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TO DETERMINE THE EFFECTIVENESS OF PERI-ARTICULAR INJECTION OF BUPIVACAINE, TRAMADOL, MAGNESIUM AND EPINEPHRINE FOR POSTOPERATIVE ANALGESIA IN KNEE JOINT ARTHROPLASTY

Anaesthesiology

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ABSTRACT

AIM OF THE STUDY: To determine the effectiveness of peri-articular injection of bupivacaine, tramadol, magnesium and epinephrine for postoperative analgesia in knee joint arthroplasty

INTRODUCTION: One of the analgesic techniques for pain management of knee joint arthroplasty is the peri-articular infiltration route.Excessive postoperative pain in arthroplasty of the knee may cause discomfort, delayed rehabilitation and discharge from the hospital. so,aggressive pain management in the early postoperative period is essential.

Several medications are commonly injected peri-articularly and intraarticularly for postoperative analgesia after knee arthroplasty. Among them,bupivacaine(2,3,4,5,8) , tramadol(7), magnesium(1,6) have been shown to reduce postoperative pain considerably.

MATERIAL AND METHODS: Following institute ethics committee approval,informed and written consent will be obtained from 60 patients of ASA class 1 and 2,scheduled to undergo knee arthroplasty of age 18-80 years and body mass index < 30.

Exclusion criteria; patients with severe systemic disease (heart failure,renal insufficiency,or coagulopathy) ,allergy or intolerance to study drugs, psychiatric illness, seizure disorder,regular narcotic use and refusal by the patient.

All patients will be familiarized with a 10 cm visual analogue scale (VAS) preoperatively with 0: no pain,1-3:mild pain,4-6:moderate pain,7-9:severe pain, and 10: the worst imaginable pain. Preoperative VAS scores will be obtained from all patients by asking the average intensity of pain at rest and on active movement of the knee.

Premedication will be given with tab Ranitidine 150 mg tab and Alprazolam 0.25 mg. Patients will be assigned into three groups randomly. The drug will be blinded to the surgeon and the anesthetist.The drug will be given peri-articularly atleast 10 min before the release of the tourniquet. Group BTME will be given 150 mg of 0.5 % bupivacaine(30ml) ,150 mg of tramadol(3ml),1gm of magnesium(2ml) and 0.5 ml of adrenaline (1:1000)-35.5ml made upto 100 ml solution with normal saline. Group BTE will be given 150 mg of 0.5 % bupivacaine(30ml),150 mg of tramadol(3ml),and 0.5 ml of adrenaline (1:1000)-33.5ml made upto 100 ml solution.Group NS will receive 100 ml normal saline. The first aliquot of 20 ml of the mixture will be injected,just prior to implantation of the component,into the posterior aspect of the capsule as well as the medial and lateral collateral ligaments. Care will be taken to avoid excessive infiltration in the area of the common peroneal nerve. Then when the cement will be curing,the quadriceps and the retinacular tissues will be infiltrated with 20 ml of the mixture. Finally,the remaining 60 ml will be used to infiltrate the fat and subcuticular tissues. All peri-articular injections will be performed by the surgeon.

In all groups regional anesthetic technique will be used. A dose of 3 ml of 0.5 % heavy bupivacaine +25 mcg fentanyl will be used. Neither intravenous narcotics nor ketamine will be administered during the surgery. The operations will be performed with the use of a tourniquet. A vacuum drain will be inserted before joint closure and will be removed on the first postoperative day. Standard monitoring techniques like ECG, blood pressure, pulse oximetry, capnography, heart rate will be used. All patients will receive oxygen via face mask throughout the procedure.

After the operation, patients will be transferred to post operative ward where VAS pain scores will be obtained from all patients at 1,2,4,6,8,12 and 24 hrs. Incase of inadequate analgesia (VAS>5),patients of all groups will receive Tramadol 100 mg, i.m. as a rescue medication once it is requested upto a maximum dose of 150 mg. The time to first analgesic consumption will be recorded. Analgesic duration will be defined as the time from completion of surgery until the first request for Tramadol.

Patients will be asked to indicate the degree of overall satisfaction with postoperative pain management on a 4- point satisfaction scale before discharge: 0=unsatisfactory/poor, 1=somewhat satisfactory/adequate,2=satisfactory/adequate, 3=very good, 4=excellent.

Blood pressure, heart rate,respiratory rate,and oxygen saturation and the presence of side effects such as nausea, vomiting, sedation, hypotension, dizziness, headache, drymouth,allergic reaction, respiratory depression and urinary retention will be recorded postoperatively for each patient at the same time as pain measurements.

Data will be analysed using Graph pad version 4,using nonparametric tests by Kruskal wallis test and using parametric tests by Anova test and Dunns multiple comparison test and performed post hoc test if P value is less than 0.05.

P value less than 0.05 is considered statistically significant between groups.

