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RESEARCH ARTICLE

A COMPARATIVE STUDY OF TRANSDERMAL BUPRENORPHINE WITH TRANSDERMAL FENTANYL FOR POSTOPERATIVE ANALGESIA IN PATIENTS UNDERGOING POSTERIOR STABILIZATION OF LUMBAR SPINE.

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Abstract

Background and Objectives: Posterior stabilization of lumbar spine is associated with high degree of postoperative pain and hence, effective analgesia is a priority in this patient population as inadequate management of acute pain in the long run can result in chronic pain. Newer modalities of analgesia that are safe, non-invasive and user friendly are constantly being investigated. One such example of an analgesic is the transdermal system of opioid drugs. The pharmacological and clinical profiles of buprenorphine and fentanyl make them suitable for transdermal use. We conducted this study to find out which among the two is more effective for postoperative analgesia and which drug patch has a better side-effect profile.

Methods: Sixty patients who gave their informed consent, aged between 18-60 years undergoing elective posterior stabilization of lumbar spine, were divided into two groups of 30 each and were assigned to receive either a fentanyl patch (25 µg/hour) or a buprenorphine patch (10µg/hr). Vitals were closely monitored in the postoperative period and if the VAS scores were >4, rescue analgesia was administered.

Results: VAS scores were significantly lower in the group that received fentanyl patch. Those who received the buprenorphine patch experienced more frequent breakthrough pain and thus needed more rescue analgesia. However, fentanyl group experienced more nausea.

Conclusion: The study hence concluded that for postoperative analgesia, transdermal fentanyl holds promise. More studies on a larger scale need to be conducted to consolidate this finding.

Introduction:-

Patients undergoing spine surgeries are known to experience severe degrees of pain in the post-operative period. Persistent, intense pain activates secondary mechanisms both at the periphery and within the central nervous system that cause allodynia, hyperalgesia and hyperapathia that can diminish normal functioning and may lead to chronic pain(1).

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Adequate pain management is a challenge to the pain physician as there are many adverse psychological and physiological effects associated with it.(2) Hence, effective analgesia in this population is essential to accelerate functional recovery and enable patients to return to their normal activity more quickly after rehabilitation.
Although many methods are available for post-operative pain management, newer approaches are constantly being investigated. Usually, post-operative analgesia includes NSAIDs or opioid drugs like morphine and fentanyl taken intravenously, intramuscularly or per-orally.

Recent times have witnessed the introduction of a newer modality of therapy: transdermal patches containing opioids for pain relief. Although its use is more prevalent in treating patients experiencing severe cancer pain, studies are now being conducted to popularize it for post-operative analgesia. Buprenorphine and fentanyl are two such opioid analgesics available as transdermal patches that are being used for their analgesic effects in the post-operative period.

Buprenorphine is a non-selective mixed agonist–antagonist opioid receptor modulator, acting as a partial agonist of the μ receptor, an antagonist of the κ and the δ-receptors, but with very low affinity to the δ-receptor. Its active metabolite norbuprenorphine, acts as a strong agonist at the δ-receptors.(3) It has physico-chemical properties, including a low molecular weight and high analgesic potency that makes it an excellent compound for transdermal drug delivery. The new technology of transdermal buprenorphine (TDB) is an advanced system that contains the active drug incorporated into a polymer matrix, which is at the same time the adhesive layer. The patch precisely controls the rate of drug delivery and produces stable plasma concentrations within 48 hours of the first application. Patch adhesion analysis shows the appropriateness of the seven day application period.(4)(5)
Fentanyl is a pure μ-opioid receptor agonist known for its analgesic and sedative effects. It bypasses the first pass metabolism in the liver and hence has high bioavailability. Moreover owing to the high lipophilic action, it is an ideal agent for transdermal delivery and it achieves a large volume of distribution. The transdermal patch provides consistent diffusion of fentanyl over a 72-hour period.(6)

The purpose of this study is to find out which transdermal opioid analgesic among the two is more efficacious in terms of postoperative analgesia and which one has a better side effect profile.

Objectives:-

1. To compare the analgesic efficacy, adverse effects and need for rescue analgesics while using transdermal buprenorphine versus transdermal fentanyl for postoperative pain in patients undergoing posterior stabilization of lumbar spine.
2. To determine if there is a significant difference between the two study groups allowing consideration towards better analgesia for the patient

Review of literature:-

Transdermal drug delivery system:
Transdermal drug delivery system refers to the administration of therapeutic agents through intact skin for systemic effect. It has emerged as one of the most rapidly advancing areas of novel drug delivery system by improving the therapeutic efficacy and safety. It maintains a steady state of the drugs in plasma by releasing the drug at a predetermined and controlled rate. It also overcomes significant drawbacks of the conventional oral dosage forms and parenteral preparations.

Transdermal delivery of lipophilic drugs like buprenorphine and fentanyl is facilitated by diffusion through blood, lymphatics and interstitial transport to deep tissues.(7) The zero-order (constant rate of delivery) kinetics of transdermal delivery has been one of the cornerstones in the development of transdermal systems.(8)

From a global perspective, advances in transdermal delivery systems can be categorized as undergoing three generations of development from the first generation of systems that produced many of today's patches by judicious selection of drugs that can cross the skin at therapeutic rates with little or no enhancement; through the second generation that has yielded additional advances for small molecule delivery by increasing skin permeability and driving forces for transdermal transport; to the third generation that will enable transdermal delivery of small molecule drugs, macromolecules (including proteins and DNA) and virus-based/other vaccines through targeted permeabilization of the skin's stratum corneum.

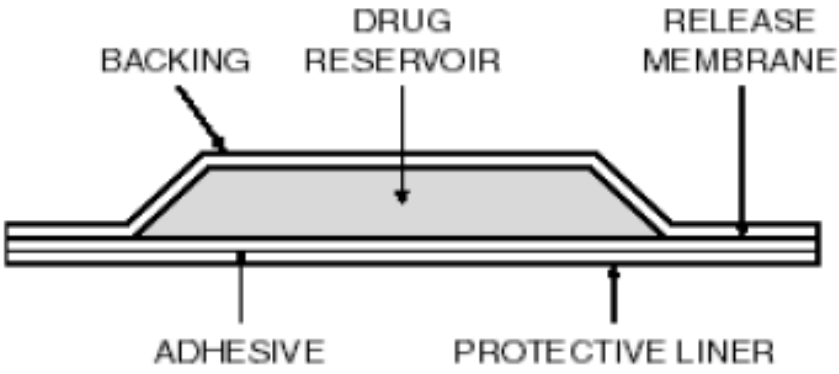

Fig 1:-Transdermal patch design

APPLIED ANATOMY OF SKIN:

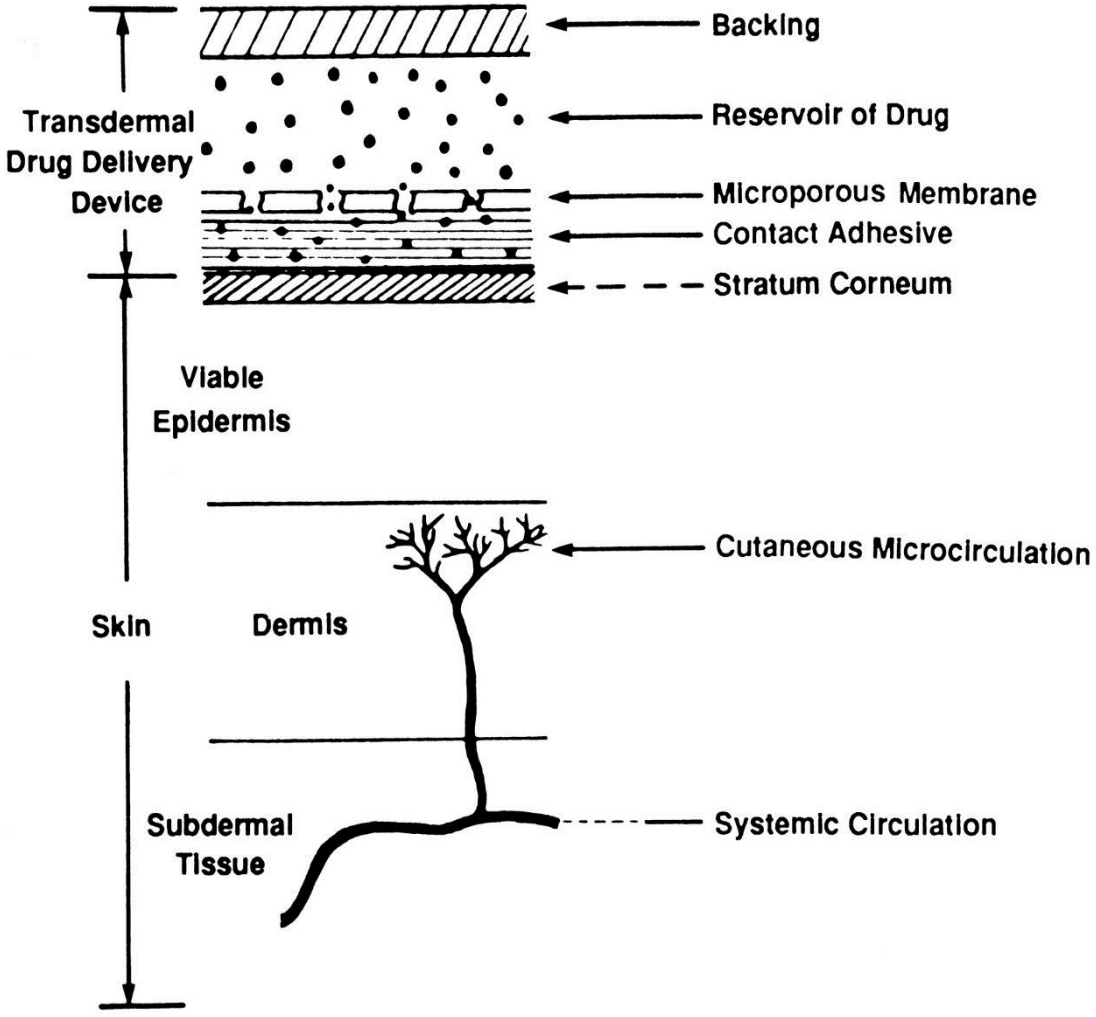

Fig 2:-Transdermal drug delivery

The first-generation approach to transdermal delivery is limited primarily by the barrier posed by skin's outermost layer called stratum corneum, which is 10 to 20 µm thick (Fig 2.). Underneath this layer is the viable epidermis, which measures 50 to 100 µm and is avascular. Deeper still is the dermis, which is 1–2 mm thick and contains a rich capillary bed for systemic drug absorption just below the dermal–epidermal junction. Drug transport across the stratum corneum typically involves diffusion through the intercellular lipids via a path that winds tortuously around

corneocytes, where hydrophilic molecules travel through the lipid head group regions and lipophilic molecules travel through the lipid tails. This transport pathway is highly constrained by the structural and solubility requirements for solution and diffusion within stratum corneum lipid bilayers.(9)

