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POST OPERATIVE ANALGESIA

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ABSTRACT:

AIM AND OBJECTIVE:

To do a review on post-operative analgesia.

BACKGROUND:*The concept of the analgesia is to reduce the magnitude and duration of the post-operative pain. post-operative pain is one of the most frequently reported symptoms. Identification of the predictive factors is to facilitate the early intervention, and better pain management. Analgesic treatment is important to obtain efficient reduction of post injury pain hypersensitivity. Development of safe and short-acting anaesthetics, improved pain relief by early intervention with multimodal analgesia, and stress reduction by regional anaesthetic techniques, β-blockers, or glucocorticoids have provided important possibilities for enhanced recovery. When these techniques are combined with a change in preoperative care enhancement of recovery and decrease in hospital stay can be achieved, even in major operations.*

REASON: *The reason is to gain current knowledge on post-operative analgesia.*

KEYWORDS: *Aspirin, paracetamol, ibuprofen, morphine, ketamine etc.*

1. INTRODUCTION:

Post-surgical pain is traditionally managed with the use of systemic analgesics. In oral surgery the period of post-surgical pain is usually circumscribed and lasts for 8-12 hours. Different classes of analgesia reflect their effects through different mechanisms. Their side effects tend to be different and may be dose related. The Current concept of postoperative analgesia is mainly based on the combination of opioids, non-steroidal anti-inflammatory drugs NSAIDs or paracetamol, small dose ketamine, and preoperative administration of local anaesthetic [1] eg.pratracted nausea and vomiting,instability, ataxia,etc.Interventional techniques such as epidural are effective but requires additional work and carries the potential risk of serious complications.The use of opioids may be limited by adverse effects, such as nausea, vomiting, excessive sedation, pruritus, and urinary retention etc. Opioid analgesic agents in high doses of adults may leads to cause changes in levels of cortisol,catecholamines,vasopressor and growth hormone.[2] The availability of a long acting local anaesthetic leads to decrease the post-operative pain.Different classes of analgesics exert their effects through different mechanisms e.g., respiratory depression with opioids or enteropathy with nonsteroidal anti-inflammatory drugs NSAIDs tend to be different and may be dose related. A

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combination of analgesics from different classes may provide additive analgesic effects with fewer side effects than when a single therapeutic drug is used.

There has been a trend over recent years for combining NSAIDs with paracetamol acetaminophen for the management of acute postoperative pain.[3] but the therapeutic superiority of the combination over either drug alone remains controversial.[4,5] In 2002, Hillesden et al.5 noted that paracetamol,NSAID combinations showed superior pain relief over paracetamol alone in 5 of 7 studies, but over an NSAID alone in only 2 of 4 studies, whereas Romsing et al.2 noted an advantage for such combinations over paracetamol alone in 6 of 9 studies but over an NSAID alone in only 2 of 6 studies.postoperative pulmonary dysfunction may delay recovery and, if severe, can be life-threatening. Hypoxia may impair wound healing and cognitive function, the latter especially in the elderly. Atelectasis predisposes patients to chest infection, and chest infection predisposes patients to respiratory failure. It is widely assumed that when postoperative patients are relatively pain-free, their pulmonary function is improved. They can readily expand their chests, breathe deeply, cough well, and cooperate with physical therapy [6,7,8] They are therefore less likely to develop atelectasis, hypoxia, or pulmonary infection, and more likely to recover quickly and uneventfully. In the process of preparing a clinical practice guideline on the management of postoperative pain [9]. we examined the scientific evidence related to possible beneficial effects of various pain therapies on respiratory function. We present metaanalyses of data from randomized, controlled trials (RCTs) that assess the effect of specific pain treatments on respiratory function in postoperative patients.