KEYWORDS

INTRODUCTION

Total knee arthroplasty is associated with considerable postoperative pain.[1-2] Good pain relief is important for postoperative knee rehabilitation, and it may influence the overall outcome.[3]It is severe in 60-90% of patients[1] and pain control during the immediate postoperative period remains difficult. [4-5]When inadequately treated, it intensifies reflex responses, which can cause serious complications, such as pulmonary or urinary problems, thromboembolism, hyperdynamic circulation, and increased oxygen consumption.[6] Moreover, it hinders early intense physical therapy, the most influential factor for good postoperative knee rehabilitation.[3] [7] But perioperative pain control is suboptimal.[8-11]

The use of opioid drugs, administered by means of either patient-controlled analgesia or other methods, deals with postoperative pain efficiently but is often associated with side effects, including nausea and vomiting, respiratory depression, drowsiness, pruritus, reduced gut motility, and urinary retention.[8,10,12]

Epidural analgesia is of proven benefit[13-16] but is associated with side effects such as spinal headache, urinary retention, hypotension, respiratory depression, and a risk of spinal infection. However, the adoption of low-molecular weight heparin thromboprophylaxis protocols has raised concerns regarding spinal hematoma formation with the use of continuous lumbar epidural analgesia.

Femoral and obturator nerve blocks (3-in-1 block)[17-19], lumbar plexus block,femoral and sciatic nerve blocks and femoral block alone[20] improve postoperative pain control and reduce consumption of narcotics at the cost of other potential problems, such as lack of technical expertise,urinary retention, and nerve damage, variable block of all the three nerves.

Continuous infusion of opioids and bupivacaine into the knee has provided good postoperative pain control but may be associated with prolonged wound drainage[12].

Providing analgesia locally in the area of surgical trauma, with minimal systemic side effects, is an attractive option.

Intraarticular injections of different analgesics following knee surgery have been shown to reduce requirements for postoperative analgesia and may lead to an earlier discharge from the hospital.

To reduce the occurrence of side effects or complications, an analgesia protocol should preferably be multimodal and should block pain at its origin and allow active physical therapy, and reduce venous stasis. Periarticular injection of local anesthetics is a possible option to achieve these goals[21-24].

The objective of this study was to assess the benefits and safety of a multimodal analgesia protocol that included periarticular soft-tissue injection of large doses of a local anesthetic for pain relief after total knee arthroplasty.

AIM OF THE STUDY

To determine the effectiveness of peri-articular injection of bupivacaine, tramadol, magnesium and epinephrine for postoperative analgesia in knee joint arthroplasty.

MATERIAL AND METHODS

Following institutional ethics committee approval, informed and written consent was obtained from 60 patients of ASA class 1 and 2, scheduled to undergo knee arthroplasty of ages 18-80 years and body mass index < 30.

The exclusion criteria were patients with severe systemic disease, ASA classs 3 and 4, allergy or intolerance to study drugs, psychiatric illness, seizure disorder, regular narcotic use and refusal by the patient.

All patients were familiarized with a 10 cm visual analogue scale (VAS) preoperatively with
0: no pain,
1-3:mild pain,
4-6:moderate pain,
7-9:severe pain, and
10: the worst imaginable pain.
Preoperative VAS scores was obtained from all patients by asking the average intensity of pain at rest and on active movement of the knee at the preanaesthetic checkup.

Premedication consisted of tab Ranitidine 150 mg tab and Alprazolam 0.25 mg.All patients received spinal anesthesia consisting of 3 ml of 0.5 % heavy bupivacaine +25 mcg fentanyl. No intravenous narcotics or ketamine was administered during the surgery. The operation was performed under tourniquet. A vacuum drain was placed before joint closure and removed on the first postoperative day by the surgical team. Standard monitoring techniques like ECG, blood pressure, pulse oximetry, capnography, heart rate were employed.

Patients were assigned into three groups by random envelope method. Both the surgeon and the anesthetist were blinded to the study drug. The drug was injected peri-articularly atleast 10 min before the release of the tourniquet by the surgeon.

1) Group BTME was given 150 mg of 0.5 % bupivacaine(30ml) +150 mg of tramadol(3ml)+1gm of magnesium(2ml) and 0.5 ml of adrenaline (1:1000)--35.5ml made upto 100 ml solution with normal saline.
2) Group BTE was given 150 mg of 0.5 % bupivacaine(30ml)+150 mg of tramadol(3ml)+and 0.5 ml of adrenaline (1:1000)-- 33.5ml made upto 100 ml solution.
3) Group NS will receive 100 ml normal saline.

The first aliquot of 20 ml of the mixture was injected prior to implantation of the component,into the posterior aspect of the capsule as well as the medial and lateral collateral ligaments. During the cement curing,the quadriceps and the retinacular tissues were infiltrated with 20 ml of the mixture. Finally,the remaining 60 ml was used to infiltrate the fat and subcuticular tissues. All peri-articular injections were performed by the operating surgeon.