Pharmacology:

Buprenorphine:

It is a semisynthetic derivative of thebaine, a morphine alkaloid. It is a safe and potent analgesic. Buprenorphine is a highly lipophilic drug that is a non-selective mixed agonist–antagonist opioid receptor modulator, acting as a partial agonist of the μ receptor, an antagonist of the κ and the δ-receptors, but with very low affinity to the δ-receptor. Its active metabolite norbuprenorphine, acts as a strong agonist at the δ-receptors.(3) Transdermal system consists of the drug homogenously incorporated in a solid polymer matrix patch which is adhesive and it slowly releases the drug into the systemic circulation in a simple and compliant fashion.(15)(16)(17)

Structure: $C_{29}H_{41}NO_4$

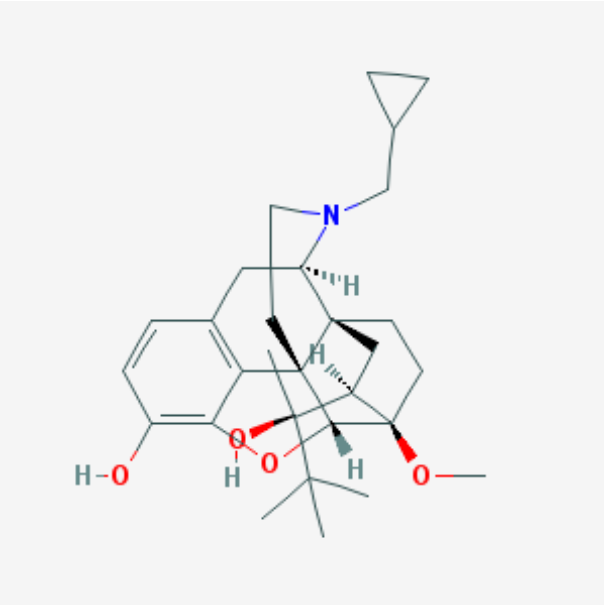

Fig 3:-Chemical structure of Buprenorphine

Mechanism of action:

Buprenorphine is a partial agonist at the μ-opioid receptor and an antagonist at the kappa-opioid receptors, an agonist at delta-opioid receptors and a partial agonist at nociception receptors. Buprenorphine interacts predominately with the opioid μ-receptor. These μ-binding sites are discretely distributed in the human brain, spinal cord and other tissues. In clinical settings, buprenorphine exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation.

Pharmacokinetics:(18)

pKa- 8.31
Plasma protein bound- 96%
Terminal half-life- 2.2 hours
Clearance-1-1.2L/min
Volume of distribution- 188-335L
Bioavailability- 31%

Absorption:

Each buprenorphine patch is designed to deliver the drug for a period of seven days. Steady state is achieved by the third day. Application of heat directly to the patch can cause a 26-55% increase in blood concentration of buprenorphine and the levels came down within 5 hours after the heat was removed. Fever may increase the permeability of the skin hence febrile patients must be monitored closely for adverse effects.

Distribution:
Buprenorphine is approximately 96% plasma protein bound and intravenous administration has shown to have a large volume of distribution.

Elimination:
Metabolism is by the liver and it undergoes both glucuronidation by UGT- isoenzymes and N-dealkylation by cytochrome P-450 3A4 isozyme to norbuprenorphine which is an active metabolite and has one-fifth of the pharmacologic activity of the parent compound and can further undergo glucuronidation. It is primarily eliminated via faeces while the remaining 10-30% of the dose is excreted in urine. Since metabolism and excretion of buprenorphine occur mainly via hepatic elimination, reductions in hepatic blood flow induced by some general anesthetics (e.g., halothane) and other drugs may result in a decreased rate of hepatic elimination of the drug, leading to increased plasma concentrations.

Pharmacodynamics:
1. Effects on central nervous system: Buprenorphine produces respiratory depression by direct action on the brainstem respiratory centres. It also depresses the cough reflex and constricts the pupils.
2. Effects on gastrointestinal system and other smooth muscle: Similar to fentanyl, it can reduce peristalsis and cause constipation.
3. Effect on the cardiovascular system: Buprenorphine can cause peripheral vasodilation and lead to hypotension. At doses of 40mcg/ hour, prolongation of QTc was seen.
4. Effect on endocrine system: Just like other opioids, buprenorphine can inhibit secretion of ACTH, cortisol and LH and stimulate prolactin, GH, insulin and glucagon secretions.
5. Effect on immune system: There may be modest immunosuppression.
   Buprenorphine may increase the patient's tolerance for pain and decrease its perception. In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur.

Dosage:

Buprenorphine Delivery Rate (mcg/hour)	Active Surface Area (cm2)	Total Buprenorphine Content (mg)
Buprenorphine 10	12.5	10
Buprenorphine 15	18.75	15
Buprenorphine 20	25	20

Table 1:-TDB dosages

Uses:
Moderate to severe pain, perioperative analgesia and opioid dependence

Precaution:
1. -There is a risk of addiction and abuse among buprenorphine users.
2. -Dose reduction must be done in the geriatric and debilitated patients as well as those with hepatic and renal impairment. Safety and efficacy of buprenorphine is not evaluated in patients under 18 years of age.
3. -Serious respiratory depression and coma can result if concomitantly used with other CNS depressants and benzodiazepines.
4. -Also, one needs to be cautious while administering buprenorphine to head trauma patients with raised intracranial pressures and those with impaired consciousness as it might reduce respiratory drive and the resultant CO2 retention can further increase the intracranial pressure.
5. -Neonatal opioid withdrawal syndrome is seen if there was prolonged use during pregnancy. Avoid buprenorphine patch during lactation.
6. -Exceeding 40mcg/hour can result in prolonged QTc interval.

Drug interaction**:** If used with benzodiazepines or other CNS depressant drugs including alcohol, there may be fatal additive effects. If used with serotonergic drugs, serotonin syndrome could result.
Special instructions to the patients and care-takers:
Patients receiving opioid transdermal patches must be educated regarding life threatening respiratory depression, methods of disposal of the patch and risk of accidental exposure in children. They should be informed about drug interactions and how to recognize emergencies such as anaphylactic reactions. Patients need to be warned regarding

the potential for temperature dependent increases in opioid release from the patch which could result in an overdose. Using buprenorphine patch may impair their ability to drive or operate heavy machinery.
The graph below (Fig. 5) compares the measured plasma concentration for buprenorphine and fentanyl at various time intervals. It can be observed that the maximum plasma concentration of fentanyl was attained between 12-24 hours and for buprenorphine it was around 72 hours.

Fentanyl:
Fentanyl was first synthesized as an intravenous anaesthetic by Paul Janssen in 1960. It is a potent agonist of the μ-opioid receptor which is responsible for its analgesic and sedative properties. It is almost 100 times more potent than morphine and has a relatively wide therapeutic index, which makes it a very safe anaesthetic drug when monitored carefully.

The transdermal patch containing fentanyl was introduced in the mid-1990s. Fentanyl is now on the WHO's list of essential medicines, the most effective and safe medicines needed in a health system(10). It bypasses first pass metabolism and hence has high bioavailability. Due to its highly lipophilic action, it achieves a large volume of distribution.

Structure:
$C_{22}H_{28}N_2O$
Chemical name: N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide

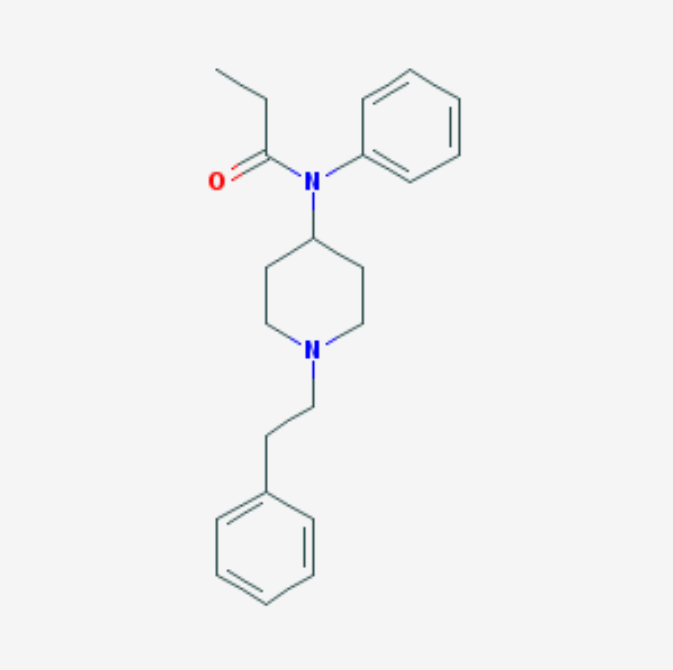

Fig 4:-Chemical structure of Fentanyl

Mechanism of action:
Fentanyl selectively binds to the μ-receptor in the central nervous system (CNS) thereby mimicking the effects of endogenous opiates. Stimulation of the μ-subtype opioid receptor stimulates the exchange of GTP for GDP on the G-protein complex and subsequently inhibits adenylate cyclase. This results in a decrease in intracellular cAMP and leads to a reduction in the release of neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline. The analgesic effect of fentanyl is likely due to its metabolites, which induce opening of G-protein-coupled inwardly rectifying potassium channels and blocks the opening of N-type voltage-gated calcium channels, thereby resulting in hyperpolarization and reduced neuronal excitability.(11)

Pharmacokinetics:(12)
pKa-8.4
Plasma protein bound- 84%
Terminal half-life- 3.5 hours

Clearance- 0.8-1.0 ml/min/kg
Volume of distribution- 3-5 L/Kg
Bioavailability of transdermal patch- 92%

Absorption:
Fentanyl is released from the adhesive matrix at a nearly constant amount per unit time. The skin under the system absorbs fentanyl and a depot of fentanyl concentrates in the upper skin layers. The concentration gradient existing between the matrix and the lower concentration in the skin drives the drug release. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial patch application, generally levelling off between 12-24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Peak serum concentrations of fentanyl generally occurred between 20 and 72 hours after initial application. (13)

Studies have shown that the application of heat over the Fentanyl Transdermal System increased mean overall fentanyl exposure by 120% and average maximum fentanyl level by 61%.(14)

	Mean (SD) Time to Maximal Concentration Tmax (h)	**Mean (SD) Maximal Concentration Cmax (ng/mL)**
Fentanyl Transdermal System 25 mcg/h	31.7 (16.5)	0.85 (0.26)

Table 2:-Mean time to maximal concentration

Distribution:
Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood.

