INTRA-ARTICULAR MORPHINE AND BUPIVACAINE FOR PAIN RELIEF AFTER THERAPEUTIC ARTHROSCOPIC KNEE SURGERY

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ABSTRACT

This randomised, double-blind study compared the analgesic properties of intra-articular injection of morphine and bupivacaine during therapeutic arthroscopic knee surgery. Forty male patients were randomly divided into 4 groups of 10 patients each. Group A received intra-articular injection of 1 mg morphine sulphate in 20 ml saline, Group B received 20 ml of 0.25% bupivacaine while Group C received 1 mg morphine sulphate in 20 ml of 0.25% bupivacaine injected intra-articularly. Group D did not receive intra-articular injection and acted as control. Post-operative pain was assessed by visual analogue score.

The morphine group had significantly lower pain score compared to the control group from 4 hours onwards throughout the 24-hour study period ($p < 0.05$ at 4 hours and $p < 0.001$ at 24 hours). The bupivacaine group had lower pain score than the control group during the first 4 hours ($p < 0.001$ at 1 hour and $p < 0.05$ at 2 hours). At 4 hours, it showed similar analgesic efficacy as morphine. There was no significant analgesic effect at the end of the study period. The combination of the two drugs resulted in satisfactory analgesia throughout the entire study period ($p < 0.001$ at 1, 2 and 24 hours and $p < 0.05$ at 4 hours) and appeared to be a simple, safe and effective analgesic technique for patients who underwent therapeutic arthroscopic knee surgery.

Keywords: *intra-articular injection, morphine, bupivacaine, analgesia, therapeutic arthroscopic knee surgery.*

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INTRODUCTION

Arthroscopic knee surgery is commonly performed by orthopaedic surgeons in local hospitals. They often result in considerable post-operative discomfort and pain. Various methods of pain relief have been practised over the years. Intra-articular injection of bupivacaine at the end of surgery has been found to be effective[1] and safe when the dose of bupivacaine is less than 100 mg[2]. Use of a tourniquet further reduces systemic absorption of the bupivacaine injected. As a result, this method of pain relief has enjoyed great popularity among local orthopaedic surgeons.

Recent evidence has indicated that opioid agonists like morphine and fentanyl are able to mediate analgesia by a peripheral mechanism besides its well recognised central mechanism of action. When injected peripherally into inflamed tissues, small doses devoid of central effects have been found to produce dose related, stereospecific analgesia at the injected area[3,4]. This analgesic property is found to be reversed by local administration of naloxone, an opioid antagonist[4]. This further supports the theory of the presence of receptors mediating opioid analgesia in peripheral tissues.

The following study was designed to compare analgesic property of intra-articular morphine injection with that of intra-articular injection of bupivacaine after therapeutic arthroscopic knee surgery.

METHODS

This randomised, double-blind study was conducted over four months in Alexandra Hospital and Toa Payoh Hospital. Forty male patients, ASA 1 and 2, undergoing therapeutic arthroscopic knee surgery gave informed consent to participate in the study. Patients who are in the following categories were excluded from the study: those who were receiving analgesics prc-operatively, those who had simple diagnostic arthroscopy done and those who required post-operative intra-articular drainage.

All patients had oral diazepam as premedication when they were being brought to the operating theatre. Patients who weighed less than 50 kg received diazepam 5 mg while those who weighed more than 50 kg rceived diazepam 10 mg.

All 40 patients received general anaesthesia. Thiopentone 4 mg/kg was given during induction. Suxamethonium 1 mg/kg was given to facilitate endotracheal intubation. Anaesthesia was then maintained with nitrous oxide-oxygen mixture with a volatile anaesthetic agent (either halothane or isoflurane was used) and an appropriate non-depolarising muscle relaxant. A single dose of intravenous fentanyl 1 mcg/kg was given after induction to provide intra-operative analgesia. All patients had tourniquets applied to the thigh intra-operatively. The tourniquet was only released 5 minutes after the respectivc intra-articular injection was administered.

At the conclusion of surgery but before the arthroscope was removed, the patients received one of the following intra-articular injections through the arthroscope according to the group which they have been randomly assigned. Group A (n=10) received 1 mg preservative free morphine sulphate diluted in 20 ml normal saline. Group B (n=10) received 20 ml of 0.25% bupivacaine (50 mg). Group C (n=10) received 1 mg preservative free morphine sulphate in 20 ml of 0.25% bupivacaine. Group D did not receive intra-articular injection and they served as the control group in the study.

After the respective intra-articular injections, general anaesthesia was terminated. The effects of muscle relaxants were reversed and the patients were extubated.

