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Analgesic Efficacy of Preemptive Intra-articular Injection of Bupivacaine alone versus

Bupivacaine in Combination with Tramadol or Neostigmine

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Abstract

The present comparative study was designed to evaluate the

postoperative (PO) analgesia of preemptive intra-articular (IA)

injection of neostigmine or tramadol in comparison to bupivacaine in

patients undergoing therapeutic knee arthroscopy. The study included

60 patients (31 males and. 19 females; 53 patients were ASA I and 7

patients were ASA II). Patients were randomly allocated into 3 equal

groups according to IA medication used; Neostigmine group received

500 ug neostigmine plus BupivacaineO.25%,Tramadol group received

100 mg tramadol plus BupivacineO.25% and Bupivacaine group

received30 ml of 0.25% bupivacaine; all medications were injected

3D-minutes prior to skin incision. Arrival at the postanesthetic care

unit (PACU) was recorded as time zero. Postoperative pain was

assessed using the visual analog scale (VAS); a 100-mm scale

included 0 as an indication of "no pain at all", and 100 as an indication

of "the worst possible pain" at 1,4,8, 12, and 24 hours after operation.

Duration of effective analgesia was measured from the time o (T-O)

until first use of analgesic rescue medication at VAS score 2:40 and

the total amount of analgesic rescue medication was assessed over

24h. Combination of tramadol or neostigmine with bupivacaine

provided significantly superior PO analgesia in comparison to

bupivacaine only manifested as longer duration of PO analgesia and

lower pain VAS scores extending till 12-hrswith neostigmine and 24-

hrs with tramadol in comparison to only 4-hrs PO analgesia with

bupivacaine with a significant reduction of requests for and dose of

rescue analgesia in neostigmine and tramadol groups, compared to

bupivacaine group. Tramadol provided more profound analgesic effect

than neostigmine manifested as significantly longer duration of

analgesia compared to bupivacaine or neostigmine groups. Mean of

total VAS score recorded in neostigmine and tramadol groups was

significantly lower compared to that recorded in bupivacaine group

with a non-significant difference in favor of tramado!. There were no

differences between the studied groups regarding the frequency of PO

adverse effects throughout the follow-up period. In conclusion,

preemptive intra-articular analgesia is an effective postoperative pain

control modality and combination therapy is more effective than

bupivacaine alone. Combination of tramadol and bupivacaine

provided superior postoperative analgesia and spares rescue analgesia

consumption.

Key Word: Intra-articular, tramadol, neostigmine

Introduction

The recent growth in outpatient surgery has presented

new challenges in the field of postoperative pain management.

Difficulties in adapting common methods of acute

postoperative pain management in hospitalized patients to

outpatients have resulted in inadequate treatment of pain

following outpatient's surgery. Thus, the search continues for

an ideal analgesic technique that is specific, long lasting,

easily administered and has a high therapeutic safety index

[I].

Although intra-articular injection of bupivacaine following

arthroscopy has been demonstrated to be safe, and effective in

providing postoperative analgesia [2], the mean duration of

analgesia is only 2 hours [3].

Heard et al. [4] compared the effect of intra-articular

bupivacaine, morphine versus normal saline on postoperative

analgesia after arthroscopic knee surgery and found no

significant differences in total 24-h analgesic requirements

among the groups. However, Khoury et al. [5] compare the

antinociceptive effects of morphine with those of bupivacaine

administered intra-articularly upon pain following

arthroscopic knee surgery and concluded that intra-articular

morphine produces an analgesic effect of delayed onset but of

remarkably long duration, but the combination of these two

drugs results in satisfactory analgesia throughout the entire

observation period.

Tramadol is an aminocyclohexanole derivative with u-agonist

activity and inhibits noradrenalin and 5-hydroxytryptamine

neuronal uptakes, thus prolonging the duration of their action

[6]. The combination of opioid- and nonopioid-mechanisms is

believed to result in synergistic potentiation of analgesia [7].