Elimination:
Fentanyl is metabolized primarily via cytochrome P450 3A4 isoenzyme to undergo oxidative N-dealkylation to norfentanyl and other inactive metabolites. Within 72 hours of administration, approximately 75% of the dose is excreted in the urine and about 9% in faeces. (6)

Pharmacodynamics:
1. Effect on the central nervous system: Fentanyl produces respiratory depression and subsequent hypoventilation by direct action on the brainstem respiratory centres which maybe resistant to carbon dioxide retention.
2. Fentanyl causes miosis, even in total darkness.
3. Effect on gastrointestinal system and other smooth muscles: Fentanyl causes reduction in motility and an increase in the smooth muscle tone of the stomach antrum. Digestion is delayed and the propulsive peristaltic waves in the colon is decreased resulting in constipation. Other opioid induced effects may include spasm of sphincter of Oddi and reduced biliary and pancreatic secretions.
4. Effects on the cardiovascular system: Fentanyl produces peripheral vasodilation leading to orthostatic hypotension/syncope. Clinically significant histamine release rarely occurs with fentanyl administration.
5. Effects on endocrine system: Opioids inhibit secretion of adrenocorticotropic hormone (ACTH), cortisol and luteinizing hormone (LH). They stimulate prolactin, growth hormone (GH) secretion and pancreatic secretion of insulin and glucagon. Chronic use may influence hypothalamo-pituitary-gonadal axis which may manifest as low libido, impotence, erectile dysfunction, amenorrhoea and infertility.
6. Effects on immune system: In animal models, opioids appear to be modestly immunosuppressive.

Dosage:

Fentanyl Delivery Rate (mcg/hour)	**Active Surface Area (cm2)**	**Total fentanyl Content (mg)**
Fentanyl 25	10.5	25
Fentanyl 50	21	50
Fentanyl 75	31.5	75
Fentanyl 100	42	100

Table 3:-TDF dosages

Uses:
Chronic severe pain in opioid tolerant patients who need round the clock therapy and in whom other treatment options are inadequate. E.g. Cancer pain.

Precaution:
1. -Cardiac disease: Fentanyl may produce bradycardia and hence it should be administered with caution to patients with bradycardia.
2. -Hepatic or renal disease: Fentanyl is dependent on the liver for metabolism and kidneys for excretion and hence doses should be accordingly adjusted in those with deranged hepatic and renal parameters.
3. -Paediatric use: Transdermal fentanyl is not studied or recommended in children under two years of age.
4. -Pregnancy and lactation: TDF belongs to category C for teratogenic effects. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported. Fentanyl is excreted in human milk and hence is not recommended for nursing women.
5. -Geriatric use: A study conducted with the fentanyl transdermal system in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients or when opioids are given in conjunction with other agents that depress respiration. Fentanyl transdermal system should be used with caution in elderly, cachectic or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance.

Physical dependence:
Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood concentration of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, or increased blood pressure, respiratory rate, or heart rate.
In general, opioids should not be abruptly discontinued.

Ambulatory patients:
Patients who have been given fentanyl transdermal system should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug as strong opioid impair mental or physical abilities required for performing these tasks.

Drug interactions:
Concomitant use of fentanyl with all cytochrome P450 3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.

Using fentanyl along with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, anxiolytics (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants and alcohol, may cause respiratory depression, hypotension and profound sedation or potentially result in coma or death. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

Special instructions to the patients and care-takers:
Patients receiving fentanyl patch should be counselled regarding its addiction, abuse and misuse potential. Also, they must be educated regarding life threatening respiratory depression, methods of disposal of the patch and risk of accidental exposure in children. They should be informed about drug interactions and how to recognize emergencies such as allergic reactions. Patients need to be warned regarding the potential for temperature dependent increases in

fentanyl release from the patch which could result in an overdose. Fentanyl may impair their ability to drive or operate heavy machinery.

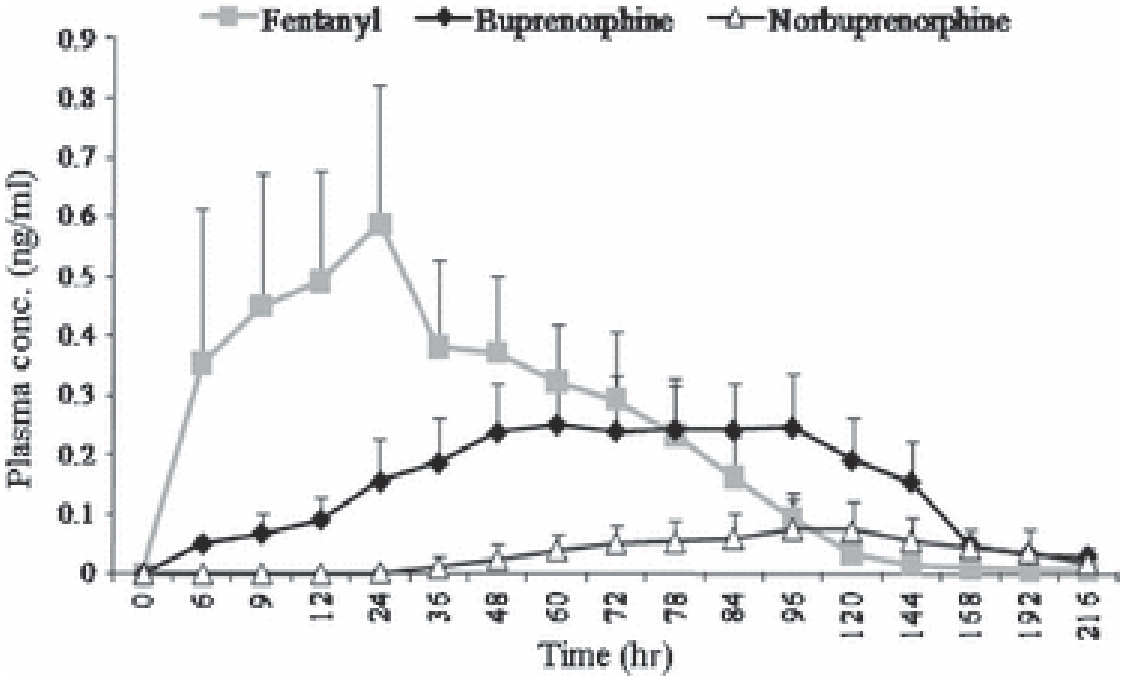

Fig 5:-Graph showing the measured plasma concentration for buprenorphine, fentanyl and norbuprenorphine (error bars: SD). Venous blood samples were drawn at baseline 0 and 6, 9, 12, 24, 36, 48, 60, 72, 78, 84, 96, 120, 144, 168, 192 and 216 hours after application of the transdermal patches(19)

Review of past studies:

1. Kilbride et al (1994) tried transdermal fentanyl (TDF) vs placebo for postoperative analgesia on 42 patients who underwent haemorrhoidectomy and found that 10/17 patients in the fentanyl group required narcotics vs 21/21 patients of the placebo group ($p < 0.05$ Fishers exact test). Amount of meperidine consumed was lower in the fentanyl group (97.05mg+/-23.27) vs the placebo group (236.19 +/-30.46) ($p<0.05$ students t-test). Hence it can be concluded that TDF is an effective analgesic that improves the transition to non-invasive outpatient pain management in patients undergoing haemorrhoidectomy.(20)
2. Katz et al (1996) followed up thirty patients who had under gone thoracotomy with an aim to identify predictors of long term post-thoracotomy pain by measuring the VAS scores at rest and on movement, Mc Gill Pain Questionnaire, patient controlled morphine consumption and pain threshold to pressure applied on the rib contralateral to thoracotomy incision. They found that 52% of patients reported long term pain and that early postoperative pain was the only factor that significantly predicted this. Hence, aggressive management of early postoperative pain may reduce the likelihood of long term post thoracotomy pain.(2)
3. Lehman LJ et al (1997) conducted a placebo-controlled study on 40 individuals posted for abdominal surgery under general anaesthesia with an aim to determine the safety and effectiveness of TDF for postoperative pain relief. He divided the subjects randomly into two groups of twenty each. The test group received TDF (0.16mg/cm^2) depending on their body weight i.e. for <60 kgs, a 30cm^2 patch and for >60kgs, a 40cm^2 patch respectively while the control group received placebo patches approximately 60 minutes before induction of anesthesia. Patients were followed up in the postoperative ward for 36 hours to assess pain levels and rescue analgesia was administered accordingly. During the observation period, 30 doses of 30 mg ketorolac and 14 doses of 1.3 g acetaminophen were administered to 13 patients in the placebo group and 18 doses of ketorolac and 8 doses of acetaminophen were given to 16 in the fentanyl group. Hence it can be deduced that the differences in postoperative analgesic requirement were significant. Also, in the fentanyl group, 12 patients experienced nausea vs 5 patients in the control group. TDF 50-75mcg/h, did not depress the respiratory rate or oxygen saturation. Hence, if used properly, the TDS can be effective in providing a background of analgesia and thereby assist in the management of acute postoperative pain.(21)

