

## Spectrum of Transdermal Analgesia in Postoperative Knee Arthroplasty -A Tertiary Experience

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**Abstract:** Post operative pain management in knee arthroplasty is of utmost concern as it increases chances of mobilisation, physiotherapy and prevention of deep venous thrombosis. Recent advances in transdermal drug delivery in the form of opioid and NSAIDS improve the quality of analgesia and decreases the complications through other routes of administration. A transdermal analgesic patch or pain relief patch is a medicated adhesive used to relieve moderate to severe pain. There are primarily two types of pain relieving patches, patches containing counterirritants which are used for mild to moderate pain and patches containing opioids like fentanyl used to relieve moderate to severe pain in opioid tolerant patients.

**Keywords:** Total knee arthroplasty, transdermal drug delivery system, fentanyl patch, pain score, visual analogue scale.

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### I. Introduction:

Knee replacement, also known as knee arthroplasty, is a surgical procedure to replace the weight-bearing surfaces of the knee joint to relieve pain and disability. It is most commonly performed for osteoarthritis,[1] and also for other knee diseases such as rheumatoid arthritis and psoriatic arthritis. In patients with severe deformity from advanced rheumatoid arthritis, trauma, or long-standing osteoarthritis, the surgery may be more complicated and carry higher risk. Osteoporosis does not typically cause knee pain, deformity, or inflammation and is not a reason to perform knee replacement.

Knee replacement surgery can be performed as a partial or a total knee replacement.[2] In general, the surgery consists of replacing the diseased or damaged joint surfaces of the knee with metal and plastic components shaped to allow continued motion of the knee.



The operation typically involves substantial postoperative pain, and includes vigorous physical rehabilitation. The recovery period may be 6 weeks or longer and may involve the use of mobility aids (e.g. walking frames, canes, crutches) to enable the patient's return to preoperative mobility.

The length of post-operative hospitalization is 5 days on average depending on the health status of the patient and the amount of support available outside the hospital setting.[3] Protected weight bearing on crutches or a walker is required until specified by the surgeon because of weakness in the quadriceps muscle.

For post-operative knee replacement patients, immobility is a factor precipitated by pain and other complications. Mobility is known as an important aspect of human biology that has many beneficial effects on the body system.[4] It is well documented in literature that physical immobility affects every body system and contributes to functional complications of prolonged illness. In most medical-surgical hospital units that perform knee replacements, ambulation is a key aspect of nursing care that is promoted to patients. Early ambulation can decrease the risk of complications associated with immobilization such as pressure ulcers, deep vein thrombosis (DVT), impaired pulmonary function, and loss of functional mobility. Nurses' promotion and execution of early ambulation on patients has found that it greatly reduces the complications listed above, as well as decreases length of stay and costs associated with further hospitalization. Nurses may also work with teams such as physical therapy and occupational therapy to accomplish ambulation goals and reduce complications.

## II. Transdermal Drug Delivery System:

### DEFINITION:

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered by this method. A wide variety of pharmaceuticals are now available in transdermal patch form.

The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979. These patches administered scopolamine for motion sickness.[5]

### COMPONENTS:

The main components to a transdermal patch are:

**Liner** - Protects the patch during storage. The liner is removed prior to use.

**Drug** - Drug solution in direct contact with release liner

**Adhesive** - Serves to adhere the components of the patch together along with adhering the patch to the skin

**Membrane** - Controls the release of the drug from the reservoir and multi-layer patches

**Backing** - Protects the patch from the outer environment



**Permeation Enhancer** - These are permeation promoters for drugs, which increases delivery of drug.

**Matrix Filler** - It provides bulk to matrix as well as some of fillers acts as matrix stiffening agent.

Other components includes: Stabilizer (anti oxidants), Preservatives etc.

There are five main types of transdermal patches.