However, tramadol did not possess sufficient sedative activity

and could not be recommended for intraoperative use, but as a

supplement to local or regional anesthesia, intravenous

tramadol was effective [9].

Local or regional administration of tramadol as supplement to

local anesthetics was proved effective for postoperative

analgesia in multiple studies; Batra et al. [9] reported that

caudal tramadol could safely be used for postoperative

analgesia with a longer duration as compared to caudal

bupivacaine. Gunes et al. [10] found ropivacaine, ropivacaine

plus ketamine and ropivacaine plus tramadol provide

sufficient analgesia in children, but the duration of analgesia

was longer in ropivacaine plus tramadol group. In addition,

Robaux et al. [11] demonstrated that tramadol, added to

mepivacaine for brachial plexus anesthesia, extends the

duration and improves the quality of postoperative analgesia

in a dose dependent fashion with acceptable side effects.

Ketamine, a derivative of phencyclidine, works at a number of

different target sites which could explain its analgesic effects

irrespective of route of administration. It is an antagonist at Nmethyl-

D-aspartate (NMDA) receptors, with a

stereoselectivity [12]. NMDA receptors are found throughout

the central nervous system, and play an important role in

nociceptive processing [13]. Analgesic effects of ketamine

may also result from agonist activity at mu-opioid receptors

[14] and interaction with voltage-sensitive sodium channels

[IS].

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Neostigmine, a cholinesterase inhibitor, exhibits

antinociceptive action .when administered neuraxiaIIy [16].

The neuraxial administration of neostigmine is known to

produce analgesia in animals, human volunteers and patients

with chronic pain [17] and acute postoperative pain [18]. The

role of neostigmine as an analgesic administered by the

extradural route is now well established in children and adults.

Extradural neostigmine with local anesthetic has been found to

produce a dose-independent analgesic effect in adult patients

without increasing the incidence of adverse effects [19].

This prospective comparative study was designed to evaluate

the postoperative analgesia of preemptive intra-articular

injection of neostigmine or tramadol in comparison to the

local anesthetic, bupivacaine in patients undergoing

therapeutic knee arthroscopy

Patients & Methods

After obtaining approval from the Ethics Committee and

informed parental consent, 60 patients, classified as ASA

physical status I or II, and scheduled for therapeutic

arthroscopy, were enrolled in this study. Patients with cruciate

ligament tears, requirement for postoperative intra-articular

drainage, and the use of analgesia within the last 24 hours

before the study or history of allergy to any of study

medications were excluded off the study.

Patients were randomly allocated into 3 equal groups (n=20):

Neostigmine group received IA injection of 500 ug

neostigmine plus BupivacaineO.25%, Tramadol group

received IA injection of 100 mg tramadol plus

BupivacaineO.25% and Bupivacaine group received IA

injection of 30 ml of 0.25% bupivacaine; all medications were

mixed in 30 ml physiologic saline. Intra-articular medications

were injected 30-minutes prior to skin incision.

General anesthesia was scheduled for all surgeries. No

premedication was given. Standard monitoring was used

during the operation. Anesthesia was induced with intravenous

thiopental, 5mglkg, and fentanyl 2 ug/kg and tracheal

intubation was facilitated with succinylcholine 1 mglkg given

intravenously .. Controlled ventilation was maintained in a

semi closed valvular system using 66% nitrous oxide with 34%

oxygen. Anesthesia was achieved by the co-administration of

1-2% isoflurane and maintained until the end of surgery.

Surgical procedures were similar and performed by a single

surgeon in the three groups. No intra-articular drainage was

used for any patient.