4. Sittl R et al (2003) conducted a double blinded RCT on 157 patients with chronic severe pain with an aim to compare the analgesic efficacy and tolerability of 3 doses of transdermal buprenorphine (TDB) (35mcg/h, 52.5mcg/h and 70mcg/h) with a placebo and found that pain intensity decreased in the TDB group in a dose dependent manner, the duration of sleep improved and there was less need for additional enteral analgesics.(16)
5. In 2003 Evans et al conducted trials evaluating the effectiveness and tolerance of TDB in patients suffering from chronic pain and found that the requirement for rescue medication was reduced from baseline in >50% of patients treated with TDB. Furthermore, despite the availability of rescue medication to all patients, those receiving TDB tended to experience greater pain relief, reduced pain intensity and longer pain-free sleep compared to weak opioids. TDB was generally well tolerated. Systemic adverse events were typical of opioid treatment or were attributable to the underlying disease.(22)
6. Dahan et al (2005) conducted an experiment to study whether an apparent ceiling effect existed for respiratory depression induced by buprenorphine by comparing the respiratory effects of fentanyl and buprenorphine in humans and rats. They found that fentanyl produced a dose dependent depression of minute ventilation with apnoea at doses of >=2.9mcg/kg; buprenorphine caused depression of minute ventilation which levelled off at doses >=3mcg/kg. In rats, the relationship of arterial PCO2 and fentanyl dose was linear, with maximum respiratory depression at 20 min (maximum PaCO2 8.0 kPa). Irrespective of the time at which measurements were obtained, buprenorphine showed a non-linear effect on PaCO2, with a ceiling effect at doses > 1.4 mcg/kg. The effect on PaCO2 was modest (maximum value measured, 5.5 kPa). Hence, it was confirmed that a ceiling effect of buprenorphine with respect to respiratory depression does exist but not with fentanyl.(23)
7. Sittl R et al (2005) conducted a retrospective study on patients with cancer and non-cancer pain with an aim to compare the calculated equipotent oral morphine doses of TDF with equipotent oral morphine doses of TDB prescribed in clinical practice. They concluded that for conversion of TDB to equipotent oral morphine dose, an equipotent ratio of 1:110 to 1:115 may be more appropriate than the earlier proposed ratio of 1:75.(24)
8. Griessinger N et al (2005) conducted an open, observational post marketing surveillance study in 13,179 patients who had moderate to severe cancer or non-cancer pain, with an objective of collecting data on the safety limit and effectiveness of TDB. They concluded that TDB patches were well tolerated and effective in the treatment of pain and there was no clinically relevant development of tolerance.(25)
9. In 2006, Sittl R et al compared TDF and TDB with respect to dosage increases, dosage stability, and the nature of dosage changes. A significantly larger proportion of patients receiving TDB had stable dosages over the entire treatment period compared with patients receiving TDF (non cancer groups: 56.9% vs 41.6%; cancer groups: 50.0% vs 26.2% [both, $P < 0.05$]). Compared with TDB, the proportion of patients with alternating dosage changes was significantly greater in patients receiving TDF (non cancer groups: 22.7% vs 13.1%; cancer groups: 30.6% vs 11.8% [both, $P < 0.05$]). They concluded that compared with TDB, the increase in mean daily dosage was significantly greater in patients treated with TDF. Also, alternating dosage changes were seen in a significantly greater proportion of patients receiving TDF. On the other hand, a significantly greater proportion of patients treated with TDB had stable dosages over their entire treatment periods.(26)
10. Minville et al (2008) conducted a study to assess postoperative analgesia on 30 patients undergoing total hip arthroplasty. Group T received a 50mcg/h TDF which was applied ~10 hours before surgery and PCA in the postoperative ward while group P received only PCA in the postoperative ward. They found that morphine consumption in the postoperative ward was 3.5+/-3 mg in group T versus 13+/-5 mg in group P ($P<0.0001$). VAS was 37+/-22 mm in group T versus 73+/-13 mm in group P ($P<0.0001$). Total morphine consumption at the end of day 1 was 43+/-16 mg in group P and 4+/-3 mg in group T ($P<0.0001$) & at the end of day 2 was 54+/-26 mg in group P and 5+/-4 mg in group T ($P<0.0001$). Hence it can be concluded that preoperative application of TDF significantly reduced pain and morphine consumption for 2 days in the postoperative ward.(27)
11. Mercadante S et al (2009) evaluated the equianalgesic ratio of TDB with oral morphine and TDF and suggested that patients receiving high doses of oral morphine or TDF can be safely switched to TDB by using a ratio of 70:1 and 0.6:0.8 respectively, maintaining the same level of analgesia.(28)
12. Wirz S et al (2009) conducted a trial to analyse the effect of long term treatment with oral sustained release hydromorphone, TDF and TDB on nausea, emesis and constipation. They found that the incidence of constipation was significantly higher with TD opioids (22% with TDF, 21% with TDB, 2% with hydromorphone PO; p=0.003). The mean NRS for nausea (TDF-1.3, TDB- 1.2, oral hydromorphone-1.5; p=0.6) and the consumption of antiemetics (TDF-42%, TDB-33%, oral hydromorphone-36%; p=0.6) did not differ significantly in contrast to the score for emesis (TDF-16%, TDB- 13%, oral hydromorphone-33%; p=0.02).(29)
13. Nelson et al (2009) reviewed multiple data to evaluate the underlying pharmacological safety and misuse/abuse potential of TDF and they found that TDF is an extremely high potency opioid that maintains a steady serum

concentration, thereby improving efficacy and compliance. But its use can also complicate the drugs safety due to improper application or prescription. It is also prone to abuse potential and can carry a high risk of morbidity. Hence, physician awareness and education in this matter will result in fewer poor outcomes.(6)

14. Andresen et al (2011) described the tissue differentiated analgesic effects between TDB and TDF. TDB significantly attenuated the bone pain, heat pain, nerve growth factor- induced soreness and cold pressor pain while fentanyl significantly decreased the cold pressor pain.(3)
15. Plosker GL et al (2012) found that TDB is indicated in the management of chronic non-malignant pain and its analgesic efficacy in patients suffering from osteoarthritis has been demonstrated to be equivalent to sublingual buprenorphine. If used in a combination with oral paracetamol, TDB was similar to codeine plus paracetamol.(30)
16. Wolff RF et al (2012) assessed the safety and efficacy of TDB with TDF in patients with moderate to severe pain from 14 trials using indirect comparisons as there were no head to head trials juxtaposing the two and they concluded that TDF and TDB were comparable in terms of pain relief and TDB was associated with significantly fewer side effects.(31)
17. Setti T (2012) evaluated the efficacy of different doses of TDB for postoperative pain control in gynaecological surgeries in terms of rescue analgesia required and found that the efficacy of TDB was directly proportional to its strength, although additional analgesia was required in the first hour following surgery. Also, increasing the dose of the drug did not cause a higher incidence of side effects.(32)
18. Kapil RP et al (2013) studied the TDB system for sustained analgesic efficacy in a randomized open label study to designate the steady state buprenorphine pharmacokinetics and found that steady state in plasma was reached within 48 hours of the first application of the BTDS and the patch adhesion analysis confirmed the the appropriateness of the 1 week regimen.(4)
19. Lee et al (2013) conducted a non-blinded multicentre prospective observational series across 17 tertiary hospitals where the pain management protocols in 393 patients who underwent spinal surgery were evaluated using a questionnaire. 79 patients received pre-emptive analgesics (e.g. COX-2 inhibitors) immediately before the surgery and these patients reported significantly less use of PCA in the postoperative period ($p<0.05$). Also, the activity level, anxiety and self-care improved significantly in the pre-emptive analgesia group when measured at 2 weeks postoperatively ($p<0.05$). Hence, it can be concluded that pre-emptive analgesia and multimodal pain management after spinal surgery may lead to a better quality of life and greater patient satisfaction.(33)
20. Canneti et al (2013) studied the safety and efficacy of TDB and TDF in the treatment of neuropathic pain in AIDS patients and found that both were well tolerated. Neither buprenorphine nor fentanyl affected CD4+ or CD8+ levels but particularly the buprenorphine group resulted in more stable CD4+ concentrations.(34)
21. Sathitkarnmanee T et al (2014) studied the role of TDF in 40 patients undergoing total knee arthroplasty for postoperative analgesia. Patients were divided into two groups of twenty each and each group received either a fentanyl 50mcg/h TD patch or a placebo patch 10-12 hours before surgery. They found that the morphine consumption after day 1 and day 2 in the fentanyl group vs the placebo group was 15.40±12.65 mg and 24.90±20.11 mg versus 33.60±19.06 mg and 57.80±12.65 mg ($P \leq 0.001$). Numeric rating scale scores at rest and during movement were significantly lower in the fentanyl group. Sedation over 48 hours was not statistically different between the two groups, however nausea and vomiting scores were significantly higher in the fentanyl group and there was no severe respiratory depression.(35)
22. Arshad z et al (2015) compared transdermal fentanyl (25mcg/hr) and transdermal buprenorphine (10mcg/h) in 60 patients undergoing major abdominal surgeries and found that they were both effective and safe in controlling post-operative pain. Although the fentanyl group did not need rescue analgesia and experienced less sedation when compared to the buprenorphine group, the difference in rescue analgesic requirement is not quite statistically significant (p-value 0.05). 20% patients in the fentanyl group and 16.7% patients in the buprenorphine group experienced nausea and vomiting. (36)
23. Matsumoto et al (2015) compared the effects of TDF (12.5mcg/h) with nonsteroidal anti-inflammatory drugs (NSAIDs) in 52 patients undergoing primary total knee arthroplasty. Postoperative pain was analysed based on the visual analogue scale (VAS) at rest and during movement (mVAS). They found that mVAS score was significantly smaller in the TDF group than the NSAID group on postoperative day 7 ($p=0.0026$) and postoperative day 14 ($p=0.007$). Also, muscle strength recovered faster in the fentanyl group and hence this led to early functional recovery following surgery.(37)
24. Kumar S et al (2016) evaluated the efficacy of three different strengths of TDB in postoperative pain management for lower abdominal surgery after randomizing 90 patients into 3 groups of thirty each. Group A received a placebo patch, group B received buprenorphine 10mg and group C received TDB 20mg.

Haemodynamic and analgesic effects were compared using ANOVA & Turkeys post hoc test and side effects were compared using the chi square test. They found that haemodynamic changes were comparable in all 3 groups and the VAS score of group A subjects was significantly higher (4.93±0.98) as compared to Group B (1.73±0.64) and Group C (1.40±0.50). On second postoperative day, no pain was reported by the Group C patients and on 4th day after surgery, no pain was reported by Group B patients. Hence it was concluded that TDB 20 mg was effective in attenuating postoperative pain, maintaining haemodynamic stability requiring no rescue analgesia while fewer postoperative rescue analgesic requirements were seen in the TDB 10mg group.(38)

25. Conaghan P et al (2016) conducted an observational study on patients affected with osteoarthritis in the UK and found that those who were treated with TDB were more satisfied and compliant with their medication and reported a higher quality of life than those treated with paracetamol-codeine combination or tramadol.(39)
26. Pergolizzi et al (2017) evaluated the safety of TDB in the management of chronic pain in older adults by conducting a retrospective analysis of 16 placebo and active controlled and uncontrolled studies (N=6566) and found that the incidence of adverse events was similar in the >65year old and <65year old patient (63.8% and 61%, respectively). TDB appeared to be a viable option for the management of pain in the age group of 65-98 years but the benefits need to be tempered by potential risks among the older adults.(40)

Methodology:-

Source of data collection:

The study group comprised of 60 patients posted for posterior stabilization of lumbar spine based on the inclusion and exclusion criteria mentioned below. It was carried out in Father Muller Medical College Hospital, Mangalore from November 2015 to May 2017.