Patients were transferred to post operative ward where VAS pain scores were obtained from all patients at 1,2,4,6,8,12 and 24 hrs. Incase of inadequate analgesia (VAS >5),patients of all groups received Tramadol 100 mg, as a rescue medication upto a maximum dose of 150 mg. The time to first analgesic consumption was recorded. Analgesic duration was defined as the time from completion of surgery upto the first request for Tramadol.

Patients were to indicate the degree of overall satisfaction with postoperative pain management on a 4- point satisfaction scale before discharge: 0=unsatisfactory/poor,
1= somewhat satisfactory/adequate,
2= satisfactory/adequate,
3= very good,
4= excellent.

Blood pressure,heart rate,respiratory rate,and oxygen saturation and the presence of side effects such as nausea, vomiting, sedation, hypotension, dizziness,headache, drymouth,allergic reaction, respiratory depression and urinary retention were recorded postoperatively for each patient at the same time as pain assessment over 24 hrs.

Data was analysed using Graph pad version 4,using nonparametric tests by Kruskal wallis test and using parametric tests by Anova test and Dunns multiple comparison test and performed post hoc test if P value is less than 0.05.

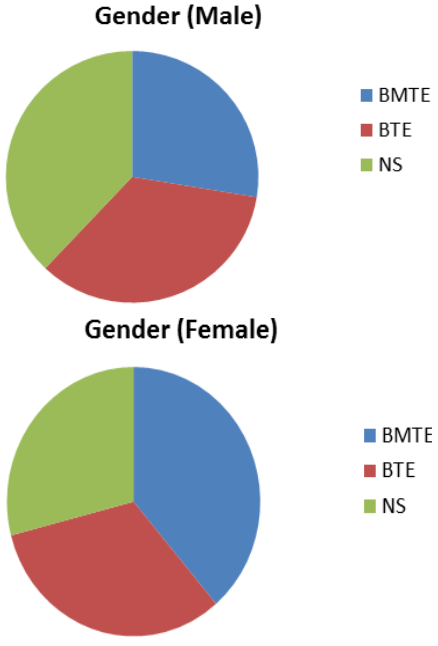
P value less than 0.05 is considered statistically significant between groups.

RESULTS

All the groups were comparable with respect to demographic variables (age, gender, weight). P value > 0.05 considered not significant compared to NS group.

Demographic data are presented in Table 1.
Pie diagram 1 and 2 depicts gender distribution.

Graph 1 showing distribution of Age and weight (mean values) among the groups.

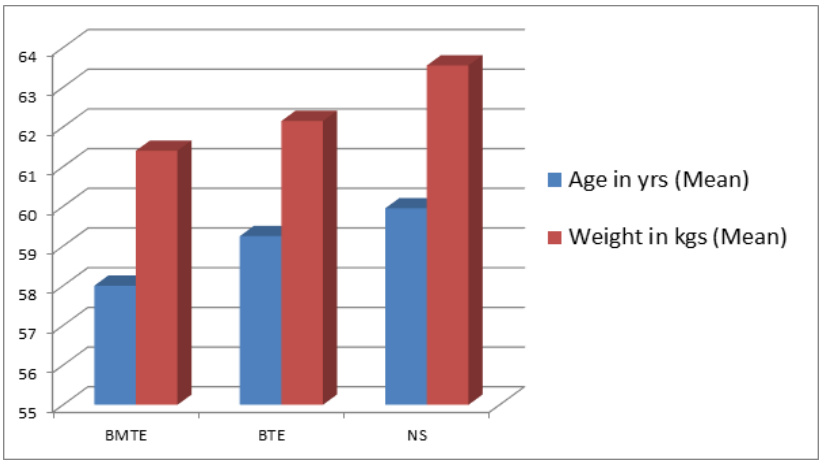


Pie diagram 1 and 2 showing Male and Female distribution among 3 groups.

Table 1 showing demographic variables:

Groups	Sex (m/f)	Age (Mean±SD(SEM))	Weight (Mean±SD (SEM))
BMTE	8/12	58±8.96 (2)	61.4±8.15 (1.82)
BTE	10/10	59.25±11.2 (2.52)	62.15±8.44 (1.88)
NS	9/11	59.95±10.7 (2.4)	63.55±7.17 (1.6)

P value > 0.05 considered not significant.



Graph 1 showing Age in years(Mean) and Weight in kgs(Mean) distribution among the 3 groups:

The changes in VAS pain score at 1st, 2nd, 4th,6th, 8th, 12th and 24th hour after completion of surgery are depicted in Table 2.