Meta-analysis, defined as the quantitative synthesis of data from multiple trials, has become a scientific discipline with well described principles and methods [10,11,12]. It uses an explicit, systematic approach to literature retrieval, combined with specific statistical methods to integrate and interpret the results of separate investigations to improve on the traditional subjective process of drafting a narrative review article. The current concept of multimodal postoperative analgesia is mainly based on the combination of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol, small-dose ketamine, and perioperative administration of local anaesthetics. The use of opioids may be limited by adverse effects, such as nausea, vomiting, excessive sedation, pruritus, and urinary retention, the incidences of which have been reported to be 25%, 20%, 3%, 15%, and 23%, respectively [13]. Interventional techniques such as epidural analgesia is effective but require additional work and carry the potential risk of serious complications. NSAIDs are associated with damage to gastrointestinal mucosa, bleeding, renal toxicity, allergic reactions, and heart failure. [14] Cyclooxygenase-2 selective NSAIDs may have prothrombotic properties, increasing the risk of stroke and myocardial ischemia. A drug that has analgesic properties, opioid-sparing effects, possibly reduces opioid tolerance, relieves anxiety, and is not associated with the adverse effects typical for the traditional analgesics would be an attractive adjuvant for perioperative analgesia.

POST OPERATIVE ANALGESICS:

NSAID (NON-STEROIDAL ANTI-INFLAMMATORY DRUG)

Non-steroidal anti-inflammatory drug (NSAID's) are aspirin type or non-opioid analgesics. It has anti-inflammatory, antipyretic and uricosuric properties. It consists of both non selective cox inhibitors and selective cox inhibitors.

MECHANISM OF ACTION:

During inflammation arachidonic acid liberated from membrane phospholipids is converted to prostaglandins [PGs], catalysed by the enzyme cycle oxygenase [COX]. NSAIDs inhibit the prostaglandin synthesis by inhibiting the enzyme cyclooxygenase. The mechanism of action of gabapentin and its successor, pregabalin is likely mediated by

binding to the 21 subunits of the presynaptic voltage gated calcium channels, which are up regulated in the dorsal root ganglia and spinal cord after surgical trauma.

ASPIRIN:

Aspirin is good analgesic and relieves pain of inflammatory origin. This is because PGs is formed during the inflammation and they sensitise the tissues to pain and aspirin inhibits PG synthesis and act as an Analgesic. The main advantages of aspirin are pain originating from the integumental structures like muscles, bones, joints and pain in connective tissues is relieved, the disadvantage is that vague visceral pain, aspirin is relatively ineffective. It can be taken as a prototype. Aspirin has good antipyretic and anti-inflammatory action.[15] The benefits of anti-platelet therapy for the prevention of thrombotic events in cardiovascular diseases are evident. Statistical studies have shown that secondary prevention by anti-platelet agents reduces the risk of nonfatal myocardial infarction (MI) and stroke by 25% to 30%, and the rate of vascular death by about 15%, resulting in a significant reduction in overall mortality [16,17,18].

These data demonstrate that blood platelets, circulating in an activated state, are important determinants of arterial thrombus formation and vessel occlusion and these processes can be antagonised by appropriate anti platelet therapy. However, it is also clear that one of the major problems in clinical use will be the separation of the antithrombotic efficacy of anti-platelet agent from interference with the physiological platelet function in hemostasis.[19] Anti platelet drugs are classified on the basis of their site of action, that is, drugs that inhibit (i) platelet adhesion, (ii) platelet activation, (iii) platelet aggregation, and (iv) platelet mediated links with inflammation. Aspirin belongs to the group of drugs that inhibit platelet activation. As seen before, platelet activation can be blocked by inhibited the TXA2 pathway, ADP pathway, thrombin pathway, and phosphodiesterase (PDE). Aspirin meets its effects by inhibiting the TXA2 pathway in a dose dependent manner.[20] COX converts AA, a -6polyunsaturated fatty acid PUFA, to prostaglandin H2 (PGH2), the precursor of the series-2 prostanoids. The enzyme contains two active sites: a heme with peroxidase activity, responsible for the reduction of PGG2 to PGH2, and a cyclooxygenase site, where AA is converted into the hydroperoxyendoperoxide PGG2. The reaction proceeds through H atom abstraction from AA by a tyrosine radical generated by the peroxidase active site. Two O2 molecules then react with the arachidonic acid radical, yielding PGG2 [21]. Lowdose 75–81 mg aspirin inhibits cycloxygenase-1 (COX-1) in such a way that only TXA2 production is inhibited and not of PGI2. Gastrointestinal tract (GIT) bleeding, drug interactions, and resistance are major drawbacks of aspirin. To avoid these drug reactions, work is ongoing for new strategies such as inhibition of thromboxane synthetase enzyme and blockade of TPRs receptors. TXA2 synthetase is not much efficacious clinically, because blockade of this enzyme results in accumulation of endoperoxide precursors which are themselves platelet TPR agonists [22]. In brief, aspirin irreversibly inhibits COX-1 by acetylating serine, thereby inhibiting the production of TXA2, a promoter of platelet aggregation, and prostaglandin, a potent inhibitor of platelet aggregation and powerful vasodilator, in platelets and vascular endothelial cells, respectively. In the absence of protein synthesis in platelets, TXA2 inhibition persists for the lifetime of the platelet compared with vascular endothelial cells, which recover COX-1 activity shortly after exposure to aspirin. For over 50 years, aspirin has been the basis of anti-platelet therapy, and it remains so today [23].