Inclusion criteria:

1. Men and women between 18-60 years, who have given their consent.
2. ASA classes I and II.
3. Posted for posterior stabilization of lumbar spine.

Exclusion criteria:

1. History of allergy to opioids
2. History of/ongoing drug abuse
3. Patients who are already using a transdermal opioid patch
4. Pregnant patients

Study design:

A prospective, interventional, randomized, single blinded clinical study.

Sample size and sampling procedure:

Sample size was 60 and it comprised of men and women in more or less equal proportion.

Study procedure:

Group B: 30 patients who received transdermal buprenorphine 10µg/hour
Group F: 30 patients who received transdermal fentanyl 25µg/hour.

After institutional ethical committee clearance, patients falling within the inclusion criteria were selected for the study after a pre-anaesthetic evaluation was carried out and an informed consent taken. Patients were randomly allotted into the two groups mentioned above using sealed envelope technique. They were premedicated with Tab. Ranitidine 150mg on the night before the surgery and on the morning of the surgery. The transdermal patch was applied onto a clean, hairless portion of the skin (the upper back or chest of the patient) on the previous night of the surgery and the patients vitals were monitored closely. Patients were educated regarding the transdermal patch with an information leaflet and they were familiarized with the visual analog scale (VAS) for pain assessment (0 being no pain and 10 being the worst possible pain).

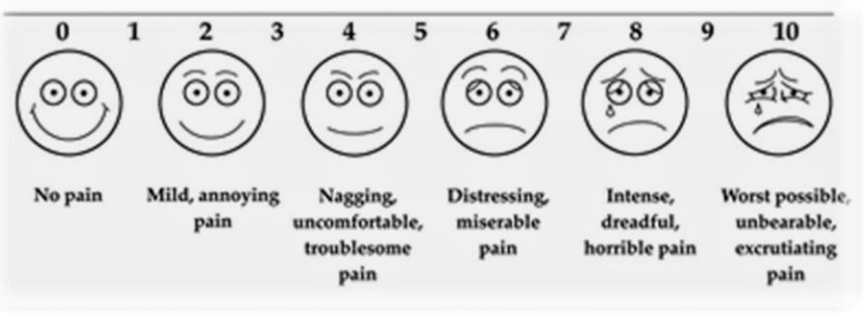

Fig 6:-Visual Analog Scale

Pre-operatively:
A baseline recording of the vital parameters- heart rate (HR), non-invasive blood pressure (NIBP), respiratory rate (RR) and oxygen saturation (SpO_2) was done.

Intra-operatively:
On the day of the surgery, in the operation theatre, patient was connected to the monitors using pulse-oximeter, ECG leads and blood pressure cuff. An 18G intravenous cannula was secured on the upper limb. Patient was induced for general anaesthesia with injections morphine (0.1mg/kg), propofol (2mg/kg) and vecuronium (0.1mg/kg) and intubated with an armoured endotracheal tube; maintained with inhalational anaesthetic, nitrous oxide and oxygen. Patient was positioned prone and care was taken to pad the pressure points. Hemodynamic parameters, respiration and SpO_2 were monitored.

Half an hour before the surgery was completed, all the patients received paracetamol infusion (15mg/kg) over 15 minutes. Once the surgery was completed, patients were repositioned, reversed, extubated and shifted to the post-operative unit where he/she was monitored every second hourly for 24 hours to assess the severity of pain (VAS), vitals, adverse effects and use of rescue analgesia.

The patients received intravenous analgesics in the form of continuous morphine infusion (1mg/hour) for the first post-operative day. If the patient experienced any breakthrough pain (VAS >4), rescue drugs such as injection ketorolac (0.5 mg/kg) or injection diclofenac (1.5 mg/kg) was administered immediately and time was noted. Oxygen saturation was continuously monitored using a pulse-oximeter and the respiratory rate was also kept track of. In case of severe bradypnoea (RR<8/min), injection Naloxone (0.4-2mg/kg) was kept ready. The patients were asked to report pain and three of the most frequent adverse effects (nausea, drowsiness and local irritation due to the patch) every two hours on the first day and thereafter every four hours for the second and third days. In case of nausea, they were treated with ondansetron (0.1mg/kg). The patch was discontinued in case of local irritation or drowsiness.

Patients were asked to rate their adverse effects with either 1 – nothing, 2 – light feeling, 3 – moderate feeling and 4 – intolerable feeling. All other adverse effects reported spontaneously by the subjects were recorded and rated in the same way.

Using the visual analog scale (VAS), the severity of pain was assessed and compared between both the groups. Also the demand for rescue drugs was monitored and compared between the two groups.

Modified Ramsay sedation score (RSS) (41) was used to assess the degree of sedation.
1. Paralyzed; unable to evaluate
2. Awake
3. Lightly sedated
4. Moderately sedated, follows simple commands
5. Deeply sedated, responds to non-painful stimuli
6. Deeply sedated, responds to painful stimuli
7. Deeply sedated, unresponsive to painful stimuli

Results:-

Statistical analysis:

Power analysis from similar studies suggest that a sample size of 30 patients/group is required to get the power of study to 80 %, with 0.05 level of significance. All the data was fed into the IBM SPSS software, mean and standard deviation was used for continuous data and median for non-parametric data. Age, weight and hemodynamic parameters were compared using students' t-test. Sedation and VAS scores were compared using independent t-test.

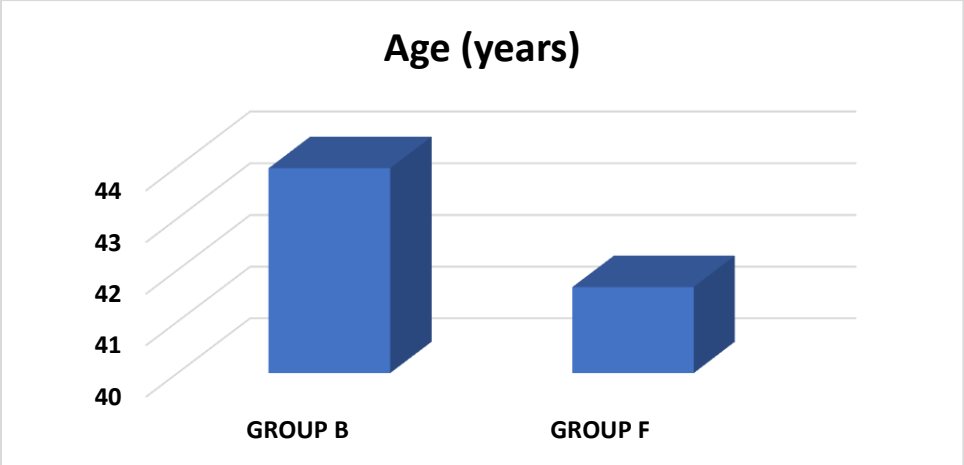

Fig 7:-Comparison of age

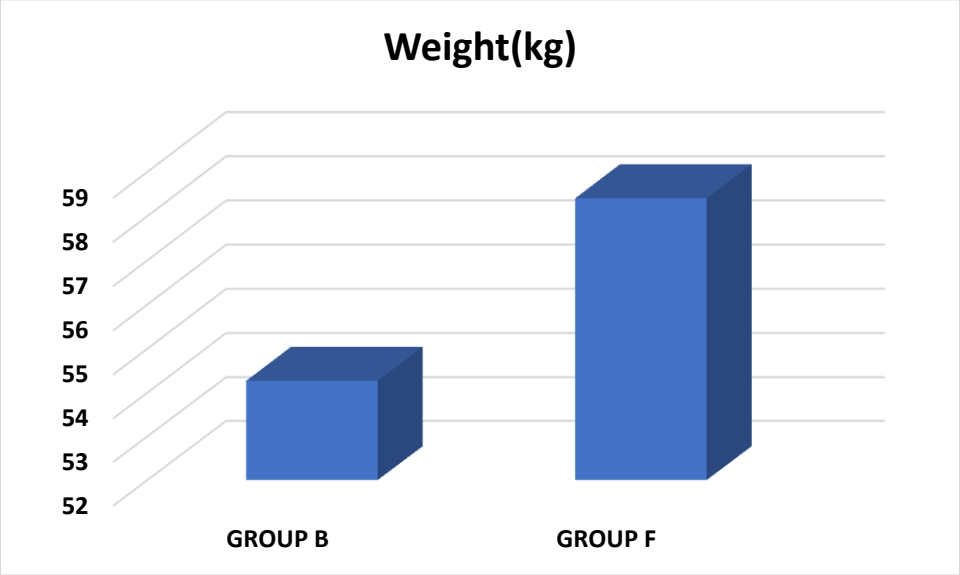

Fig 8:-Comparison of weight

The mean age in group B was 43.97+/-12.34 and in group F was 41.67+/-13.797. With a p- value of 0.4, these groups were comparable in terms of age. The mean weight in group B was 54.27+/-6.3 and in group F was 58.4+/-6.32. P-value was 0.014 and this means that there was statistically significant higher weight in the fentanyl group when compared to the buprenorphine group.

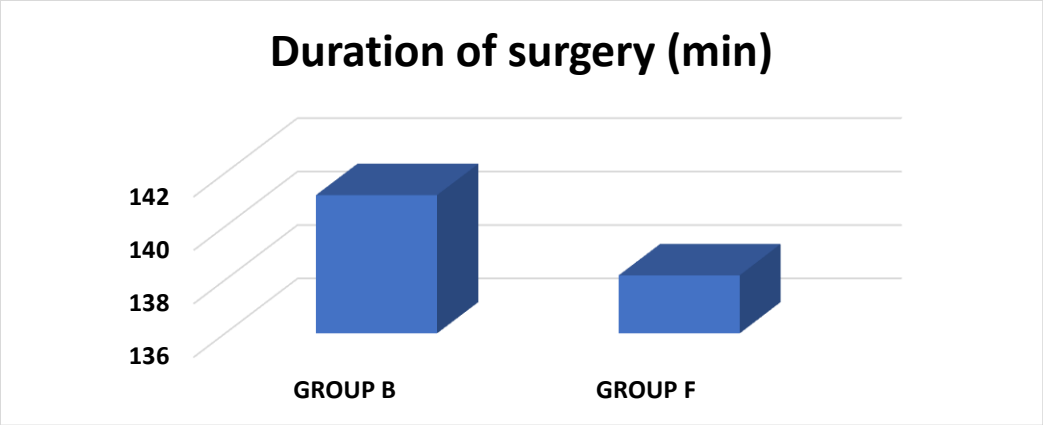

Fig 9:-Comparison of duration of surgery

With a p-value of 0.6, the duration of surgery between the two groups is comparable as the mean duration was 141.17+/-22.7 in group B and 138.17+/-24.86 in group F respectively.

