Clinical Investigation

Analgesic efficacy of three different dosages of intra-articular morphine in arthroscopic knee surgeries: Randomised double-blind trial

Address for correspondence:
Dr. Babita Gupta,
I-22, Ground Floor,
South City II,
Gurgaon - 122 001,
Haryana, India.
E-mail: drbabitagupta@hotmail.com

Babita Gupta, Sumantra Banerjee, Arunima Prasad, Kamran Farooque[1], Vijay Sharma[1], Vivek Trikha[1]

Departments of Anaesthesiology and [1]Orthopaedics, JPNATC, AIIMS, New Delhi, India

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.167479

Quick response code

ABSTRACT

Background and Aims: Arthroscopic knee surgery is a common procedure and may cause enough pain to delay rehabilitation. Intra-articular (IA) morphine is a known modality for post-operative pain relief. However, the optimal dose of IA morphine has not been studied. The current study has been conducted to find out the optimal dosage of IA morphine when administered with 0.25% bupivacaine. **Methods:** Sixty adult patients of either sex, aged between 18 and 60 years, undergoing diagnostic/therapeutic knee arthroscopic surgery were included in the study and randomised into three groups. All patients underwent surgery under subarachnoid block. After the surgical closure, 20 ml of 0.25% bupivacaine with 1 mg, 3 mg and 5 mg of morphine as additive was injected intra-articularly in Group A, B and C patients, respectively. Post-operative pain assessment was performed with visual analogue scale score in the 1st, 2nd, 6th, 12th and 24th post-operative hour. The common complications were also recorded. **Results:** There was statistically significant analgesia in Group B and C than Group A in the 1st and 2nd post-operative hour; while at the 24th post-operative hour, Group C had statistically significant analgesia than the other two groups. Time to first rescue analgesia was statistically significantly less and consumption of supplemental analgesia was significantly higher in Group A than the other two groups. **Conclusion:** IA dose of 3 mg and 5 mg morphine with 20 ml of 0.25% bupivacaine provided adequate analgesia. However, 3 mg morphine group patients had fewer side effects than 5 mg group patients although the difference was not statistically significant.

Key words: Analgesia, arthroscopy, intra-articular, morphine, pain post-operative

INTRODUCTION

Arthroscopy of the knee joint is a common procedure that is routinely performed on an out-patient basis. Arthroscopic procedures may cause enough pain and swelling, thus delaying rehabilitation and return to work. Several techniques are available to treat pain following arthroscopic knee surgery.[1] Intra-articular (IA) local anaesthetics are frequently used in perioperative pain management. Bupivacaine, a local anaesthetic, is often utilised because of its extended duration of action.[2] Experimental research indicates that locally administered opioid agonists can also produce analgesic effects by binding with peripheral opioid receptors.[3-5] IA morphine as an additive to bupivacaine is one of the modalities used for post-operative pain relief for arthroscopic knee surgery. Gupta *et al.* performed a systematic review of the literature and meta-analysis of the peripheral effects of morphine injected intra-articularly.[6] The results of meta-analysis concluded that administration of IA morphine has a definite analgesic effect, albeit mild.

How to cite this article: Gupta B, Banerjee S, Prasad A, Farooque K, Sharma V, Trikha V. Analgesic efficacy of three different dosages of intra-articular morphine in arthroscopic knee surgeries: Randomised double-blind trial. Indian J Anaesth 2015;59:642-7.

The efficacy of IA morphine may be dose-dependent; however, effect due to systemic absorption cannot be completely excluded. Moreover, the type of opioid, its optimal dose and volume were not commented upon. Variable doses of IA morphine, ranging from 1 to 10 mg, have been used in various published clinical trials.[7-12]

Despite numerous studies on this subject, there is no consensus as regards to the optimal dose of IA morphine when added to bupivacaine, the volume of local anaesthetic injected intra-articularly and the duration of analgesia. We conducted this study with the primary objective to analyse the analgesic efficacy of IA bupivacaine with different dosages of morphine in arthroscopic knee surgeries and to find out the optimal dosage of IA morphine providing adequate post-operative analgesia with minimal/no side effects. The primary outcome measured was the visual analogue scale (VAS) scores with various doses of IA morphine with bupivacaine and secondary outcome measured was incidence of complications with IA morphine.