Aspirin may also be of benefit in the primary prevention of cardiovascular events, but the effect is more modest, and its recommendation is highly debated due to the fact that ischemic benefit may be offset by bleeding complications. Although aspirin is a cost-effective therapy, it is a weak antiplatelet agent [24], and a considerable

number of patients continue to experience atherothrombotic complications, especially highrisk patients, such as those presented with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).

PARACETAMOL:

Is the first drug used in this group is banned due to severe adverse effects. Paracetamol is a metabolite of phenacetin, is found to be safer and effective. It has analgesic, good antipyretic and weak anti-inflammatory properties. Due to weak pG inhibitory activity in the periphery, it has poor anti-inflammatory actions.

This review suggests that combining paracetamol and NSAID confers additional analgesic efficiency over the drug alone. The combination of paracetamol and NSAID was more effective than paracetamol or NSAID alone in85% to 60% of the studies.

There are some disadvantages in combining NSAID's and Paracetamol, the combination may be disadvantages when individual drugs are specifically suited to patients' symptoms, combining analgesics may increase the incidence of adverse effects. Paracetamol should be used with caution with pre-existing liver disease whereas the history of gastrointestinal ulcer or renal impairment precludes the use of NSAID's. Paracetamol is also one of the most commonly used drugs worldwide with non-prescription sales exceeding 25 thousand million doses per year in the United States of America. The haemodynamic effects of the intravenous paracetamol formulations are largely understudied. There is an emerging body of evidence suggesting that intravenous paracetamol may cause iatrogenic hypotension. Little is known as to the mechanisms of this phenomenon if intravenous paracetamol indeed does cause hypotension.

More recently, it has been suggested that paracetamol may also be linked with both direct and indirect stimulation of the nitric oxide synthase, and serotonergic pathways. The overall consensus is that paracetamol has a central site of action with little if any peripheral effect. It is likely that paracetamol has a multifactorial mechanism of action, which may include the activation of different pain pathways hence the difficulty in elucidating its precise mechanism of action. Intravenous (IV) paracetamol was introduced in the hospital setting in 1985 [22] and indicated when enteral administration is not possible [24]. Therefore, the majority of patients receiving IV paracetamol are critically ill and surgical patients. While recent studies suggest an increase in the use of IV paracetamol, there is a paucity of prospective controlled studies demonstrating its efficacy and safety in surgical and critically ill patients.

The pharmacological importance of paracetamol has been established by the vast number of non-prescription and prescription formulations available. While the oral route of paracetamol administration is common in the hospital setting, its clinical application is limited to subgroups such as critically ill, heavily sedated, anaesthetised or postoperative patients. The rectal route may be used in this setting, [25] however rectal suppositories have an unpredictable bioavailability of 24-98%, similar to that of the oral formulation bioavailability of 63-89%. The raw form, paracetamol has negligible solubility in water and, in aqueous medium; it is highly sensitive to oxygen and light. As a result, the formulation of IV paracetamol contained the active ingredient paracetamol hydrochloride. Intravenous propacetamol was produced by Bristol-Myers Squibb, France, in 1985 under the trade name Prodafalgan. Propacetamol is rapidly hydrolysed in a 1:1 ratio to produce paracetamol and N, N-diethyl- glycine by non-specific plasma esterase. Every 2 g of propacetamol yields a total of 1g paracetamol.