Groups	Restpain	movementpain	1st hr pain	2nd hr pain	4th hr pain	6th hr pain	8th hr pain	12th hr pain	24th hr pain
BMTE	0.45±0.94 (0.21)	6.15±1.63 (0.36)	0±0*# (0)	0.95±1.09*# (0.24)	0.95±1.09*# (0.24)	4.47±1.8 (0.41)	4.65±0.93 (0.2)	5.1±1.29 (0.28)	3.95±1.27# (0.28)
BTE	0.25±0.78 (0.17)	6.1±1.41 (0.31)	0.35±1.08 (0.24)	1.55±1.5 (0.33)	1.55±1.5 (0.33)	5.35±1.22 (0.27)	4.95±1.31 (0.29)	5.2±1.32 (0.29)	3.85±1.84# (0.41)
NS	0.45±0.94 (0.21)	6.25±1.07 (0.23)	1.4±1.95 (0.43)	6±1.37 (0.3)	6.1±1.33 (0.29)	6.5±1.05 (0.23)	5.9±1.02 (0.22)	6.05±0.94 (0.21)	5.45±1.09 (0.24)

*- P value <0.05 considered significant. #- P value <0.01 considered extremely significant.

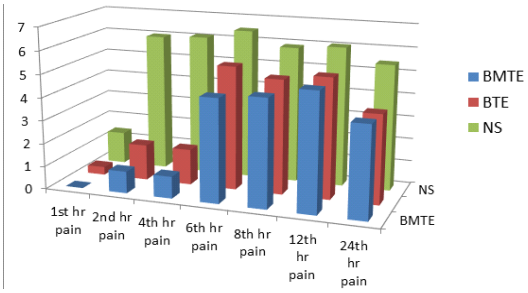
There was no statistically significant difference in VAS pain scores recorded at rest and movement in all 3 groups preoperatively.

VAS pain scores are very low in BMTE group in the first 4 hrs compared to BTE and NS groups and is considered significant (P value <0.05). But there was no significant difference between BMTE and BTE groups in the first 6 hrs postoperatively.

VAS pain scores were considered very significant between BMTE and NS group (P value <0.01) and no significant difference is seen between BMTE and BTE group, and the BTE and NS group in the 8th hr postoperative pain scores.

There is no statistically significant difference in VAS pain scores between all the 3 groups in the 12th hr postoperatively.

There was no significant difference between BMTE and BTE group but very significant difference was seen between BMTE and NS group(P value <0.01), and the BTE and NS group(P value <0.01) in the 24th hr pain scores. This difference may be due to the rescue medication received by BMTE and BTE groups.

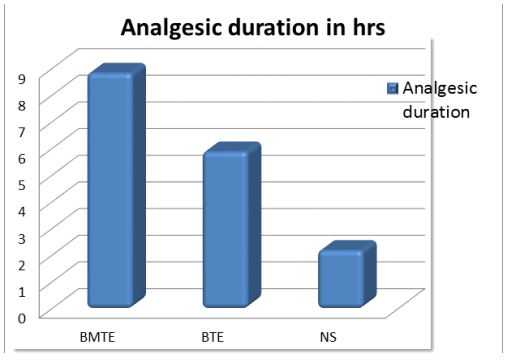


Graph 2 showing mean VAS scores at 1,2,4,6,8,12,24th hr for each group:

Table 3 showing Analgesic duration, Tramadol consumption and Degree of satisfaction scale:

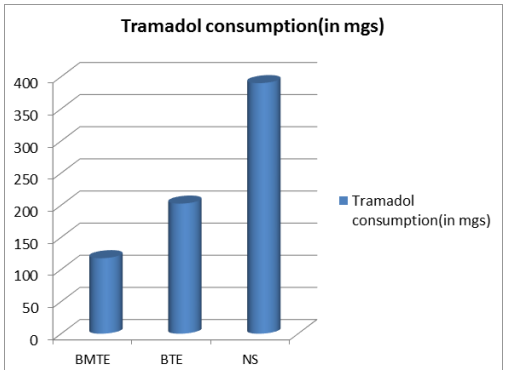
Groups	Analgesic duration	Tramadol consumption	Degree of Satisfaction
BMTE	8.85±4.25* (0.95)	117.5±63.4* (14.1)	3.15±0.58* (0.13)
BTE	5.9±4.4 * (0.98)	202.5±76.9* (17.1)	2.25±0.71* (0.16)
NS	2.2±0.61 (0.13)	390±71.8 (16)	0.35±0.58 (0.13)

*- P value <0.001 considered statistically highly significant.



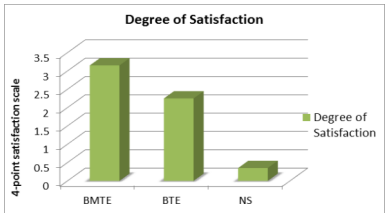
Graph showing Analgesic duration (Mean) between BMTE, BTE, and NS groups: P value is < 0.0001 is considered extremely significant.

Time to first analgesic consumption was significantly longer in Magnesium group (8.85±4.25 hrs) compared to Tramadol (5.9± 4.4 hrs) and Normal saline group (2.2± 0.61 hrs). P value is < 0.0001 is considered extremely significant.



Graph showing Tramadol consumption (Mean) between BMTE, BTE,and NS groups: P value is < 0.0001 (considered extremely significant)

The consumption of Tramadol was significantly higher in Normal saline group (390±71.8 mg) compared to Magnesium (117.5±63.4 mg) and Tramadol group (202.5±76.9 mg). P value is < 0.0001 (considered extremely significant).