METHODS

The study was conducted at a Tertiary Care Hospital from June 2010 to May 2014. After approval of the protocol by the Institutional Review Board, 60 adult patients aged between 18 and 60 years, scheduled for diagnostic or therapeutic (anterior cruciate ligament reconstruction/meniscal tear repair/meniscectomy) knee arthroscopic surgery under subarachnoid block were recruited for the study over a period of 36 months. Patients of either sex aged between 18 and 60 years with American Society of Anaesthesiologists physical status grade I or II , who were willing to give informed consent, were included in the study. Uncooperative patients, those allergic to local anaesthetics, patients in whom IA drain was left *in situ* and patients with any contraindication to spinal anaesthesia or bupivacaine were excluded from the study. Patients in whom combined spinal epidural analgesia was used and epidural catheter was left *in situ* were also excluded from the study. During the pre-operative period, all the patients were taught the use of the10 point VAS with 0 corresponding to no pain and 10 being the worst imaginable pain for post-operative pain assessment. All the patients were pre-medicated with tablet alprazolam 0.25 mg night prior surgery.

All the 60 patients were given subarachnoid block with 12.5–15 mg of hyperbaric bupivacaine under aseptic precautions for the surgery. No opioid was used for the subarachnoid block. All the surgeries were performed by two senior orthopaedic surgeons with more than 20 years of experience in arthroscopic surgeries. The scope used was of 4 mm calibre in all the surgeries. At the end of surgery, the participants were randomly assigned following simple randomisation procedure (computerised random numbers) to one of three treatment groups. 20 ml of 0.25% bupivacaine was injected intra-articularly with 1mg, 3 mg and 5 mg of morphine as additive in Group A, B and C patients, respectively, by the operating orthopaedic surgeon. Each injection was prepared by an anaesthesiologist not involved in the study. The drug was injected by the orthopaedic surgeon after skin suturing. The pressure dressing was applied and the tourniquet was released thereafter. Post-operative pain was assessed with 10-point VAS, which was recorded immediately after surgery and 1, 2, 6, 12 and 24 h after surgery by an anaesthesiologist not present during surgery. Both, the surgeon and the anaesthesiologist assessing post-operative pain were blinded to the amount of morphine being injected. Pulse rate, respiratory rate and blood pressure were also recorded along with the VAS. Injection diclofenac sodium (75 mg) intramuscularly was given if the patient reported VAS >4. If pain was not relieved within 45 min of inj. diclofenac administration, injection tramadol 50 mg intravenous was administered. The common complications, that is, pruritus, nausea, respiratory depression and urinary retention were also recorded. Inability to start urinating or emptying the bladder was defined as urinary retention.

Since there was no similar study done before, the sample size was calculated extrapolating the results of pilot study conducted at the same hospital. Assuming that in 3 mg IA morphine with 0.25% bupivacaine Group (B), the mean VAS score would be 3.5 ± 1.6 and in 5 mg IA morphine Group (C), mean VAS score to be 2.4 ± 1.4 and in 1 mg morphine Group (A), mean VAS score to be 5.6 ± 0.5, with an α error of 5% and power of 90%, with five follow-ups and 1:1 ratio, we required to enrol 54 cases in the study by method of change that is 18 in each group. Assuming a 10% defaulter rate, number of cases required in each group was 20. Statistical analysis was carried out using Stata version 11.0 (College Station Texas, USA). Data were presented as number (%) or mean ± Standard deviation/ median (minimum-maximum) as appropriate. The pain score was tested for normal distribution using Shapiro–Wilks test. Since the pain score was not following normal distribution, the median pain

score among the three groups were compared using Kruskal–Wallis test and the pairwise comparisons were done using Bonferroni correction. The $P < 0.05$ was considered statistically significant.

RESULTS

There was no statistically significant difference between the three morphine groups with respect to age and sex distribution of the patients as shown in Table 1. The surgery performed in all three groups was comparable; with diagnostic arthroscopy being performed in 4, 5 and 4 patients and anterior cruciate ligament reconstruction in 12, 11 and 12 patients in Group A, B and C, respectively, while meniscal repair or meniscectomy was performed in 4 patients in each group.

The VAS scores at different time intervals are depicted in Table 2. No patient had pain immediately after surgery due to the residual effect of spinal anaesthesia. There was statistically significant difference in VAS scores in the 1st, 2nd and 24th h in the post-operative period. The difference between VAS scores between Group A, Group B and Group C in the 1st, 2nd and 24th post-operative hour is shown in Table 3. The difference in the median VAS scores at 6th and 12th post-operative hour in all three groups was not statistically significant.