**Single-layer Drug-in-Adhesive:**

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

**Multi-layer Drug-in-Adhesive:**

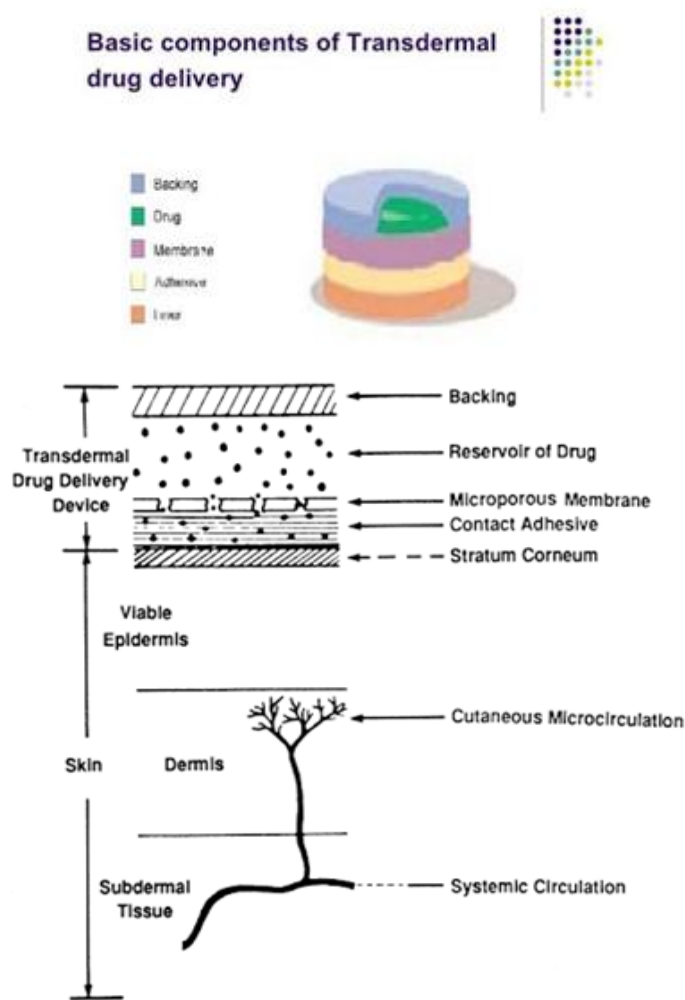
The multi-layer drug-in-adhesive patch is similar to the single-layer system; the multi-layer system is different, however, in that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). One of the layers is for immediate release of the drug and other layer is for drug-in-adhesive, usually separated by a membrane (but not in all cases). One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. This patch also has a temporary liner-layer and a permanent backing. The drug release from this depends on membrane permeability and diffusion of drug molecules.

**Reservoir:**

Unlike the single-layer and multi-layer drug-in-adhesive systems, the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. The drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate, with a rate-controlling membrane made of a polymer like vinyl acetate on one surface. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

**Matrix:** The matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer, partially overlaying it. Also known as a monolithic device.

**Vapour Patch** : In a vapour patch, the adhesive layer not only serves to adhere the various layers together but also to release vapour. Vapour patches release essential oils for up to 6 hours and are mainly used for decongestion. Other vapour patches on the market improve quality of sleep or aid in smoking cessation.



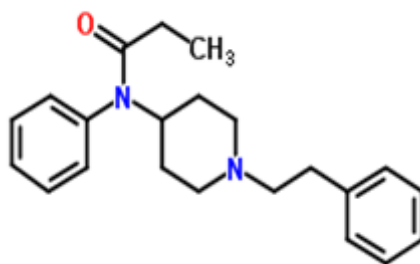
Two opioid medications used to provide round-the-clock relief for severe pain are often prescribed in patch form, fentanyl CII (marketed as Duragesic) and buprenorphine CIII (marketed as BuTrans).

#### **FENTANYL:**

Fentanyl, also known as fentanil, is an opioid which is used as a pain medication and together with other medications for anesthesia. It has a rapid onset and effects generally last less than an hour or two. Fentanyl is available in a number of forms including by injection, as a skin patch, and to be the tissues.

Fentanyl was first made by Paul Janssen in 1960 and approved for medical use in the United States in 1968. It was developed by testing chemicals similar in structure to pethidine (meperidine) for opioid activity.[6] In 2015, 1,600 kilograms (3,500 lb) were used globally.[8] As of 2017, fentanyl was the most widely used synthetic opioid in medicine.