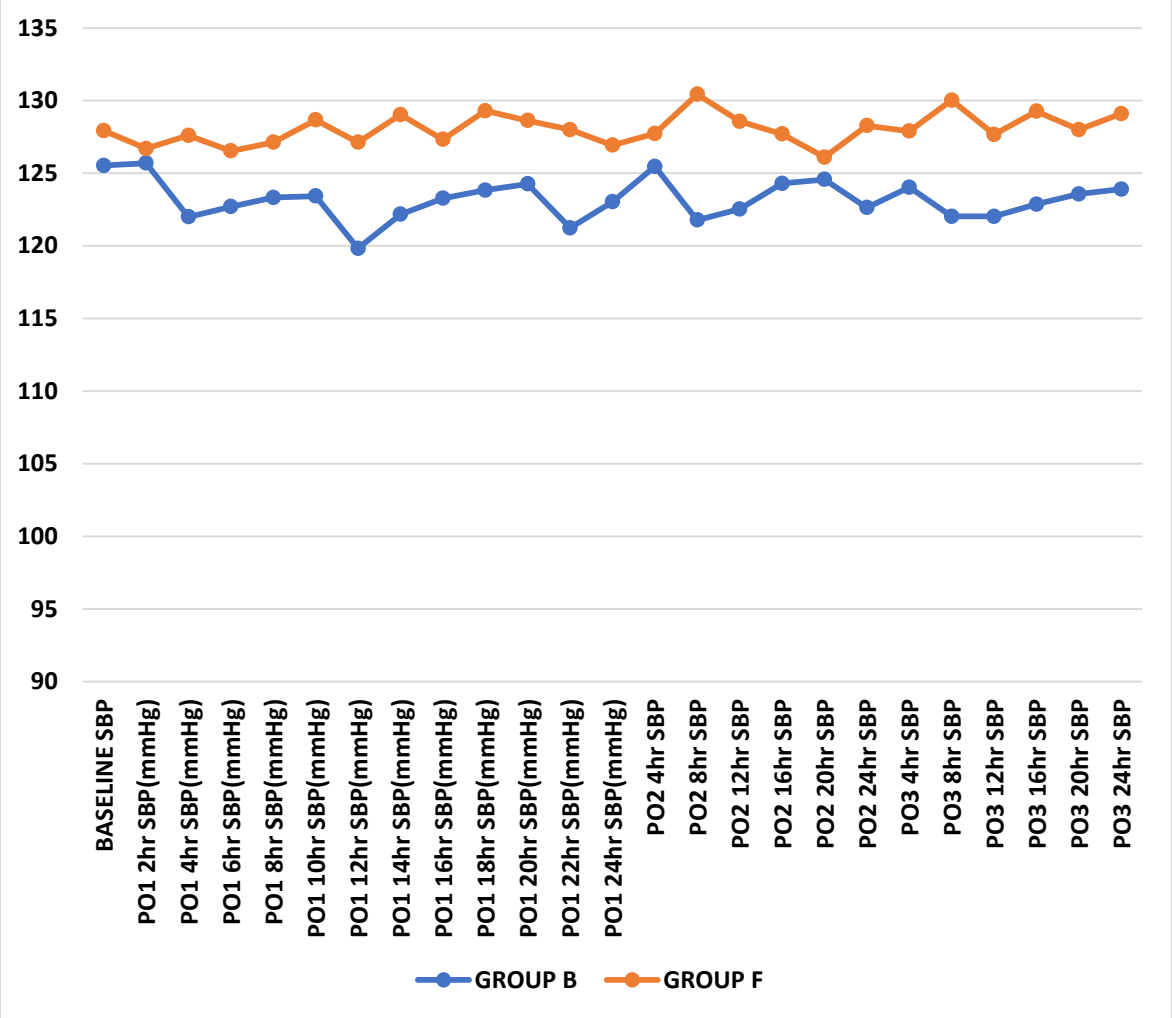

Fig 10:-Comparison of SBP

Comparison of the SBP between both the groups was overall statistically insignificant and hence it was comparable.

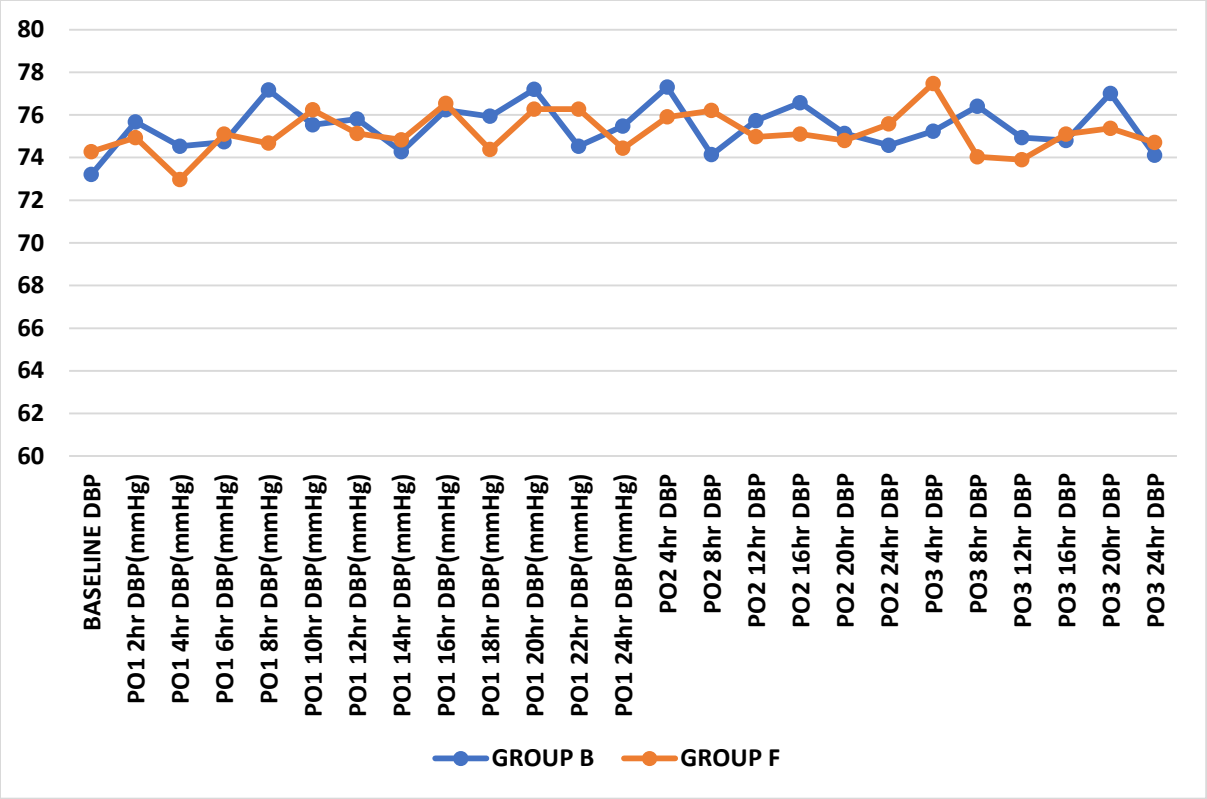

Fig 11:-Comparison of DBP between the two groups

Comparison of the DBP between both the groups was overall statistically insignificant and hence it was comparable.

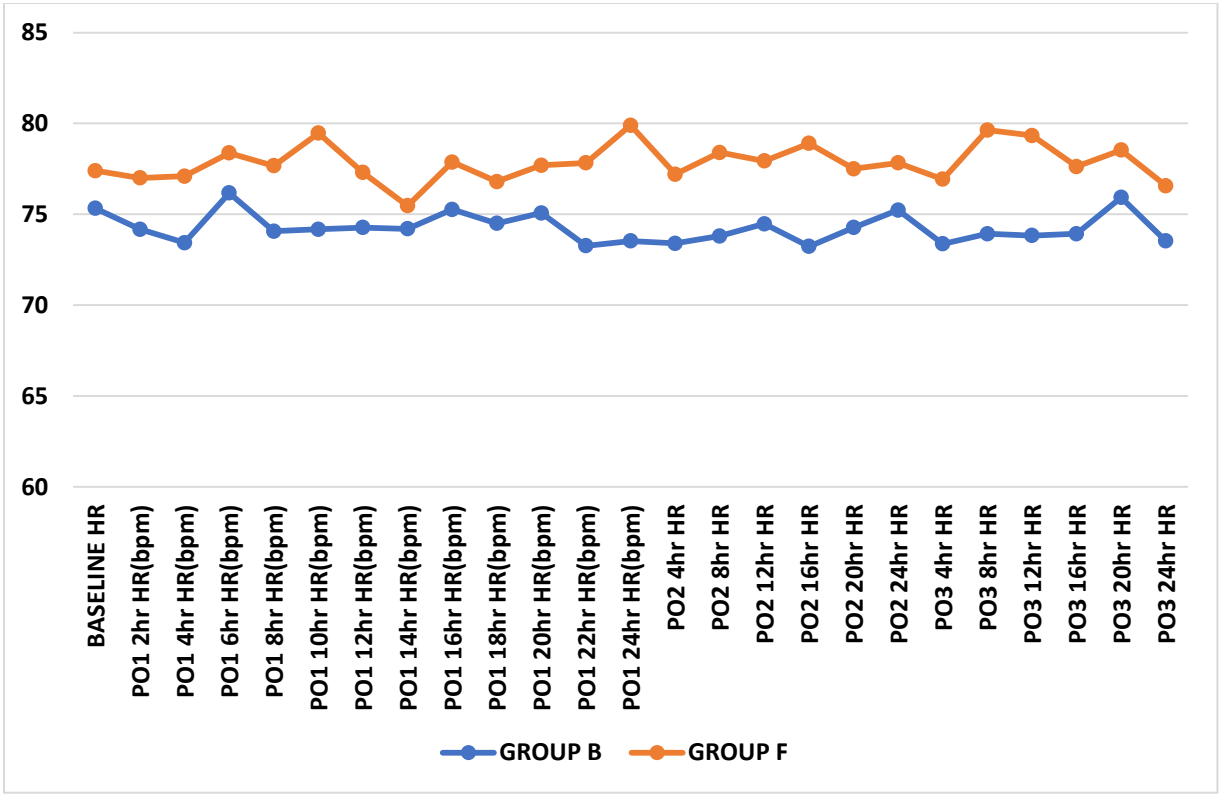

Fig 12:-Comparison of HR between the two groups

Comparison of the HR between both the groups was overall statistically and clinically insignificant.