Arrival at PACU was recorded as time zero. Postoperative

pain was assessed using the visual analog scale (VAS); a 100-

mm scale included 0 as an indication of "no pain at all", and

100 as an indication of "the worst possible pain" [20]. The

VAS scores were assessed at I, 4, 8, 12, and 24 hours after

operation. Duration of effective analgesia was measured from

the time 0 until first use of analgesic rescue medication at

VAS score 2':40 and the total amount of analgesic rescue

medication, intramuscular diclophenac sodium (75 mg in 3 ml

ampoule) was assessed over 24h and recorded in total of

milligrams of diclophenac sodium given throughout the 24

hours.

Evaluation of adverse effects included assessment of the

occurrence of postoperative emesis and nausea (yes or no),

pruritus, bradycardia (heart rate <50 beat per min), urinary

retention (voiding possible <8h after operation) by

interviewing the patients throughout the first 24 postoperative

hours. Metochlopramide, 10 mg intravenously was

administered during the occurrence of nausea or vomiting and

bradycardia was treated with incremental doses of atropine

sulfate, 0.25 mg intravenously.

Statistical analysis

Data were analyzed using Wilcoxon analysis for unpaired data

and Chi-square (X2) test for comparisons of non-parametric

results. Statistical analysis was conducted using the SPSS

(Version 10,2002) for Windows statistical package. A P value

<0.05 was considered statistically significant.

Results

All the 60 patients completed the study. There were 31 males

and 19 females; 53 patients were ASA I and 7 patients were

ASA II. There was no significant intergroup difference with

regard to age, sex distribution, ASA grade, weight, or duration

of anesthesia, (Table I). Some patients had had several

procedures performed, thus the total number of procedures

performed was 95 procedures with a no significant difference

between studied groups as regards professional diagnosis and

number of procedures performed, (Table 2).

Table (1): Demographic data of patients scheduled for

therapeutic arthroscopy

Neostigmine Tramadol Bupivacaine

group group group

Age (Years) 40.7±IOJ 42.55±10 42.2±10.8

(22-55) (29-58) (22-55)

Sex;M:F 13:7 14:6 14:6

Weight (Kg) 73.5±8.4 73.6±9.4 73±12.6

(62-84) (60-94) (62-94)

ASA; I:II 17:3 18:2 18:2

Duration of 166J±25.2 167.5±24.8 I77±22.6

anesthesia (min) (120-208) (121-210) (125-205)

Values are presented as mean±SD, ranges are in parenthesis

Table (2): Postoperative diagnoses and procedures performed

according to type of anesthetic provided

Neostigmine Tramadol Bupivacaine

group group group

Diagnosis

Osteoarthrosis 8 9 9

Meniscal injury 4 5 5

Hypertrophic synovitis 3 2 4

Cruciate lig.injury 2 I 2

Chondral injury 2 2 I

Plica synovialis 0 I 0

mediopatellaris

Procedure

Partial menisectomy 15 9 12

Partial synovectomy 9 12 13

Chondroplasty 6 5 7

Resection of the plica 2 3 I

Removal of free body I I 0

Tramadol provided significantly superior analgesia throughout

observation period in comparison to the preceding reading,

while the analgesic effect of neostigmine was significant till

12-hrs and that ofbupivacaine till only 4-hr after admission to

PACU. Mean of total VAS score recorded in neostigmine and

tramadol groups was significantly lower compared to that

recorded in bupivacaine group with a non-significant

difference in favor oftramadol, (Fig. I

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Fig. (1): Mean (!SO) oftotal VPSscores recorded throughout

24·hours after adllission to PPCUin the studied groups

At time of admission to PACU, there was a non-significant

difference of reported VAS scores in the three groups despite

being lower in neostigmine and tramadol groups compared to

bupivacaine group. One-hour later, patients included in

neostigmine and tramadol groups had significantly lower VAS

scores compared bupivacaine group with a non-significant

difference in-between. At 4-hr after admission to PACU, VAS

scores were significantly lower in tramadol group compared to

the other two groups that showed a non-significant difference

in favor of neostigmine, (Fig. 2). Thereafter, intergroup

difference was non-significant till at 24-hrs after admission to

PACU, when VAS scores recorded in tramadol group were

significantly lower compared to the other two groups that

showed a non-significant difference in favor of neostigmine,

(Table 3).