Fentanyl patches are on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.



Fentanyl transdermal patches (Durogesic/Duragesic) are used in chronic pain management. The patches work by slowly releasing fentanyl through the skin into the bloodstream over 48 to 72 hours, allowing for long-lasting pain management. Dosage is based on the size of the patch, since, in general, the transdermal absorption rate is constant at a constant skin temperature. Rate of absorption is dependent on a number of factors. Body temperature, skin type, amount of body fat, and placement of the patch can have major effects. The different delivery systems used by different makers will also affect individual rates of absorption. Under normal circumstances, the patch will reach its full effect within 12 to 24 hours; thus, fentanyl patches are often prescribed with a fast-acting opioid (such as morphine or oxycodone) to handle breakthrough pain.

It is unclear if fentanyl gives long term pain relief to people with neuropathic pain. In palliative care, transdermal fentanyl has a definite, but limited, role for people already stabilized on other opioids who have persistent swallowing problems and cannot tolerate other parenteral routes such as subcutaneous administration. people with moderate to severe kidney failure.

troublesome side effects of oral morphine, hydromorphone, or oxycodone.[citation needed] Care must be taken to guard against the application of external heat sources (such as direct sunlight, heating pads, etc.) which in certain circumstances can trigger the release of too much medication and cause life-threatening complications. people with moderate to severe kidney failure troublesome side effects of oral morphine, hydromorphone, or oxycodone.[citation needed] Care must be taken to guard against the application of external heat sources (such as direct sunlight, heating pads, etc.) which in certain circumstances can trigger the release of too much medication and cause life-threatening complications.

Duragesic was first approved by the College ter Beoordeling van Geneesmiddelen, the Medicines Evaluation Board in the Netherlands, on July 17, 1995, as 25, 50, 75 and 100 µg/h formulations after a set of successful clinical trials, and on October 27, 2004, the 12 µg/h (actually 12.5 µg/h) formulation was approved as well. On January 28, 2005, the U.S. Food and Drug Administration approved first-time generic formulations of 25, 50, 75, and 100 µg/h fentanyl transdermal systems (made by Mylan Technologies, Inc.; brand name Duragesic, made by Alza Corp.) through an FTC consent agreement derailing the possibility of a monopoly in the treatment of breakthrough chronic pain by Alza Corp. In some cases, physicians instruct patients to apply more than one patch at a time, giving a much wider range of possible dosages. For example, a patient may be prescribed a 37.5 µg dosage by applying one 12.5 µg patch and one 25 µg patch simultaneously, or contingent on the large size of the (largest) 100 µg/h patch, multiple patches are commonly prescribed for doses exceeding 100µg/h, such as two 75 µg/h patches worn to afford a 150 µg/h dosage regimen. Although the commonly referred to dosage rates are 12/25/50/75/100 µg/h, the "12 µg" patch actually releases 12.5 µg/h.[21] It is designed to release half the dose of the 25 µg/h dose patch.

**Storage and disposal** :The fentanyl patch is one of a small number of medications that may be especially harmful, and in some cases fatal, with just one dose, if used by someone other than the person for whom the medication was prescribed.[8] Unused fentanyl patches should be kept in a secure location that is out of children's sight and reach, such as a locked cabinet.

When patches cannot be disposed of through a medication take-back program, flushing is recommended for fentanyl patches because it is the fastest and surest way to remove them from the home so they cannot harm children, pets and others who were not intended to use them.

In February 2004, a leading fentanyl supplier, Janssen Pharmaceutica Products, L.P., recalled one lot, and then later, additional lots of fentanyl (brand name: Duragesic) patches because of seal breaches which might have allowed the medication to leak from the patch.



A series of Class II recalls was initiated in March 2004, and in February 2008 ALZA Corporation recalled their 25 µg/h Duragesic patches due to a concern that small cuts in the gel reservoir could result in accidental exposure of patients or health care providers to the fentanyl gel.[9]

In February 2011, the manufacturer suspended production of all Duragesic patches due to quality control issues involving unspecified "microscopic crystallization" detected during the manufacturing process of the 100 µg/h strength.