Graph showing 4-point satisfaction scale (Mean) between BMTE, BTE and NS groups: P value is < 0.0001 (considered extremely significant).

The degree of overall satisfaction with postoperative pain management on a 4-point satisfaction scale was better in Magnesium group (3.15±0.58) compared to Tramadol (2.25±0.71) and Normal saline groups (0.35±0.58).P value is < 0.0001(considered extremely significant).

Groups	Nausea	Vomitting	Sedation	Allergic reaction	Urinary retension
BMTE	1	0	0	0	0
BTE	1	1	0	0	0
NS	0	1	0	0	0

Table showing side effects in all the 3 groups:

Side effects like Nausea, vomiting, allergic reaction, dry mouth, respiratory depression, and urinary retention were not observed significantly in any of the groups and there were no differences between the groups.

Most of the intra-articularstructures of the knee, including the synovial tissue, the anterior fat pad, and the joint capsule, have free nerve-endings that are capable of sensing painful stimuli and producing severepain.[63]

Operative procedures produce an initial afferent barrage ofpain signals and generate a secondary inflammatory response, both of which contribute substantially to postoperative pain. The signals have the capacity to initiate prolonged changes in both the peripheral and the central nervous system that will lead to the amplification and prolongation of postoperativepain.[64]

Peripheral sensitization, a reduction in the threshold of nociceptor afferent peripheral terminals, is a result of inflammation at the site of surgical trauma. Central sensitization, an activity-dependent increase in the excitability of spinalneurons, is a result of persistent exposure to nociceptive afferentinput from the peripheral neurons. Taken together, these two processes contribute to the postoperative hypersensitivity state ("spinal wind-up") that is responsible for a decrease in the pain threshold, both at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia).[64]

After open knee surgery, pain can be associated with severe reflex spasms of the quadriceps muscle,causing further pain and impaired muscle function. Rather perplexingly, these spasms begin as soon as the patient begins to ambulate, and their mechanisms are unknown. Animal data suggest that the massive nociceptive input from stimulation of nociceptive afferents produces sensitization not only of the peripheral nociceptors, but also of dorsal horn neurons. This increased excitability in the spinal cord is strong and prolonged. Consequently, nonnociceptive input (e.g., touch, proprioception) triggers increased reflex excitability with consequent spasm of the muscles supplied by the same and adjacent spinal segments . With regional anesthesia, the massive afferent nociceptive input is blocked; consequently, these reflex responses do not occur.[65]

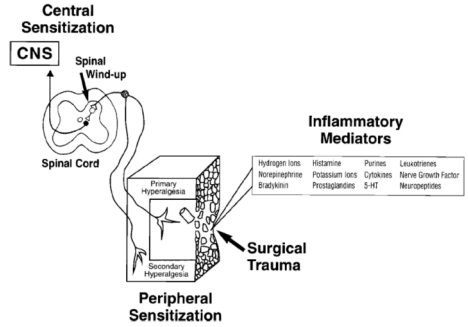


FIG. 2

Surgical trauma leads to the release of inflammatory mediators at the site of injury, resulting in a reduction in the pain threshold at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia). Peripheral sensitization results from a reduction in the threshold of nociceptor afferent terminals secondary to surgical trauma. Central sensitization is an activity-dependent increase in the excitability of spinal neurons (spinal wind-up) as a result of persistent exposure to afferent input from peripheral neurons. CNS = central nervous system, and NSAIDs = nonsteroidal anti-inflammatory drugs.

After knee surgery, poorly managed pain may inhibit the early ability to mobilize the knee joint. This, in turn, may result in adhesions, capsular contracture, and muscle atrophy, all of which may delay or permanently impair the ultimate functional outcome.[65] Good pain relief is important for postoperative knee rehabilitation, and it may influence the overall outcome.

Total or optimal pain relief allowing normal function is difficult to achieve with a single drug or method. It is currently recommendedthat combined analgesic regimens (multimodal analgesia) that operate through different mechanisms or sites be utilized.

To reduce the occurrence of side effects or complications, an analgesia protocol should block pain at its origin. Furthermore, it should maintain maximum muscle control to optimize postoperative mobilization, allow active physical therapy, and reduce venous stasis.

A multimodal analgesic regimen takes advantage of the additive or synergistic effects of various analgesics, permitting the use of smaller doses with a concomitant reduction in side effects.[63]

Busch reported that intraoperative periarticular injection with multimodal drugs can significantly reduce the requirements for patient- controlled analgesia.