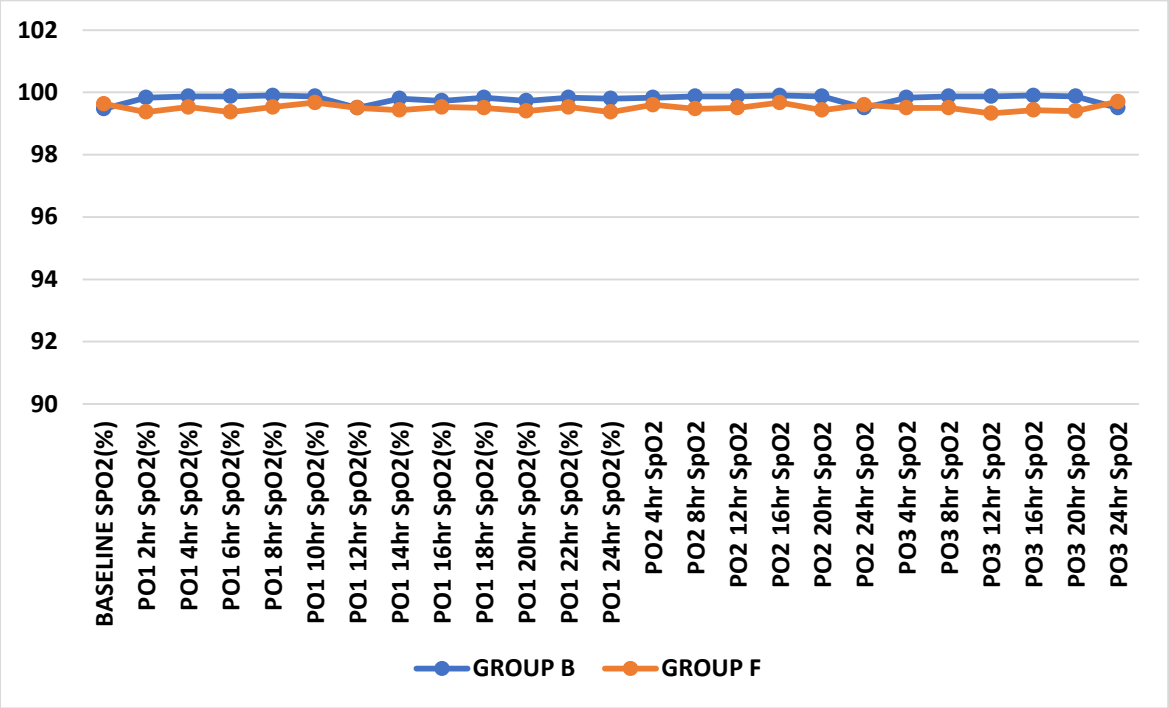

Fig 13:-Comparison of SpO2 between the two groups

There was statistically significant higher SpO2 in group B when compared to group F. however there was no clinically significant respiratory depression in group F.

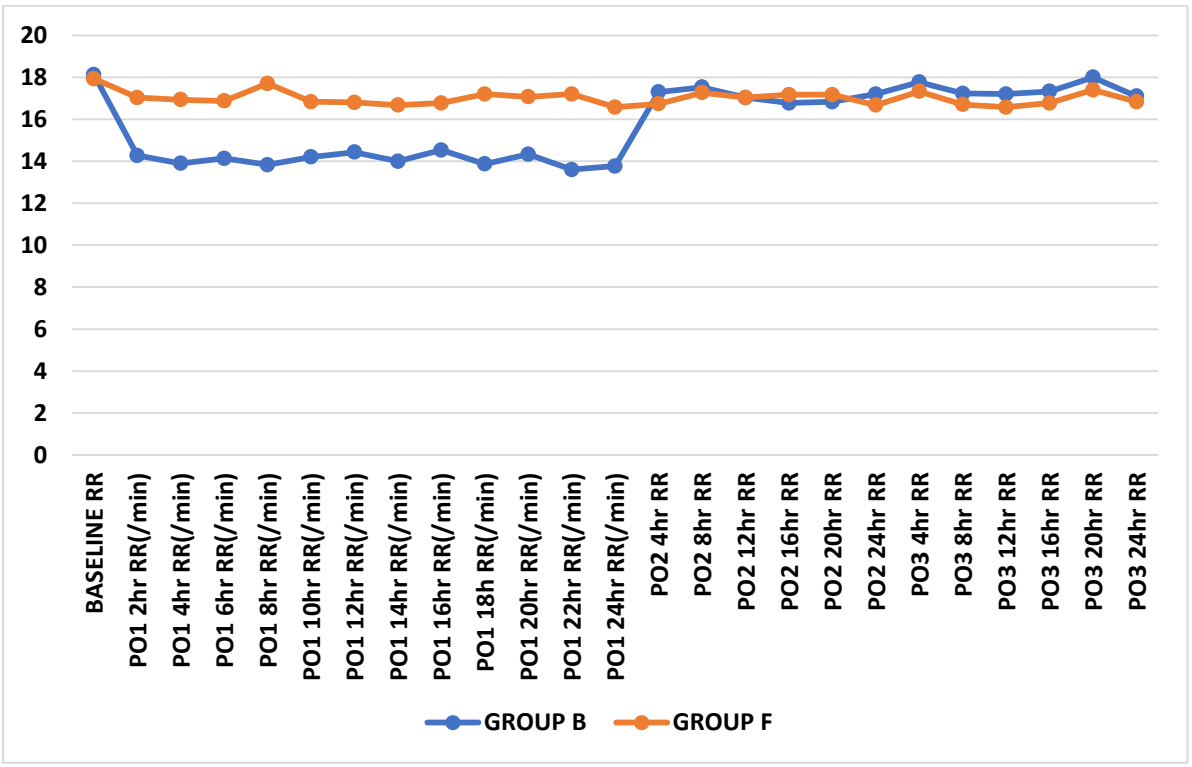

Fig 14:-Comparison of RR between the two groups

Comparison of RR between the two groups showed that there was statistically significant lower respiratory rate in group B ($p < 0.001$). It should be noted that this was not clinically significant as all the patients in group B had RR >12/min.

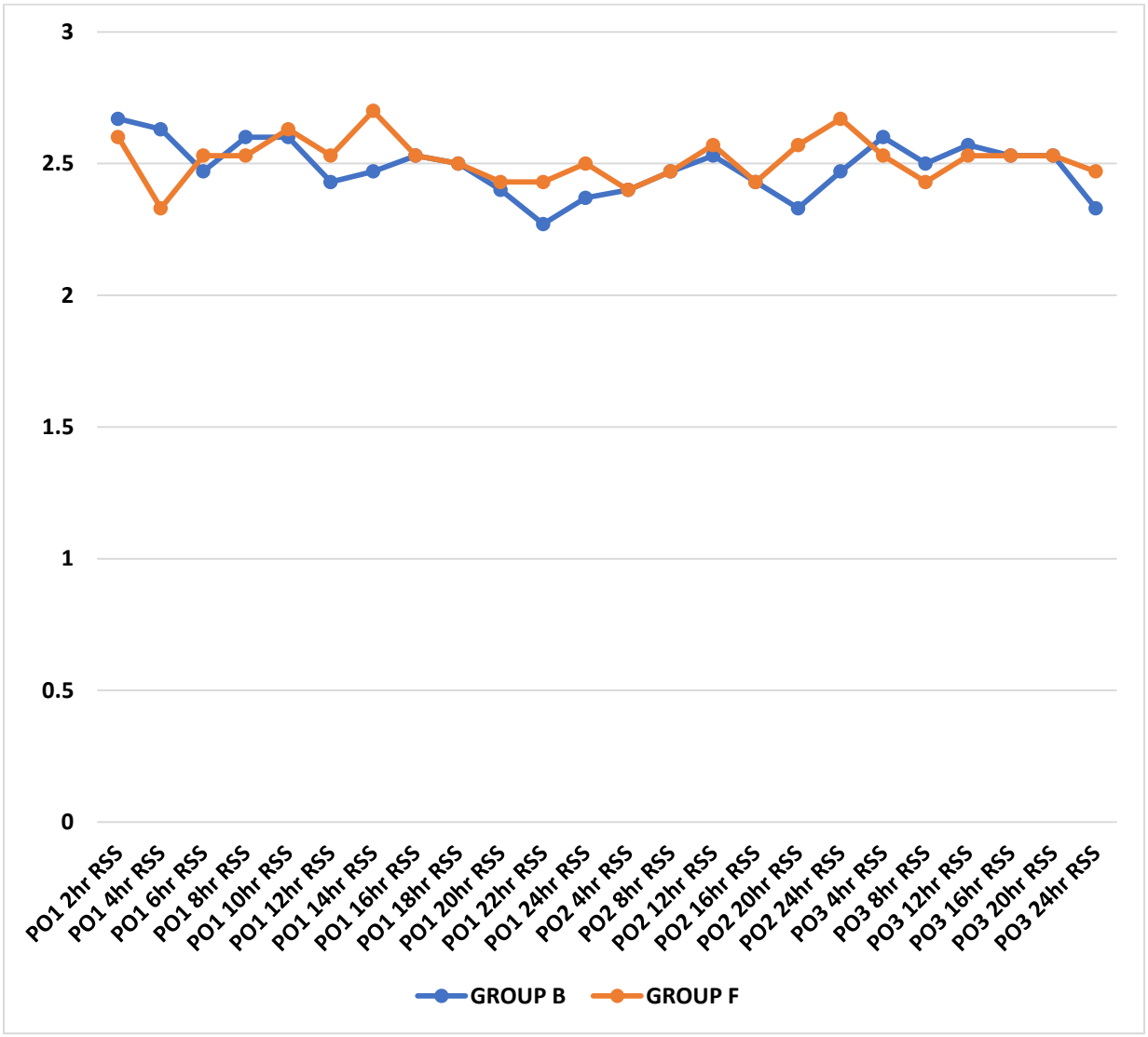

Fig 15:-Comparison of RSS between the two groups

There was no statistically or clinically significant sedation in either groups.