IBUPROFEN:

It is a propionic acid derivative, it is better tolerated than aspirin Analgesic,antipyretic,and anti-inflammatory efficiency is slightly lower than aspirin. It will bound to the plasma proteins and get metabolised in the liver, and

excreted in bile and kidneys. Adverse effects is mild compared to other NASID's.Normal dosage of ibuprofen is 400-800mg.Over all ibuprofen was one of the NSAID's most widely evaluated in the studies reviewed .The value of combining it with paracetamol is conformed all of five studies[26,27,28].Ibuprofen has well established reputation for safety and efficacy compared with other NSAID's[29,30,31].Hence for the case of combining ibuprofen with paracetamol to obtain increase analgesia without increasing the dose of NSAID is strong.When ibuprofen is administered at therapeutic doses in children of up to 10 mg/kg body weight every 6–8 hours the possible adverse events are, as for other NSAIDs related to inhibition of cyclo-oxygenase (COX-1 and COX-2) and prostaglandin (PG) pathways, gastrointestinal bleeding, renal impairment, asthma and hepatic toxicity. Rainsford et al.1997 have reviewed the safety of paracetamol and ibuprofen administered in adults at therapeutic dosages.

The authors concluded that both agents were safe as used in clinical trials, and that there are no statistically significant differences between paracetamol and ibuprofen in reports of adverse events in any organ system, irrespective of the type or frequency of event. Across a range of clinical studies in which either ibuprofen were treatments of primary interest, the overall percentage of patients having a minor adverse event was about 10% with paracetamol compared with 8% with ibuprofen, for drug exposure up to 30 days, which is not unexpected for events that are monitored prospectively. However, with such ubiquitous usage of both agents, the increased reporting of rare or idiosyncratic side effects.

Both ibuprofen and paracetamol are commonly used in the management of acute fever childhood illnesses. The incidence of NSAID or paracetamol-triggered asthma in children is thought to be less frequent than in adults. In a randomized controlled trial in febrile asthmatic children, those who received ibuprofen were less likely to be hospitalized and significantly less likely to require outpatient visits for asthma compared with children who received paracetamol Lesko et al. Debley et al.investigated the prevalence of ibuprofensensitive asthma in 127 children aged 6–18 years with mild to moderate asthma.

2. CLINICAL PHARMACOLOGY OF IBUPROFEN

Ibuprofen is supplied as tablets with a potency of 200 to 800 mg. [32]. The usual dose is 400 to 800 mg three times a day.[33] It is almost insoluble in water having pKa of 5.3. It is well absorbed orally; peak serum concentrations are attained in 1 to 2 hours after oral administration. It is rapidly bio-transformed with a serum half-life of 1 to 2 hours. The drug is completely eliminated in 24 hours after the last dose and eliminated through metabolism.[34,35]The drug is more than 99% protein bound, extensively metabolized in the liver and little is excreted unchanged.[36] Although highly bound to plasma proteins (90-99%), displacement interactions are not clinically significant, hence the dose of oral anti coagulants and oral hypoglycaemic needs not be altered.[32] More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, the major metabolites are hydroxylated and carboxylated compounds.[37,38]

Old age has no significant effects on the elimination of ibuprofen. [39,40] Renal impairment also has no effect on the kinetics of the drugs, rapid elimination still occurs as a consequence of metabolism.[41] The administration of ibuprofen tablets either under fasting conditions or immediately before meals yield quiet similar serum concentrations-time profile. When it is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption.[32]

3. DICLOFENAC:

Diclofenac is an Analgesic, antipyretic, and anti-inflammatory agent. Its tissue penetrability is good and attains good concentration in synovial fluid which is maintained for long time. Adverse effects are mild.

Dosage is 50 mg. Gel is also available for topical application ophthalmic preparation is also available for use in post-operative pain. Rectal suppository and mouth washes are also available. Miranda et al. [42] compared antinociception induced by the intraperitoneal coadministration of combinations of paracetamol with the widely used NSAIDs diclofenac, ibuprofen, ketoprofen, meloxicam, metamizole, naproxen, nimesulide, parecoxib, and piroxicam. They concluded that all of the combinations were synergistic. Qiu et al. [43]It is mainly used for chronic inflammatory conditions, rheumatoid arthritis,osteoarthritis, acute musculoskeletal pain and post-operative pain acute pulpitis, acute periapical abscess.