Badner used thirty milliliters of 0.5 per cent bupivacaine intraarticularly as this dose has been shown to be effective for patients having an arthroscopic operation on the knee.[33, 66] The dose was also chosen because studies in which a smaller volume (twenty milliliters) or a lower concentration of bupivacaine (0.25 per cent) had been used revealed inconsistent findings.[66-68]

Butterworth et al. reported the mean serum concentrations of bupivacaine measured at times were well below the toxic level of 2000 nanograms per milliliter (two micrograms per milliliter). The addition of epinephrine helps to reduce the toxicity of the local anesthetic by keeping it localized to the area of injection. The low levels may have resulted from the addition of the 1:200,000 epinephrine in saline solution, which has been shown to be effective for this purpose.[35]

Parvataneniet al. showed that periarticular injection with a multimodal protocol provides excellent pain control and functional recovery and can be substituted for conventional pain modalities. This mode of preemptive analgesia with soft tissue and intraarticular injection of long-acting local anesthetic with epinephrine has been shown to provide better pain control in the immediate postoperative period, decreased blood loss , and decrease the need for rescue narcotics and reversal agents.

Epidural anaesthesia takes a longer time to perform, has a slower onset of anesthesia, a higher failure rate, and requires more technical expertise than intra articular local anesthesia.

Thromboembolism is a serious complication of joint replacement. Despite the advantages of neuraxial techniques, patients receiving perioperative anticoagulants and anti platelet medications are often not considered candidates for epidural anaesthesia because of the risk of neurological compromise from expanding spinal hematoma.

Patients recovering from arthroscopic knee surgery may still require supplemental analgesia . Narcotic analgesics are a popular choice, but they can cause side effects, including respiratory depression, sedation, pruritus, nausea, and vomiting, that can delay discharge from the ambulatory surgical center, increase the overall morbidity of the procedure, and increase the risk to the patient while he or she is at home. Opioids administered orally may not be absorbed due to postoperative nausea, vomiting, or ileus.

Intra-articular local anesthetics are frequently used in perioperative pain management. Bupivacaine, an amide local anesthetic, is often utilizedbecause of its extended duration of action.[69] Bupivacine blocks the generation and the conduction of nerve impulses and thus inhibits afferent nociceptive activity.

Serum levels peakwithin thirty to sixty minutes after the injection and remainwell below toxic levels following injection of 150 milligramsor less into the knee joint.[70] Intra-articular bupivacaine in doses of 0.5 percent or less does not appear to be harmful to articularcartilage.[71]

Badner et al. reported that a single injection of 150 mg (30 mL) of bupivacaine after skin closure significantly decreased narcotics use during the first twenty-four postoperative hours compared with that following injection of a placebo and also significantly improved the range of motion at the time of discharge.

In a similar study, Browne et al. did not find a significant reduction in narcotics consumption following a single injection of 100 mg of bupivacaine before skin closure.

The analgesic efficacy of bupivacaine that is injected into the intra-articular space remains somewhat controversial. Several studies[67, 72] have failed to demonstrate a substantial analgesic effect, while others[73, 33,74] have documented at least some benefit. Unfortunately, these studies had serious problems with respect to design, data collection, and reporting. In addition, there were confounding variables that are known to affect postoperative pain, including the use of perioperative nonsteroidal anti-inflammatory drugs, opioids, tourniquets, and epinephrine and infiltration of portals with lidocaine or bupivacaine. The dose of bupivacaine may be an important factor.

Smith et al. believed that the lack of an observed analgesic effect in previous studies of intra-articular bupivacaine[67, 72] might have been the result of use of a concentration of only 0.25 percent. Smith et al. assessed the efficacy of 150 milligrams (thirty milliliters of a 0.5 percent solution) of bupivacaine in ninety-seven patients undergoing arthroscopic knee surgery under general anesthesia. Patients were randomized to receive either intra-articular bupivacaine or saline solution at the conclusion of the operative procedure. The patients who received 0.5 percent bupivacaine were less likely to require postoperative narcotics and used lower doses of these medications than did the placebo group. In addition, use of 0.5 percent bupivacaine resulted in earlier walking and discharge than did use of the placebo.

Another factor that may have led to a negative result in studies of the analgesic efficacy of bupivacaine is the relatively low mean visual analog pain scores (less than 3.3 centimeters) in both the bupivacaine and the control group.[67, 72] Many of the procedures in these studies were diagnostic arthroscopies, which require minimal postoperative analgesia.

In the study by Geutjens and Hambidge,[74] for example, the control (saline-solution) group required no analgesics after ten hours postoperatively. Furthermore, another variable that has not been well documented in the literature is whether patients had postoperative hemarthrosis, which can increase the level of pain and decrease the concentration of bupivacaine within the knee joint.

The addition of epinephrine helps to reduce the toxicity of the local anesthetic by keeping it localized to the area of injection. The low levels may have resulted from the addition of the 1:200,000 epinephrine in saline solution, which has been shown to be effective for this purpose.[35]

On balance, the majority of studies have suggested that intra-articular bupivacaine is an effective analgesic and have supported its use in the management of pain following arthroscopic knee surgery. Intra-articular bupivacaine may provide effective postoperative analgesia, however its effectiveness appears to be short-lived (two to four hours).[73-74] However, supplemental agents are still needed for a more conclusive analgesic effect.

