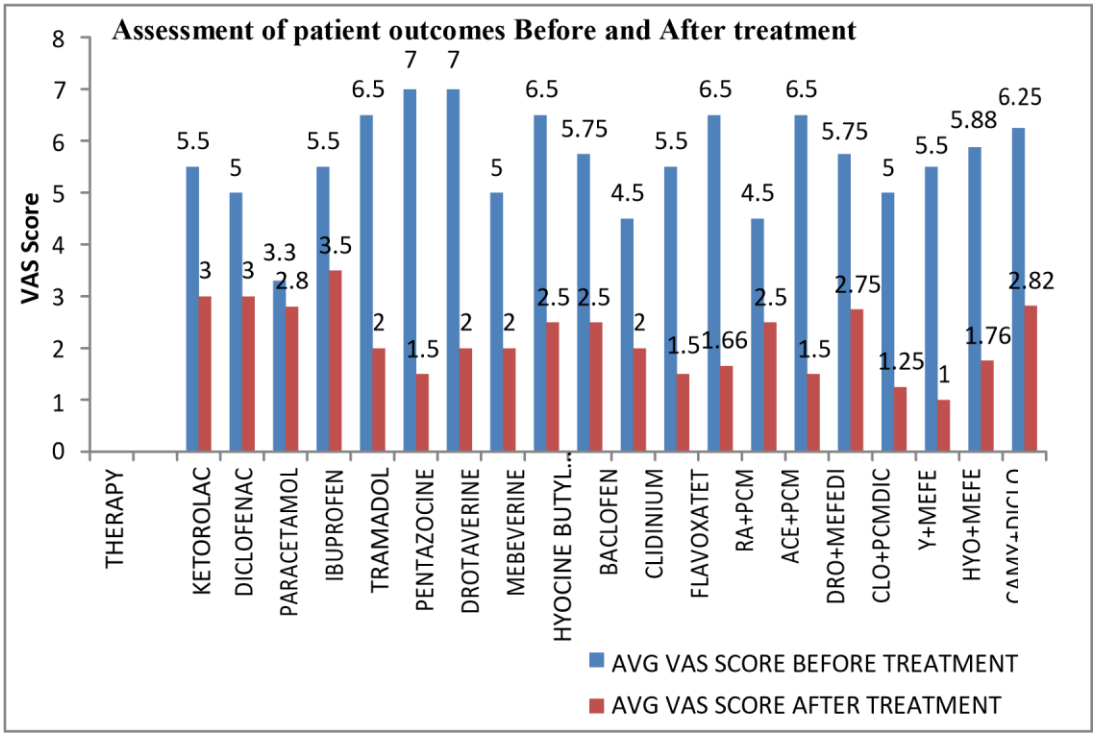


Table no 11 shows the assessment of patient outcomes before and after treatment, it was observed that, within monotherapy, mean VAS score after treatment was minimum for pentazocine and also flavoxate ,pentazocine and flavoxate had a mean VAS score after treatment of 1.5 followed by tramadol, drotaverine, mebeverine and clidinium with similar mean VAS scores of2, hyoscinebutyl bromide and baclofen with 2.5 score followed by ketorolac, diclofenac, ibuprofen with score 3 and paracetamol with score 2.8 .
Within the combination drugs, mean VAS score after treatment was least for the combinationHyoscine butyl bromide+Mefenamic Acid with score 1 followed by Dicyclomine+Mefenamic Acid with score 1.25,Drotaverine+Mefenamic Acid with score 1.5,Tramadol+Paracetamol with score 1.66,Camylofin+Diclofenac with score 1.76, Aceclofenac+Paracetamol with score 2.5,Diclofenac+Paracetamol with score 2.75 and Drotaverine+Aceclofenac with score 2.8 .

Table no 11 :showsassessment of patients outcomes before and after treatment

THERAPY	AVG VAS SCORE BEFORE TREATMENT	AVG VAS SCORE AFTER TREATMENT
KETOROLAC	5.5	3
DICLOFENAC	5	3
PARACETAMOL	3.3	2.8
IBUPROFEN	5.5	3.5
TRAMADOL	6.5	2
PENTAZOCINE	7	1.5
DROTAVERINE	7	2
MEBEVERINE	5	2
HYOSCINE BUTYL BROMIDE	6.5	2.5
BACLOFEN	5.75	2.5
CLIDINIUM	4.5	2
FLAVOXATE	5.5	1.5
TRA+PCM	6.5	1.66
ACE+PCM	4.5	2.5
DRO+MEFE	6.5	1.5
DICLO+PCM	5.75	2.75
DICY+MEFE	5	1.25
HYO+MEFE	5.5	1
CAMY+DICLO	5.88	1.76
DRO+ACE	6.25	2.82



IV. DISCUSSION

Cholelithiasis is a common presentation in most of the countries, with at least 10 % of the adults have gallstones with a recent rise in the incidence due to change in the dietary factors. In India, it is estimated to be around 4%.