All the patients have been introduced to a 10 cm visual analogue scale during their pre-operative visit by the anaesthetists. The score will range from 0 which is "no pain at all" to 10 which means "the worst pain imagined". After the operation, the patients were visited by an observer who was unaware of the type of injection the respective patient received. The patients were visited at 1, 2, 4 and 24 hours after the intra-

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articular injection when the visual analogue score (VAS) was taken. All 40 patients were given Mefenamic acid 500 mg 8 hourly during the post-operative period.

Analysis of variance (ANOVA) was used to analyse the age, weight and duration of surgery of the 4 groups of patients. Comparison of pain scores was made using the Wilcoxon Rank-Sum Test. A p value of less than 0.05 was considered as significant.

RESULTS

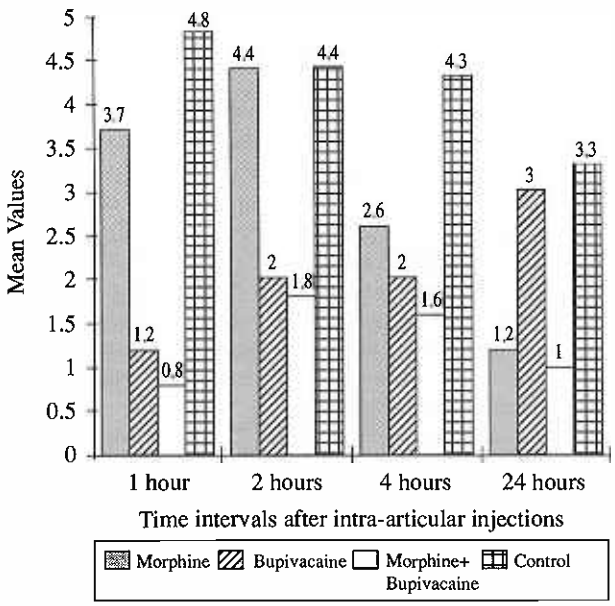
There was no significant difference in the age, weight and duration of surgery among the four groups of patients (Table I).

Table I – Age, weight and duration of surgery

	Age (years)	Weight (kg)	Duration (min)
Group A (n=10)	24.8 ± 7.11	67.15 ± 13.22	39 ± 11.01
Group B (n=10)	30.7 ± 11.09	68.25 ± 8.03	39 ± 8.76
Group C (n=10)	24.1 ± 5.64	62.85 ± 9.15	42 ± 9.49
Group D (n=10)	26.3 ± 6.94	66.20 ± 13.33	50 ± 8.83

Mean ± SD are given.

Fig 1 – The mean value of the visual analogue scores



By applying the Wilcoxon Rank Sum Test, morphine 1 mg injected intra-articularly (Group A) produced no significant decrease in pain score when compared to the control group at 1 and 2 hours after injection. However, at 4 hours after the injection, pain score was significantly lowered ($p < 0.05$). Twenty-four hours after injection, the pain score was further reduced ($p < 0.001$) when compared to the control group.

In contrast, intra-articular injection of 20 ml of 0.25% bupivacaine (Group B) resulted in earlier onset of analgesia. At one hour, pain score was significantly lowered ($p < 0.001$). It was still significantly lower than control group at 2 hours and 4 hours after injection ($p < 0.05$). However, it produced no significant analgesia 24 hours after injection.

Table II – The mean values and standard deviations of the visual analogue scores

	1 Hour	2 Hours	4 Hours	24 Hours
Group A (n=10)	3.7 ± 1.25	4.4 ± 1.35	2.6 ± 0.84*	1.2 ± 0.79**
Group B (n=10)	1.2 ± 1.40**	2.0 ± 0.63*	2.0 ± 1.05*	3.0 ± 0.97
Group C (n=10)	0.8 ± 0.88**	1.8 ± 1.14**	1.6 ± 0.84*	1.0 ± 0.94**
Group D (n=10)	4.8 ± 1.32	4.4 ± 1.26	4.3 ± 0.96	3.3 ± 0.67

Mean ± SD are given
* Significant difference from Group D ($p < 0.05$)
** Significant difference from Group D ($p < 0.001$)

Combination of morphine 1 mg and 20 ml of 0.25% bupivacaine (Group C) resulted in lower pain score throughout the 24-hour study period. When compared to the control group, p value was less than 0.001 at 1 hour, 2 hours and 24 hours and less than 0.05 at 4 hours after the intra-articular injection.

When Group B (bupivacaine group) was compared with Group C (morphine plus bupivacaine group), there was no significant difference in pain scores from 1 hour to 4 hours after injection. At 24 hours after injection, Group C had significantly lower pain score than Group B ($p < 0.05$). Group C also produced consistently lower pain score from 1 hour to 4 hours when compared to Group A (morphine group). P value was less than 0.001 at 1 and 2 hours but less than 0.05 at 4 hours. No significant difference was detected 24 hours after injection.