The presence of opioid receptors in the central nervous system has long been recognized, but recently they also have been demonstrated in peripheral nerve-endings[75] and have been documented by immunohistochemical analysis of biopsy specimens from inflamed synovial tissue as well as confirmed by specific binding of naloxone to receptor sites in the knee.[76]

All three opioid receptors (mu, delta, and kappa) have been isolated on peripheral nerves and shown to be responsible for mediating peripheral antinociception.[77] These receptors are synthesized in the cell bodies of primary sensory neurons located in the dorsal root ganglia and are transported distally by means of axoplasmic flow.

The fact that locally administered opioids produce analgesia in the presence of inflammation and not in normal tissue has been explained in several ways. First, it has been proposed that inflammation induces a disruption of the perineurium, allowing easier access of opioids to neuronal receptors. Alternatively, or in combination with this mechanism, previously inactive opioid receptors may be rendered active or may be unmasked under conditions of inflammation.[77]

The mechanism of the peripheral antinociceptive effect of opioids in inflamed tissues has not been precisely defined. It has been hypothesized to occur by either an analgesic effect or an anti-inflammatory effect, or both[76]. An analgesic effect has been postulated because morphine reduces the excitability of the nociceptive input terminal of C-fiber neurons. This results in a reduction in the central processing of pain. Opioids also have a direct anti-inflammatory action in peripheral tissues, since the binding of peripheral opioid receptors seems to inhibit the release of proinflammatory neuropeptides, such as substance P.[51]

Stein et al. were the first to demonstrate a prolonged analgesic effect from the intra-articular administration of morphine in humans. Since then, numerous clinical investigations have confirmed that the administration of relatively small doses of intra-articular morphine can provide effective and long-lasting analgesia.[28,66,78-79]

Plasma profiles for morphine and its metabolites following intra-articular injection have been shown to be too low to produce effective systemic analgesia.[66]

In other studies,[80-81] a dose of morphine identical to that given intra-articularly but administered through the systemic route failed to produce substantial analgesia. Finally, Stein et al. showed that the analgesic effect of intra-articular morphine was blocked by intra-articular naloxone, thus confirming a peripheral analgesic effect.

Many of the studies that have demonstrated a positive analgesic effect from intra-articular morphine have also documented a delayed onset of analgesia. Several authors have reported decreased pain scores as late as eight to twelve hours following intra-articular administration of morphine.[79,82] The effect was mild (mean reduction in pain intensity 12-17mm on VAS scale). This effect could be dose dependent, but a systemic effect of the intraarticularly administered morphine cannot be completely eliminated.

As a result, many investigators now administer a combination of intra-articular bupivacaine and morphine in an attempt to improve analgesia in the immediate postoperative period.

Several investigators[42, 52] have failed to observe any difference in the analgesic efficacy of intra-articular morphine compared with that of either intra-articular saline solution or intra-articular bupivacaine (controls). Some of these results may have been influenced by the perioperative use of systemic opioids or nonsteroidal anti-inflammatory drugs or regional anesthesia, all of which can diminish the surgical inflammatory response, thus decreasing the binding of intra-articular morphine.

Reuben, S. S. and colleagues[83] failed to demonstrate an analgesic effect from the addition of five milligrams of intra-articular morphine following anterior cruciate reconstruction. Multimodal regimens probably provide sufficient analgesia, so that intra-articular morphine provides little additional benefit. Alternatively, intra-articular morphine might not bind effectively to intra-articular opioid receptors in the presence of perioperative nonsteroidal anti-inflammatory drugs.

Another confounding variable that may affect the analgesic efficacy of intra articular morphine is the timing of tourniquet release. It is possible that by increasing the time-interval between intra-articular injection and tourniquet release, the local tissue-binding to opioid receptors can be increased, enhancing the analgesic effect.

To our knowledge, this effect of tourniquet release has been examined in only two studies, which demonstrated contradictory findings. Klinken[84] found that tourniquet time (zero, eight, or sixteen minutes) had no significant effect on the analgesic duration of intra-articular morphine or the need for supplemental analgesia within twenty-four hours.

In contrast, Whitford et al.[85] observed that keeping the tourniquet inflated for ten minutes provided superior analgesia and decreased the need for supplementary analgesics compared with releasing the

tourniquet immediately after intra-articular injection of morphine. The optimal timing of intra-articular administration of morphine is yet to be established.

Although tramadol was initially considered to be a weak mu-opioid agonist, it appears to have multimodal mechanisms of action. It is now accepted that, in addition to the mu-opioid agonist effect, tramadol enhances the function of the spinal descending inhibitory pathway by inhibition of reuptake of both 5-hydroxytryptamine (5-HT) and norepinephrine, together with presynaptic stimulation of 5-HT release .

The local anesthetic action of tramadol remains unproven. 5-HT3 receptors are expressed on the peripheral and spinal terminals of the nociceptive primary afferent fibers, as well as on the superficial lamina of the dorsal horn, which indicates possible peripheral sites of analgesic action for tramadol.