#### **Adverse effects:**

Fentanyl's most common side effects (more than 10% of patients) include diarrhoea, nausea, constipation, dry mouth, somnolence, confusion, asthenia (weakness), sweating, and less frequently (3 to 10 % of patients) abdominal pain, headache, fatigue, anorexia and weight loss, dizziness, nervousness, hallucinations, anxiety, depression, flu-like symptoms, dyspepsia (indigestion), dyspnoea (shortness of breath), hypoventilation, apnoea, and urinary retention. Fentanyl use has also been associated with aphasia.[10]

Despite being a more potent analgesic, fentanyl tends to induce less nausea, as well as less histamine-mediated itching, than morphine. Fentanyl may produce more prolonged respiratory depression than other opioid analgesics. In 2006 the U.S. Food and Drug Administration (FDA) began investigating several respiratory deaths, but doctors in the United Kingdom were not warned of the risks with fentanyl until September 2008. The FDA reported in April 2012 that twelve young children had died and twelve more made seriously ill from separate accidental exposures to fentanyl skin patches.

The precise reason for sudden respiratory depression is unclear, but there are several hypotheses: Saturation of the body fat compartment in patients with rapid and profound body fat loss (patients with cancer, cardiac or infection-induced cachexia can lose 80 % of their body fat). Early carbon dioxide retention causing cutaneous vasodilatation (releasing more fentanyl), together with acidosis, which reduces protein binding of fentanyl, releasing yet more fentanyl.

Reduced sedation, losing a useful early warning sign of opioid toxicity and resulting in levels closer to respiratory-depressant levels. Fentanyl has a therapeutic index of 270.[11]

#### **VISUAL ANALOGUE SCORE:**

The visual analogue scale or visual analog scale (VAS) is a psychometric response scale which can be used in questionnaires. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points.



**PURPOSE:**

The pain VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases.

**Structure, Orientation, and Response Options**

VAS can be presented in a number of ways, including:

scales with a middle point, graduations or numbers (numerical rating scales), meter-shaped scales (curvilinear analogue scales), "box-scales" consisting of circles equidistant from each other (one of which the subject has to mark), and scales with descriptive terms at intervals along a line (graphic rating scales or Likert scales)[11]

The most simple VAS is a straight horizontal line of fixed length, usually 100 mm. The ends are defined as the extreme limits of the parameter to be measured (symptom, pain, health)[9] orientated from the left (worst) to the right (best). In some studies, horizontal scales are orientated from the left (worst) to the right (best). In some studies, horizontal scales are orientated from right to left, and many investigators use vertical VAS. No difference between horizontal and vertical VAS has been shown in a survey involving 100 subjects[10] but other authors have suggested that the two orientations differ with regard to the number of possible angles of view. Reproducibility has been shown to vary along a vertical 100-mm VAS and along a horizontal VAS.[12] The choice of terms to define the vary along a vertical 100-mm VAS and along a horizontal VAS.[12] The choice of terms to define the anchors of a scale has also been described as important.[8]

**ADMINISTRATION:**

They are generally completed by patients themselves but are sometimes used to elicit opinions from health professionals. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.[1]

**Recall Period for items:**

Recall period for items. Varies, but most commonly respondents are asked to report "current" pain intensity or pain intensity "in the last 24 hours."

**Scoring and Interpretation:**

Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark, providing a range of scores from 0–100. A higher score indicates greater pain intensity. Based on the distribution of pain VAS scores in post-surgical patients (knee replacement, hysterectomy, or laparoscopic myomectomy) who described their postoperative pain intensity as none, mild, moderate, or severe, the following cut points on the pain VAS have been recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm) (11). Normative values are not available. The scale has to be shown to the patient otherwise it is an auditory scale not a visual one.

**Merits and Demerits:**

The VAS is widely used due to its simplicity and adaptability to a broad range of populations and settings. VAS is more sensitive to small changes than are simple descriptive ordinal scales in which symptoms are rated, for example, as mild or slight, moderate, or severe to agonizing.

These scales are of most value when looking at change within individuals. The VAS takes < 1 minute to complete. No training is required other than the ability to use a ruler to measure distance to determine a score. Minimal translation difficulties have led to an unknown number of cross-cultural adaptations. However, assessment is clearly highly subjective. Are of less value for comparing across a group of individuals at one time point.