The time of first rescue analgesic and the total number of rescue analgesics in first 24 h are depicted in Figure 1. The time for the first rescue analgesic was significantly lower in Group A than in Group B and C ($P = 0.0002$). Consumption of supplemental analgesia in 24 h was also significantly lower in Group B and C in comparison to Group A (0.0049). None of the patients required injection tramadol, as the pain was relieved by the first rescue analgesic, that is, injection diclofenac sodium.

Various side effects of the IA morphine injection in the different groups are depicted in Figure 2. Although patients of Group C encountered maximum number of side effects of the injection, there was no statistically significant difference ($P = 0.478$) among the three groups.

DISCUSSION

Our study was an effort to find out the optimal dose of IA morphine for post-operative pain relief in arthroscopic knee surgeries. Our results show that 1mg morphine when injected intra-articularly along with 20 mL 0.25% plain bupivacaine following arthroscopic knee surgeries is inferior in effectiveness when compared with 3 mg or 5 mg IA morphine for pain relief. While both 3 mg and 5 mg IA morphine provided comparable analgesia, the side effects

Table 1: Age and gender distribution in the three groups

Demographic character	Group A (20 ml 0.25% bupivacaine with 1 mg morphine) (*n*=20)	Group B (20 ml 0.25% bupivacaine with 3 mg morphine) (*n*=20)	Group C (20 ml 0.25% bupivacaine with 5 mg morphine) (*n*=20)
Age (years) (mean±SD)	29.6±8.9	30.75±9.18	31.05±7.94
Gender			
Male	17	18	18
Female	3	2	2

SD – Standard deviation

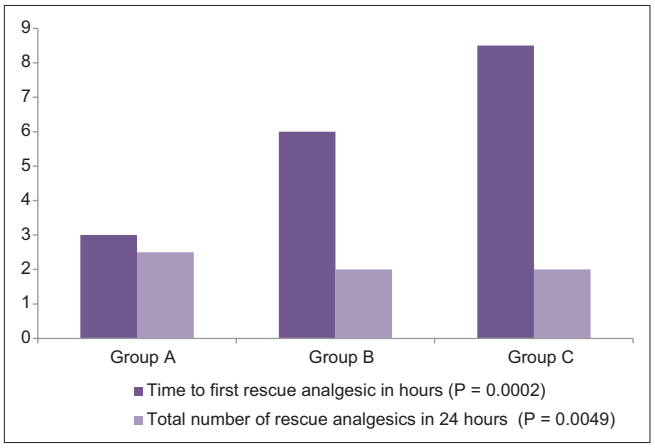

Figure 1: Time of 1st rescue analgesic and total number of rescue analgesics in first 24 h

Table 2: VAS scores with their range at different time points after surgery in the three groups

Time in hours after surgery	Median VAS score (minimum-maximum) in Group A patients	Median VAS score (minimum-maximum) in Group B patients	Median VAS score (minimum-maximum) in Group C patients	*P*
1	2 (0-6)	0 (0-3)	0 (0-2)	0.0001
2	4 (0-7)	1 (0-6)	1 (0-4)	0.0005
6	4 (1-7)	4 (0-6)	3 (0-6)	0.4668
12	4 (0-6)	3 (1-7)	4 (0-6)	0.8743
24	4 (0-8)	3 (1-7)	1.5 (0-4)	0.0160

VAS – Visual analogue scale

Table 3: VAS score difference between groups in the 1st, 2nd and 24th h after surgery

Time in hours after surgery	Group		*P*
1	B	A	0.0012
	C	A	0.0000
	C	B	0.0883
2	A	B	0.0012
	A	C	0.0000
	B	C	0.0883
24	A	B	0.8262
	A	C	0.0093
	B	C	0.0181

VAS – Visual analogue scale

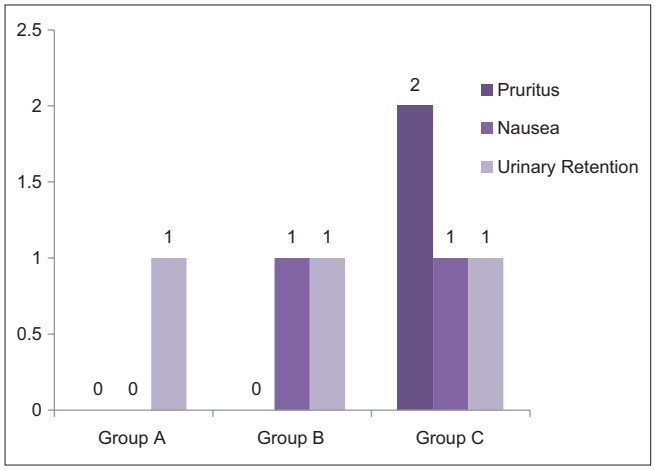

Figure 2: Number of patients having side effects in the three groups

were more in the 5 mg morphine group, albeit not statistically significant.