4. PHENYLBUTAZONE:

Phenylbutazone is a pyrazolone derivatives. It has good anti-inflammatory activity and it is more potent than diclofenac, the main disadvantage is that it has poor Analgesic and antipyretic effects. Phenylbutazone is an uricosuric agent.

It can be well absorbed orally intramuscular injection is not recommended because its absorption is slow as it binds to the tissue proteins and also causes tissue damage well bound to the plasma protein.Dosage requires 100-200mg, Small doses may be given 3-4 times a day to avoid gastric irritation. Adverse effects include it is more toxic than aspirin and it is poorly tolerated- dyspepsia, epigastric distress, nausea, vomiting are common, peptic ulcer and diarrhoea may occur.Phenylbutazone is mainly used in Rheumatoid arthritis, ankylosing spondylitis,osteoarthritis,gout and other musculoskeletal disorders.

5. INDOMETHACIN:

It is an indole acetic acid derivative, it is potent anti-inflammatory agent, antipyretic and good analgesic. It is well absorbed only 90% bound to the plasma proteins dosage requires is only25-50mg.Adverse effects are high gastrointestinal irritation with nausea, GI bleeding, vomiting, diarrhoea and peptic ulcers are common. CNS effects include headache, dizziness, ataxia, confusion, hallucinations, depression and psychosis. Indomethacin blunts the diuretic action of furosemide and anti-hypertensive action of thiazides and furosemide, beta blockers and ACE inhibitors by causing salt water retention. It is mainly used as eye drops in inflammation and as mouth rinse to suppress the gingival inflammation.

6. KETOROLAC:

Ketorolac is another PG synthesis inhibitor, having good Analgesic and anti-inflammatory properties. The advantage of ketorolac is used in Analgesic properties to relieve post-operative pain. Ketorolac is mostly used parenterally though it can also be given orally. Ketamine is psychotogenic

7. PIROXICAM:

Piroxicam is an oxicam derivative. It is long acting has good anti-inflammatory, Analgesic and antipyretic activity. In piroxicam drug interaction are not seen; it is better tolerated as it is less ulcerogenic piroxicam is a reversible cox inhibitor. Dosage requires only 20 mg. It is mainly used in post-operative pain.

8. MELOXICAM:

It is similar to piroxicam but in lower doses it causes less gastric irritation than piroxicam. It is better tolerated, Dose required is 7.5-15mg once daily.

9. MORPHINE:

Morphine is the most important alkaloid of opium, many new opioids with actions similar to morphine have been synthesised. But none of them are superior to morphine as an Analgesic, all opioid receptors are G- protein coupled receptors, stimulation of these receptors inhibit adenyl cyclase resulting in decreased intracellular camp formation. Morphine is potent Analgesic and it relieves pain without loss of consciousness. Dull visceral pain relieved than sharp pricking pain, but in higher doses it relieves the severe pain. It alters the both perception and reaction to pain. It raises the pain threshold and increases the capacity to tolerate pain. Euphoria and sedation also contribute to its Analgesic effects.Morphine is an agonist of the m and k receptors, whose activation results in analgesia. Morphinelike agonists act through the opioid receptors to cause pain relief, sedation, euphoria and respiratory depression. Morphine is glucuronidated and sulfated at positions 3 and 6, the plasma concentration ratios correlate positively with birth weight, which probably reflects increased liver weight with increasing birth weight.Moreover, morphine clearance correlates positively with gestational age and birth weight. SteadyState morphine plasma concentrations are achieved after 24-48 hours of infusion, but the glucuronide metabolite plasma concentrations do not reach steady state before 60 hours.

10. CONCLUSION:

In conclusion, for major orthopedic surgery, supplementation of spinal anesthesia with combined intrathecally injected and epidurally infused and considerably reduces patients post-operative spinal anesthesia alone, without inducing the short term or long-term adverse reactions. These encouraging findings suggest that, for intrathecal and epidural use, a low-cost, simple change in clinical anaesthesiology practice will do much to decrease patients' post-operative analgesic needs. gabapentin and pregabalin are effective in reducing pain intensity, opioid consumption and opioid-related adverse effects after surgery. Gabapentin and pregabalin have very few adverse effects of their own. Because of the heterogeneous data of these studies, no conclusions about the optimal dose and duration of the treatment can be drawn. The efficacy of gabapentin in preventing chronic pain needs to be elucidated in future studies.

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