It could be argued that a VAS is trying to produce interval/ratio data out of subjective values that are at best ordinal. The VAS is administered as a paper and pencil measure. As a result, it cannot be administered verbally or by phone. Caution is required when photo-copying the scale as this may change the length of the 10-cm line and also, the same alignment of scale should be used consistently within the same patient. Thus, some caution is required in handling such data.[1]

**Obtaining the scale:**

The pain VAS is available in the public domain at no cost.

**Psychometric Information:**

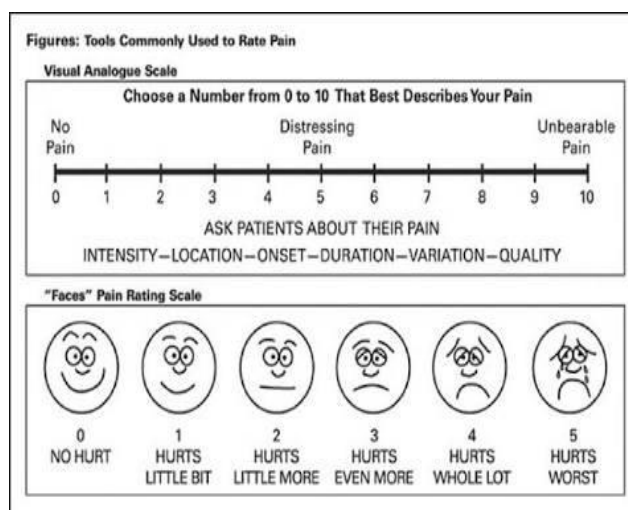
**Method of development.** The pain VAS originated from continuous visual analog scales developed in the field of psychology to measure well-being. Woodforde and Merskey first reported use of the VAS pain scale with the descriptor extremes “no pain at all” and “my pain is as bad as it could possibly be” in patients with a variety of conditions. Subsequently, others reported use of the scale to measure pain in rheumatology patients receiving pharmacologic pain therapy. While variable anchor pain descriptors have been used, there does not appear to be any rationale for selecting one set of descriptors over another.

**Acceptability:**

The pain VAS requires little training to administer and score and has been found to be acceptable to patients. However, older patients with cognitive impairment may have difficulty understanding and therefore completing the scale. Supervision during completion may minimize these errors.

**Reliability:**

Test-retest reliability has been shown to be good, but higher among literate ( $r = 0.94, P = 0.001$ ) than illiterate patients ( $r = 0.71, P = 0.001$ ) before and after attending a rheumatology outpatient clinic.



**Validity:**

In the absence of a gold standard for pain, criterion validity cannot be evaluated. For construct validity, in patients with a variety of rheumatic diseases, the pain VAS has been shown to be highly correlated with a 5-point verbal descriptive scale (“nil,” “mild,” “moderate,” “severe,” and “very severe”) and a numeric rating scale (with response options from “no pain” to “unbearable pain”), with correlations ranging from 0.71–0.78 and 0.62–0.91, respectively). The correlation between vertical and horizontal orientations of the VAS is 0.99.

**Ability to detect change:** In patients with chronic inflammatory or degenerative joint pain, the pain VAS has demonstrated sensitivity to changes in pain assessed hourly for a maximum of 4 hours and weekly for up to 4 weeks following analgesic therapy ( $P = 0.001$ ). In patients with rheumatoid arthritis, the minimal clinically significant change has been estimated as 1.1 points on an 11-point scale (or 11 points on a 100-point scale). A minimum clinically important difference of 1.37 cm has been determined for a 10-cm pain VAS in patients with rotator cuff disease evaluated after 6 weeks of nonoperative treatment.

**AIM OF STUDY:**

To study the pain scores in postoperative knee arthroplasty patients from day 2 and day 3 with transdermal fentanyl patch.