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Fig. (2): Mean V/IS scores reported In the studied

groups throughout 24-hrs after admsston to PACU

Ten patients; 2 in neostigmine and 8 in tramadol groups did

nor require rescue analgesia; 39 patients; 9 in bupivacaine, 18

in neostigmine and 12 in tramadol groups required rescue

analgesia once, while 11 patients in bupivacaine group

required rescue analgesia more than once; 7 twice and 4 trice.

There was a significant reduction of requests for rescue

analgesia in neostigmine and tramadol groups, (X2=7.41 &

9.17, p<O.OI & <0.001, respectively), compared to

bupivacaine group with a significant difference (X2=8.36,

p<O.OI) in favor of tram ado I group, (Fig. 3).

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Table (3): Mean (SD) of VAS scores recorded throughout 24-

hours after admission to PACU in the three studied groups

Bupivacaine Neostigmine Iramadol

group group group

I-O 15.3±4.9 14.6±4.4 13.4±2.3

pI >0.05 >0.05

P2 >0.05

1-hr 26.1±10.4 lS.9±5.3 16.9±3.1

pI =0.019 <0.001

P2 >0.05

P3 <0.001 <0.001 <0.001

4-hr 30.5±1l 26.7±7.7 22±3.6

Pi >0.05 =0.011

P2 =0.014

P3 <0.001 <0.001 <0.001

P4 >0.05 <0.001 <0.001

8-hr 34.7±15.2 30.6±10 27.5±5.4

Pi >0.05 >0.05

P2 >0.05

P3 -0.001 <0.001 <0.001

P4 =0.034 -0.009 <0.001

p, >0.05 =0.013 <0.001

12-hr 24.9±16.9 30±15 29.4±10.2

PI >0.05 >0.05

P2 >0.05

P3 >0.05 =0.004 <0.001

p. >0.05 =0.017 =0.001

ps >0.05 >0.05 -0.009

P6 >0.05 >0.05 -0.0l3

24·hr 26.4±14 18.1±9.S 27.2±12.2

PI >0.05 >0.05

P2 =0.007

P3 -0.001 >0.05 -0.001

p. >0.05 >0.05 -0.002

ps >0.05 -0.028 >0.05

P6 =0.01 -0.002 >0.05

P7 >0.05 >0.05 >0.05

PI: significance versus bupivacaine group

P2:significance versus neostigmine group

P3:significance versus I-O

pa: significance versus at l-hr

ps: significance versus at 4-hr

P6:significance versus at 8-hr

P7:significance versus at 12-hr

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No once Twice Trice

Fig. (3): Patients' distribution according to number

of requests of rescue analgesia

Mean total dose of rescue analgesia was significantly lower in

tramadol group compared to both bupivacaine (Z=3.624,

p<O.OOI) and neostigmine (Z=3.169, p=0.002) with a nonsignificant

reduction in neostigmine group (Z=1.897, p>0.05)

compared to bupivacaine group, (Fig. 4).

Intra-articular Bupivacaine alone versus Bupivacaine in Combination with Tramadol

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180+---------~------------------------~

170+---------~------------------------~

160+---------~------------------------~

150+---------~------------------------~

140+---------~------------------------~

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Fig. (4): Mean (:!:SD) dose of rescue analgesia consurred by

the sludied groups

The duration of analgesia as judged by time till first request of

rescue analgesia was significantly, (Z=3.066 & 2.49, p=0.002

& 0.037, respectively) longer in patients received tramadol,

(17.3±7.1; range: 8-24 hours), compared to those received

bupivacaine, (6.2±3.7; range: 1-12 hours) or neostigmine

(11.3±5.4; range: 4-24 hours) with a significant prolongation,

(Z=2.836, p=0.007) in neostigmine group, (Fig. 5).