Uncomplicated biliarycolicpresents with a significant health and financial burden to hospitals and primary care services. There is little guidance available on the correct analgesia to use on an outpatient basis.[15]

This study aims to provide information on effectiveness of oral analgesics for biliary colic and to explore the prescribing habits of physicians. However most of the studies provided information on single effective use of the drug, in contrast our observational study concentrated on use of combination drugs along with monotherapy drugs and compared them for effectiveness in pain control.VAS scoring was mostly completed by patients themselves and sometimes with the opinions from health care professionals.

In our study, out of 300 patients maximum number of patients were in the age group of 41-60(46%) and most of them were males(59.33%). 256 out of 300 cholelithiasis patients were found symptomatic(85.33%) in the study presenting with biliary colic and remaining were asymptomatic(14.66%).

It was observed that lipid profile tests were abnormal in about 42% of the patients (n=126).we have also observed about 2% of the women (n=6) who were on long term oral contraceptives developed gallstones within few years. About 11% of the patients (n=33) developed gallstones after being cirrhotic.

In most of the patients episodes of pain typically lasted for 1-3 hours and is often accompanied by nausea and vomiting (48.43%). fever (26.56%) and jaundice (11.71%) were also commonly observed.

It was observed that biliary colic among these symptomatic patients was managed either through monotherapy or combination drugs. NSAID's, anti-spasmodic‘s, opioid‘s are used accordingly in monotherapy(n=88) and in combinations (n=168). NSAID‘s were predominantly used in both the cases.In our study, we observed that combinations(65.62%) were mostly opted compared to monotherapy(34.37%). Among those patients who were opted for combination drugs we have observed that Drotaverine+Mefenamic Acid was prescribed the most i.e in 58 patients(22.65%) followed by Tramadol+Paracetamol in 41 patients(16.01%), Hyoscine butyl bromide+Mefenamic acid in 19 patients(7.42%) and respectively.

In the study, we observed that most of the patients visited hospitals with an initial pain scores of 4 with 18.66% frequency followed by 7 with 15%, 3 with 14.66%, 2 with 12%, 6 with 9.33%, 1 with 6.66%, 5 with 5.66%, 8 with 3.33%. We haven‘t observed any patients with VAS score greater than 8. Remaining 14.66% of the patients visited hospitals with co morbidities of GI tract i.e. other than biliary colic having score 0 and been asymptomatic for gallstones. We have also observed that the severity of pain experienced by females is high initially.

TahirMasudi et al conducted ―An extensive literature review on acute pain management in cholelithiasis concluded that NSAID's are safe and effective for pain control in biliary colic, and reduce the likelihood of further complications.

Fraquelli M, et al conducted a study on NSAID's for biliary colic. This study includes 828 randomised participants of whom 416 received NSAID‘s and 412 received placebo, spasmolytic drugs, or opioids. NSAID showed more pain control than spasmolytic drugs and found no difference in the proportions of participants without complete pain relief when comparing NSAID‘s versus opioids.

In another study conducted by Colli A et al, it was found that NSAID‘s are the first-choice treatments as they control pain with the same efficacy of opioids and significantly reduce the proportion of patients with severe complications.

Assessment of patients outcomes among oral monotherapy drugs conducted in over 88 patients in our study found that pentazocine is found to have a large difference in average pain score before and after treatment i.e. 5.5 which is followed by drotaverine with 5 and tramadol with 4.5, hyoscine and flavoxate with 4, baclofen with 3.25, mebeverine with 3, clidinium and ketorolac with 2.5, diclofenac and ibuprofen with 2, paracetamol with 0.5. However taking into consideration on initial VAS score, difference in VAS scores and number of participants for the drug, tramadol, drotaverine and ketorolac were found to be most effective among these patients

While assessing outcomes among oral combination drugs ,we have observed that difference in average pain scores before and after treatment is maximum for the combination Drotaverine+Mefenamic Acid with score 5 followed by Tramadol+Paracetamol with score 4.84, Hyoscine+Mefenamic Acid with 4.5, Camylofin+Diclofenac with 4.12, Dicyclomine+Mefenamic Acid with 3.75, Drotaverine+Aceclofenac with 3.43, Diclofenac+Paracetamol with 3 and Aceclofenac+Paracetamol with score 2.

Both the combinations Drotaverine+Mefenamic Acid and Tramadol+Paracetamolwere found to be most safe and effective in more than 58% of the patients taking in to consideration both number of patients and after VAS scores. No Adverse reactions and compliance issues were reported among these patients taking Drotaverine+ Mefenamic Acid andTramadol+Paracetamol.

We have found that 54 out of 300 patients went on surgical management in 6 month period.Amongpatients suffering from complications with gallstones, acute cholecystitis was the major one with 30%. Bile duct stones and obstruction in about 16% followed by obstructive jaundice (10%), acute pancreatitis(5.33%), chronic pancreatitis(5.33%) and acute cholangitis (2%).

V. CONCLUSION

The results of this study suggest the concept of use of oral combination drugs in managing outpatients with biliary colic.Combinations Drotaverine+Mefenamic Acid and Tramadol+Paracetamol are commonly prescribed and has been found to be effective in most of the biliary colic patients. It is found that these combinations were safe and could be the suitable choice for outpatient management of biliary colic.

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