**III. Materials And Methods:**

This is a retrospective study for a period of 1 year ( July 2016 to August 2017).total 50 unilaterally knee arthroplasty were studied for the year of which initial 10 patients were without transdermal patches. Visual analogue scale is reference pain scale. Scores were evaluated on day 2 and 3 in these patients. All 40 patients received transdermal fentanyl patch on chest during the end of surgical procedure and were studied in postoperative period.All the patients under study were between 50 to 60 years of age and classified american society of anaesthesiology as ASA\_GRADE 2.

**IV. Results:**

All the cases studied without transdermal fentanyl patch were ranging from a pain score of 6 to 8 in day 2 and 3 with nausea and itching in 1 patient which was treated with hydrocortisone avil.

**TABLE OF PAIN SORES IN PATIENTS WHO DIDN'T RECEIVE TRANSDERMAL PATCHES:**

VISUAL ANALOGUE SCALE	DAY 2	DAY 3	ITCHING	RESPIRATORY DEPRESSION
	7	6	Nil	Nil
	8	6	Nil	Nil
	7	7	Nil	Nil
	7	7	Nil	Nil
	8	6	Nil	Nil
	6	5	Nil	Nil
	7	7	Yes	Nil
	7	6	Nil	Nil
	7	7	Nil	Nil

All the patients who received transdermal fentanyl and diclofenac patch ranged a pain score of 3 to 5 with 1 or 2 having itching and nausea which were treated with avil, hydrocortisone and ondansetron.

**TABLE OF PAIN SORES IN PATIENTS WHO RECEIVED TRANSDERMAL PATCHES:**

PATIENTS	PAIN SCORE DAY 2	DAY 3	ITCHING	RESPIRATORY DEPRESSION
1	5	4	Nil	Nil
2	5	5	Nil	Nil
3	5	4	Nil	Nil
4	4	4	Nil	Nil
5	4	3	Nil	Nil
6	6	4	Nil	Nil
7	5	4	Nil	Nil
8	5	5	Nil	Nil

9	5	5	Nil	Nil
8	4	4	Nil	Nil
9	4	3	Nil	Nil
10	3	2	Nil	Nil
11	3	3	Nil	Nil
12	4	3	Nil	Nil
13	3	3	Nil	Nil
14	5	4	Nil	Nil

15	5	4	Nil	Nil
16	5	4	Nil	Nil
17	4	3	Nil	Nil
18	3	2	Nil	Nil
19	3	3	Nil	Nil
20	4	3	Nil	Nil
21	4	3	Nil	Nil
22	5	3	Nil	Nil
23	4	3	Nil	Nil

24	3	2	Nil	Nil
25	3	3	Nil	Nil
26	4	4	Nil	Nil
27	3	2	Nil	Nil
28	3	2	Nil	Nil
29	3	2	Nil	Nil



30	4	2	Nil	Nil
31	4	3	Nil	Nil
32	4	4	Nil	Nil

33	5	4	Nil	Nil
34	4	3	Nil	Nil
35	4	3	Nil	Nil
36	5	4	Nil	Nil
37	4	3	Nil	Nil
38	3	2	Nil	Nil
39	3	3	Nil	Nil
40	3	3	Nil	Nil

### V. Conclusion:

Fentanyl is soluble in water with a low molecular weight and high potency, it is ideal for transdermal drug delivery. The Durogesic reservoir patch is currently being phased out and replaced with DT trans \_ a matrix design. In addition to decreasing the risk of accidental overdose with membrane damage the new matrix system is smaller and thinner than the reservoir.

Fentanyl patches are designed to deliver fentanyl at four constant rates: 25, 50, 75, 100 micro grams per hour for a period of 72 h. After initial application, a depot of fentanyl forms in the upper skin layers and serum fentanyl concentration increases gradually, generally levelling off between 12 and 24 h. The steady state serum concentration is reached after 24h and maintained as long as the patch is renewed. However variations have been found in serum fentanyl concentration during the 72 h period; concentration tends to be higher in the first 24 h and decrease between patch and skin.

Thus a combined use of transdermal patches has been effective in decreasing the pain burden on the patient. The other routes of drug administration have been frequently associated with complications like nausea, vomiting, itching more frequently than the transdermal drug patches as the absorption rate is slow and drug delivered is also slow. These patches effectiveness enhances when started in intraoperative period.

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