The added local anesthetic property of Tramadol is beneficial in prolonging the duration of analgesia with out increasing the local anaesthetic toxicity.

When added to local anesthetic for various blocks[86], Tramadol significantly increased analgesic duration.

Added advantage of local anesthetic property and serotonin receptor effects makes this a more preferred local anesthetic supplement than morphine, with doubtful mu-receptor effect when the patient already received spinal anesthesia which obtunds increase of mu-receptor that normally occurs during perioperative manipulation.

Intra articular tramadol and bupivacaine either applied preoperatively or postoperatively provided better pain control compared to intra articular bupivacaine alone and analgesic effect was more significant when tramadol was applied pre-emptively.[53]

The intra-articular admixture of tramadol 100 mg with bupivacaine 0.25% provides a pronounced prolongation of analgesia compared with either drug alone in patients undergoing day care arthroscopic knee surgery.[87]

Bupivacaine 0.25% plus tramadol 1 mg/kg provided significantly longer duration of analgesia without an increase in the adverse effects when compared to bupivacaine alone.[88]

Intraarticular tramadol plus periarticular bupivacaine combination provides better pain relief and less analgesic requirement following arthroscopic outpatient partial meniscectomy surgery.[89]

In an attempt to improve fast rehabilitation after arthroscopic knee surgery, research has been directed toward new techniques for postoperative analgesia. Because systemic and intrathecal administration of magnesium enhances postoperative analgesia through its voltage-dependent block of NMDA receptors, we were interested in determining whether magnesium might provide analgesia when administered intra-articularly, especially with the evidence of NMDA receptor existence in the peripheral terminal of articular primary afferent fibres in the knee joint and on cellular elements in the joint, such as synoviocytes and immune cells; in which their activation were found to potentially play a role in nociception.

N-methyl-D-aspartate (NMDA) receptors play a major role in central nociceptive transmission, modulation and sensitization of acute pain states. In addition to their central location, recent studies identified NMDA receptors peripherally in the skin,muscles and knee joints, and found that they play a role in sensory transmission of noxious signals. In its inactive state,the NMDA receptor is blocked by the presence of a centrally positioned magnesium ion. Afferent activity in nociceptor fibres dislodges the central magnesium ion from the NMDA receptor, therefore allowing calcium influx into the cell. Magnesium can be considered as a physiological blocker of NMDA receptors.Magnesium has been demonstrated to reduce postoperative analgesic requirements.[62]

The mechanism of peripheral antinociceptive effect of NMDA antagonismhas not been precisely defined. It has been hypothesized to occur through an analgesic and anti-inflammatory effect. NMDA antagonists reduce the excitability of nociceptive input terminalsof C-fibres, which play a role in the central processing of pain.[56, 90] The anti-inflammatory action in the peripheral tissues occurs through antagonizing the release of inflammatory mediators such as histamine, cytokines and serotonin, whichin turn excite nociceptors.[56]

A longer delay between intra-articular injection of magnesium and supplementary analgesic administration was observed in Bondaks study [667 (198) min].

In the present study, intra-articular Bupivacaine, tramadol and magnesium group provided better pain control without any significant side effects, compared to intra-articular Bupivacaine,tramadol group and Normal saline group and significant analgesic effects were found which was evidenced by reduced total analgesic consumption and number of patients requiring supplementary analgesics.

The time to first analgesic request was statistically longer (8.85±4.25hrs in BMTE group, 5.9±4.4hrs in BTE group, 2.2±0.61hrs in NS group) in Bupivacaine,tramadol,magnesium group. In the literature it was reported that total analgesic consumption was a better parameter than time to first analgesic request.

The total amount of analgesics utilized in the first 24 hrs after the operation(117.5±63.4mg in BMTE group, 202.5±76.9mg in BTE group,) 390±71.8mg in NS group), and VAS pain scores (P value <0.05) are lower in Bupivacaine,tramadol,magnesium group compared to other groups.

The analgesic effect of adding intra-articular magnesium is evident in our study by the ***longer time to first analgesic request*** (8.85±4.25hrs in BMTE group, 5.9±4.4hrs in BTE group, 2.2±0.61hrs in NS group), ***lower analgesic consumption*** (117.5±63.4mg in BMTE group, 202.5±76.9mg in BTE group,) 390±71.8mg in NS group), ***lower VAS pain scores*** (P value <0.05) and a ***higher degree of satisfaction*** (3.15±0.58 in BMTE, 2.25±0.71 in BTE, 0.35±0.58 in NS) on a 4-point satisfaction scale.

The incidence of nausea and vomiting seems to be related mainly to the peak serum concentrations reached by a direct IV loading dose, which causes more symptoms than a subsequent infusion or local infiltration. This may partially explain the absence of side effects after the IA tramadol administration in our patients.

In conclusion, intra-articular bupivacaine,tramadol,magnesium provided better pain control and analgesic effect is more significant providing effective and safe postoperative analgesia in arthroscopic knee surgeries.

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