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Fig. (5): Mean (!SD) of duration of analgosia recorded after

adrrission 10 PACU in Iho studiod groups

There were no differences regarding the frequency of

postoperative adverse effects throughout the follow-up period,

two patients from neostigmine group had bradycardia, 100 and

180 min after intra-articular injection of neostigmine, but only

one patient required treatment with intravenous atropine. Two

patients from neostigmine group complained of nausea and

both required a single intravenous injection of

metochlopramide 10 mg.

Discussion

The literature on single-dose intra-articular analgesia is

controversial because of different concentrations and volumes

of local anesthetics and also as a result of the use of several

drugs and drug combinations. A systematic review of singledose

IA local anesthesia for postoperative pain relief after

arthroscopic knee surgery reported a small to moderate

effectiveness of short duration [21].

The present study aimed to evaluate the postoperative

analgesia of preemptive intra-articular injection of

neostigmine or tramadol in comparison to bupivacaine III

patients undergoing therapeutic knee arthroscopy.

Combination of tramadol or neostigmine with bupivacaine

provided significantly superior postoperative analgesia in

comparison to bupivacaine only manifested as longer duration

of postoperative analgesia and lower pain VAS scores

extending till 12-hrs with neostigmine and 24-hrs with

tramadol in comparison to only 4-hrs postoperative analgesia

with bupivacaine with a significant reduction of requests for

and dose of rescue analgesia in neostigmine andtramadol

groups, compared to bupivacaine group. These results go in

hand with Alagol et al. [22] who compared the analgesic

effects of intra-articular neostigmine, morphine, tenoxicam,

clonidine and bupivacaine in patients undergoing arthroscopic

knee surgery and found the duration of analgesia with

neostigmine and clonidine significantly longer with

significantly lower analgesic consumptions than other groups.

However, tramadol provided more profound analgesic effect

than neostigmine manifested as significantly longer duration

of analgesia as judged by time till first request of rescue

analgesia was in patients received tramadol compared to those

received bupivacaine or neostigmine, but mean of total VAS

score recorded in neostigmine and tramadol groups was

significantly lower compared to that recorded in bupivacaine

group with a non-significant difference in favor of tramadol.

These data point to a different mechanism of action for both

tramadol and neostigmine.

Administration of the enzyme inhibitor neostigmine might

cause an analgesic effect by increasing endogenous

acetylcholine levels at the peripheral nociceptors,

Acetylcholine could act there as an analgesic agonist at similar

receptor subtypes as in the spinal cord; muscarinic receptors

type 1 or 2 [23]. Because of its chemical structure,

neostigmine might display longer stability, thereby ensuring a

longer analgesic effect. Thus, it might enhance the availability

of more acetylcholine at assumed peripherally distributed

muscarinic receptors.

As an explanation for the superior analgesia provided by intraarticular

tramadol over intra-articular neostigmine, tramadol

acts through multiple mechanisms; Altunkaya et al. [24]

reported a local anesthetic effect of tramadol that can be used

for minor surgical procedures when injected subcutaneously

versus lidocaine and proposed that tramadol can be used as an

alternative drug to lidocaine for minor surgeries. In another

support oftramadollocal action, Alagol et al. [25] found intraarticular

tramadol provided longer duration of analgesia than

intravenous tramadol when administered in the same doses

and concluded that tramadol provides analgesia with a

peripheral mechanism when administered intra-articularly. In

support of tramadol local effect, Demiraran et al. [26] found

wound infiltration with tramadol may be a good choice for

postoperative analgesia in children having inguinal

herniotomy in comparison to bupivacaine. As another

mechanism of action, Bianchi et at. [27] reported significant

decrease of synovial fluid concentrations of substance P and

non-significant decrease in concentration of IL-6 and proposed

that the activity of tramadol may involve the modulation of

inflammatory mediators