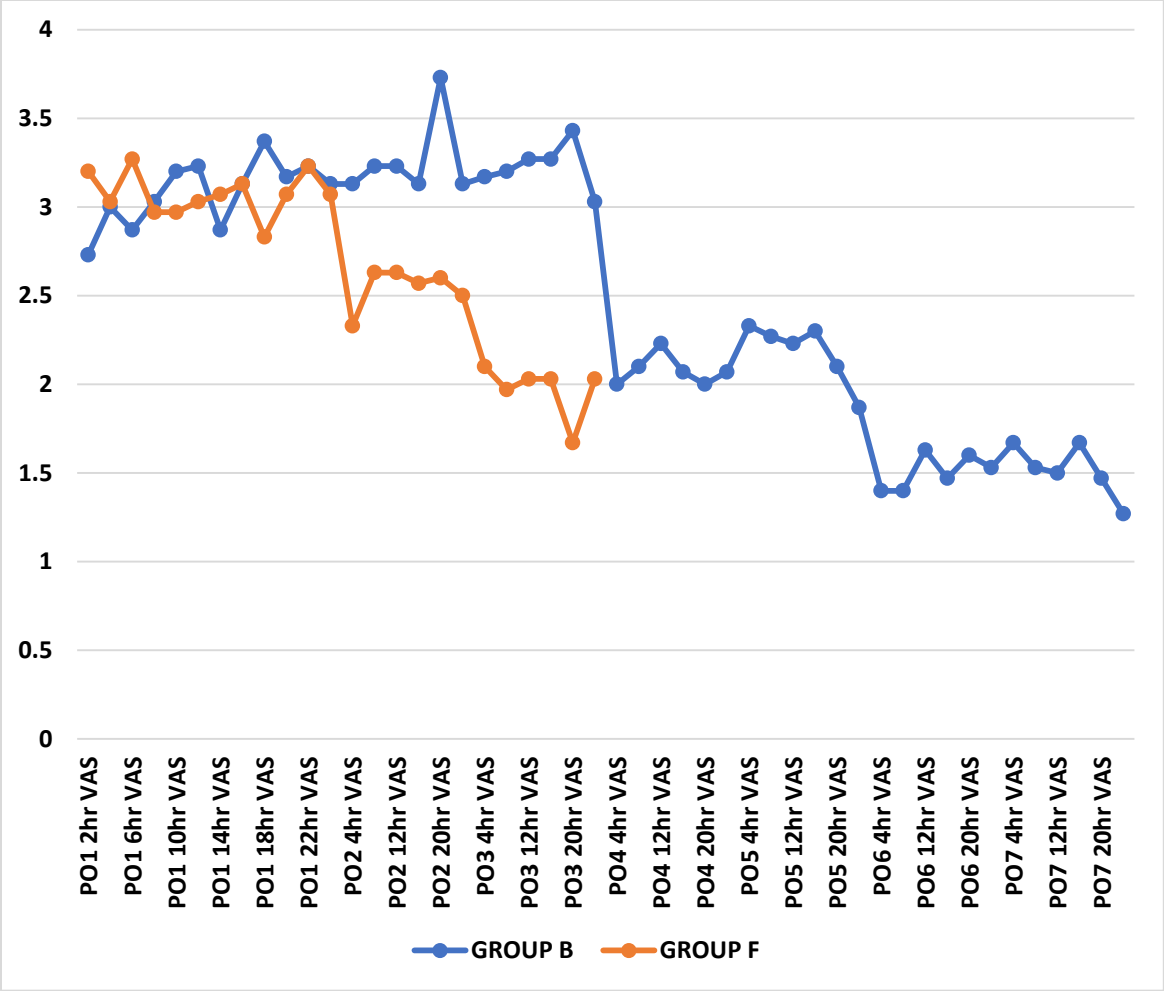

Fig 16: Comparison of VAS between the two groups

Group B showed lower VAS scores that were statistically significant in the 2nd and 6th hours of POD-1. However, after the 8th hour of POD-1, both groups had comparable VAS scores. From POD-2 onwards, VAS scores were significantly lower in group F.

Discussion:-

The goal of this study was to compare the analgesic efficacy and adverse effects, if any, between transdermal buprenorphine and transdermal fentanyl in the post-operative period in patients who underwent posterior stabilization of lumbar spine.

The dosage of each drug was decided after careful review of the various studies which use different doses of both buprenorphine and fentanyl by transdermal route and the effects of the different doses, as mentioned in the review of literature.

It was observed that 10 $\mu g/hr$ of transdermal buprenorphine and 25µg/hour of transdermal fentanyl had equianalgesic potency when compared to the standard drug morphine.

A total of 60 patients who were posted for elective posterior stabilization of lumbar spine and who gave their informed consent, were enrolled in the study.
The patients were allotted into two groups by sealed envelope technique. Since it was a single blinded study, only the patient did not know which group they belonged to. Depending on the envelope they picked, they were

categorized into either group B which received transdermal buprenorphine or group F, which received transdermal fentanyl.

During the pre-anaesthetic evaluation, all the patients were taught the visual analogue scale (VAS) and how to identify adverse reactions/emergencies, if any occurred. The respective patch was then applied onto a clean, hairless, dry area on the upper chest/back. If there was no area free of hair, then the hair over the chest was 1clipped with scissors and the patch was firmly held over the skin for 30 seconds. Patients were educated on the care to be taken while on the patch and a patient information leaflet was also provided.

Comparison of the age between the two groups shows that the age was higher in group B which was statistically not significant and hence, the groups were comparable.

Comparison of weight between the two groups shows that weight was higher in group F which was statistically significant. The increase in weight may demand a higher need for analgesia as the volume of distribution increases with weight.

Comparison of duration of surgery among the two groups shows that group B had longer surgeries which was statistically not significant. Hence the two groups are comparable with respect to duration of surgery and it can be established that the procedure was more or less similar in both groups.

The comparison of the postoperative VAS scores was done every 2 hours on the first postoperative day and was statistically significant with group F having higher VA scores at the 2^{nd} and 6^{th} hours. On the second and third postoperative days, there was a statistically significant difference in the VAS scores with group B having relatively higher scores throughout the day. This leads us to the understanding that transdermal fentanyl takes around 16-18 hours to reach maximum serum concentrations and has better analgesic effect when compared to buprenorphine which may have an earlier onset of action but is less potent than fentanyl.

Comparison of the RSS between the two groups showed that there was no statistically significant change or drop in RSS except for 4 hours postoperatively there was a statistically significant increase in Group B, which was transient and not associated with adverse effects. All patients in both groups were calm, comfortable and easily arousable throughout the study and none of them showed excessive sedation.

However, one patient in the buprenorphine group had an episode of giddiness after the second postoperative day and hence the patch was discontinued.

Comparison of the oxygen saturation postoperatively shows that on all three postoperative days, the saturation was higher in group B and was statistically significant 95% of the time, which indicates that group F causes relatively more respiratory depression than group B, although not life threatening.

Comparison of respiratory rate between the two groups shows that on the first postoperative day, RR is higher in group F which is statistically significant On the second postoperative day, the RR was higher in group B although not statistically significant. There however was no clinically significant bradypnoea in either groups.

Comparison of the SBP and DBP shows no statistically significant difference between the two groups B & F. This shows that transdermal patches as such have no significant impact on the blood pressure.

Comparison of the heart rate between the two groups show that group F had a higher heart rate although it was statistically significant only 10% of the time. It should be noted that the heart rate remained within acceptable limits of 75-80 beats per minute.

T test was used for comparing oxygen saturation between the two groups, Comparison of the SBP, HR, RR, RSS and VAS was done using independent t test. Comparison of DBP was done using student t test.

All the 60 patients showed VAS <4 in the first 2-4 hours after surgery. At 12^{th} and 22^{nd} hour, two patients in group B experienced VAS >4 and were administered the rescue analgesic. On the second postoperative day, eight patients from group B required rescue analgesic compared to two in group F. On postoperative day three, seven patients in

the TDB group required rescue analgesia versus none in the TDF group. This corresponds with good postoperative pain relief with transdermal fentanyl patch.

The incidence of nausea and vomiting was significant in group F on all three postoperative days. Two patients in group F required injection ondansetron as compared to none in group B on the first postoperative day. On the second and third postoperative days, four patients in group F required ondansetron on each day compared to none in group B. No other adverse effects were seen.

The findings of our study were in accordance with the studies done by Z. Arshad, R. Prakash and S. Gautam, in which they found that mean VAS scores were significantly lower in the fentanyl group when compared to the buprenorphine group on postoperative days 1, 2 and 3. The need for rescue analgesia, hence was higher in the buprenorphine group (5 out of 30) when compared to the fentanyl group (0 out of 30). Our study is comparable to the study conducted by Wolff RF, Reid K, Di Nisio et al where they found that there were fewer side effects in patients who received TDB than those who received TDF. Also, our study has comparable findings to that of a study conducted by Sathitkarnmanee T et al who found that patients on TDF had decreased need for rescue analgesia and a higher incidence of nausea and vomiting and there was no severe respiratory depression.

Limitations of the study:-

1. Small sample size. Bigger sample group will validate the findings further.
2. Although VAS scores and time for rescue analgesia were corresponding, the evaluation of comfort of patient could have been enhanced by questionnaires on post-operative pain relief up until the removal of the patch.
3. Ages >60 years were not included in the study and hence the effect of transdermal opioids in the elderly population was not studied.
4. Plasma levels of the drug were not measured.

Conclusion:-

Based on the findings of the study, we can conclude that for elective posterior stabilization of lumbar spine, transdermal fentanyl 25mcg/hr administered on the night prior to surgery, provides continuous, reliable and effective analgesia along with sedation, when compared to transdermal buprenorphine 10mcg/hr, which does provide analgesia but is not as potent as fentanyl. Significant nausea warranting the need for rescue anti-emetics was seen with transdermal fentanyl.

Summary:-

Postoperative analgesia is of major concern especially in patients undergoing posterior stabilization of lumbar spine, where the severity of pain is intense. Transdermal patches are a novel way of administering safe and sustained analgesia where very little health care personnel involvement is required. Moreover, it is non-invasive and evades the need for multiple painful injections.

In this study, we have compared the effects on duration of action, adequacy of analgesia and adverse effects of transdermal fentanyl and transdermal buprenorphine.

In this study, we have shown that:

1. The demographic profile was comparable in both groups with the exception of weight distribution.
2. Post-operative haemodynamics were comparable and stable in both groups.
3. Transdermal fentanyl provided more reliable and effective analgesia and hence, VAS scores were lower in this group.
4. VAS scores were higher in the buprenorphine group and hence the requirement of rescue analgesia was higher.
5. Sedation was mild and comparable among the two groups.
6. More respiratory depression, although clinically insignificant, was seen with transdermal fentanyl.
7. Incidence of nausea was higher in the fentanyl group.

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