When Group A (morphine group) was compared with Group B (bupivacaine group), the bupivacaine group had significantly lower pain score at 1 and 2 hours after injection. There was no significant difference between the two groups at 4 hours after injection.

DISCUSSION

In this study, we observed that intra-articular injection of 1 mg morphine sulphate produced significant pain relief only 4 hours after injection and its analgesic effect lasted for 24 hours or even longer. Twenty ml of 0.25% bupivacaine (50 mg) has significant analgesic property within an hour after intra-articular injection. Its effects seem to last beyond 4 hours and there is no significant pain relief by the next day. The combination of both drugs has produced satisfactory pain relief throughout the entire study period. This result is similar to observation made by Khoury and his colleagues in their study[5] except that the analgesic effect of bupivacaine 50 mg seems to have lasted longer in the present study probably because the mean weight of the patients was 66.1 kg while that of Khoury's study was 74.53 kg.

As mentioned earlier, bupivacaine has been a common agent injected intra-articularly for post-operative analgesia in arthroscopic surgery. Besides being effective[1,2,6], it was also thought to be safe as it was found to have no demonstrable harmful effects on articular cartilage[1]. When 100 mg bupivacaine was injected intra-articularly after knee arthroscopy, peak blood levels occurred within the first hour after surgery and these levels are well below those noted to produce toxic reactions. A further safety measure was recommended by the author to minimise the peak levels with shorter tourniquet inflation times and with longer injection to tourniquet release intervals[2].

In another study by Wasudev and colleagues[7], 30 ml of 0.75% bupivacaine (225 mg) was injected into the knee joint. Peak serum bupivacaine levels were reached 20 to 60 minutes

after tourniquet release and ranged from 0.2 to 3.4 mcg/ml. Previous studies examining bupivacaine toxicity after intravenous administration showed that levels of 2 mcg/ml may cause toxic symptoms if the rise to this level is rapid[8] while serum level of 1 to 1.5 mcg/ml has been associated with depressed ventricular contractility[9]. In Wasudev's study, none of the 15 patients exhibited any sign of neurotoxicity or cardiotoxicity. This was presumably due to the effects of residual general anaesthetic agents. Nonetheless, the author has recommended that the dose of bupivacaine should be limited to 2 mg/kg body weight or 150 mg total doses whichever is smaller.

In the present study, only 50 mg of bupivacaine was used. This was unlikely to have resulted in toxic serum level especially when all the patients had tourniquets applied intra-operatively and the tourniquet was only removed 5 minutes after the intra-articular injection was given. This dose of bupivacaine has resulted in significant analgesia up to approximately 4 hours. Its duration could perhaps be further lengthened by increasing the dose or addition of adrenaline to the bupivacaine.

Opioid agonists like morphine has been demonstrated to have both central as well as peripheral antinociceptive properties. The peripheral analgesic property has been observed with both mu and kappa agonists. This peripheral opiate effect may be due to its effects on peripheral nerve terminals which may be direct, by modulating nociceptive transmission, or indirect, by an anti-inflammatory effect. In addition, opiate receptors located on non-neural elements like leucocytes may participate in modulation of peripheral inflammation[3] and thus aid in producing pain relief indirectly.

In the present study, intra-articular injection of 1 mg of preservative free morphine sulphate resulted in significant pain relief from 4 hours after the injection and the analgesic effect lasted through 24 hours. This relative slow onset but prolonged duration of effect may be related to the low lipid solubility of morphine and its slow rate of uptake into the circulation. The relatively low blood flow to the articular area may also have contributed to this long duration of analgesic effect. Addition of bupivacaine to morphine has successfully combined the desirable property of the two agents and resulted in a fast onset of analgesia coupled with prolonged duration of action.

Other means of accelerating the onset of opioid mediated peripheral analgesic effect may include addition of a more lipid soluble opioid agonist like fentanyl or using a larger dose of morphine. Joshi and colleagues injected 5 mg morphine diluted in 25 ml normal saline intra-articularly after elective anterior cruciate ligament repair and found that the pain score was significantly lower from 2 hours after injection onwards, indicating a faster onset of analgesic effect compared to the present study[10].

CONCLUSION

Intra-articular injection of morphine and bupivacaine are both effectively analgesic after therapeutic arthroscopic knee surgery. Bupivacaine produces analgesic effect quickly but of relatively short duration compared to morphine. Mixture of the two agents has resulted in consistently satisfactory analgesia throughout the first 24 hours after the operation.

As intra-articular injection of bupivacaine is already a common practice among orthopaedic surgeons locally, addition of a small dose of morphine like 1 mg as in this study can effectively prolong the duration of analgesia. It is also likely to have less complications than systemic administration of opioid agonists which invariably require larger doses. It is also a simpler technique when compared to techniques like continuous epidural infusion and patient-controlled analgesia as it does not require sophisticated equipment and extensive monitoring.

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