Operative procedures produce an initial afferent barrage of pain signals and generate a secondary inflammatory response, both of which contribute substantially to post-operative 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 post-operative pain.[13]

IA local anaesthetics are frequently used in perioperative pain management. Bupivacaine, a local anaesthetic, is often utilised because of its extended duration of action. The dose of bupivacaine may be an important factor. Smith *et al*. believed that the administration of opioids, when combined with local anaesthetic, enhances post-operative analgesia by a peripheral mechanism.[14] Most of the IA structures 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 severe pain. Morphine can enhance the local anaesthetic effect of bupivacaine and may prolong the blockade of peripheral nociceptive input from surgical site of trauma.[15]

Stein *et al.* were the first to demonstrate a prolonged analgesic effect from the IA administration of morphine in humans in 1991.[16] These receptors are expressed within hours after surgical trauma and are thought to be responsible for afferent sensory input to the central nervous system.[3,6] Joshi *et al*. conducted randomised, controlled, double-blind study in elective knee arthroplasty patients with morphine (5 mg in 25 ml dilution) in study group and same volume of saline in the control group instilled intra-articularly.[7] Patients in the study group had significantly lower pain scores and required less systemic analgesics than the control group. Plasma profile of morphine and its metabolites showed that they were too low to produce effective analgesia, which suggests that analgesia was mediated by local action within the joint. They also found relation between the times from IA injection to tourniquet release, as longer the time the tourniquet was kept inflated after IA injection, better was the local tissue binding of the drug. They also concluded that dose of the drug is an important factor, as higher dose may evoke early onset of analgesia. However, their study did not compare different doses of morphine and did not use local anaesthetic. Denti *et al.* showed the analgesic effect of three doses of IA morphine (1, 2 and 5 mg) for patients undergoing anterior cruciate reconstruction.[9] The highest dose of morphine (5 mg) had better analgesia and resulted in lower supplementary analgesic consumption in the first 24 h after the procedure. Interestingly, in this same study, the authors observed that 5 mg IA morphine did not produce better results than 2 mg, in patients undergoing other arthroscopic procedures. This study supports a dose-response relationship for IA morphine for more invasive procedure such as anterior cruciate ligament reconstruction. The majority of patients in our study underwent therapeutic surgeries and did not show significant difference between 3 mg and 5 mg morphine, although the analgesic effect was better than 1 mg group.

In a randomised, controlled, double-blinded study conducted by Garcia *et al.*, the efficacy of 10 mg IA morphine was compared with placebo in 50 patients undergoing total knee arthroplasty.[8] The treatment group had significantly lower numeric scale pain scores in the 2nd and 6th post-operative hours and lower analgesic consumption in the first 24 h than

the placebo group. The incidence of side effects did not differ in the groups, and the authors concluded that IA 10 mg morphine promote longer period of analgesia with reduced consumption of supplemental analgesia. Although the surgical procedure performed in this study was more invasive than in our study, it proved the analgesic efficacy of IA morphine. We did not use such high doses of morphine, considering the less invasiveness of surgery being performed in our study population. In a study by Yari *et al*., 40 patients undergoing anterior cruciate ligament repair were recruited and divided into four groups.[11] All the patients received 20 cc of 0.5% IA bupivacaine with either NS, 5 mg, 10 mg or 15 mg morphine. The authors observed that 15 mg IA morphine with 20 cc of 0.5% bupivacaine increased the analgesia level as well as its duration. None of the patients had any complication. Again, the dose used was much higher than in our study. Moreover, the anaesthetic concentration (0.5%) of bupivacaine was used, which could have prolonged the analgesic effects.

In the review by Gupta *et al*., three issues were analysed - Does IA injection of morphine produce analgesia? Is it a dose-dependent effect, and, if so, is the effect systemic or mediated via peripheral opioid receptors?[6] Nineteen studies suitable for meta-analysis showed an improvement in analgesia after morphine compared with placebo. Studies with high-quality scores showed somewhat smaller improvements. Total analgesic consumption could not be analysed statistically, but the number of studies showing decreased analgesic consumption or no differences between groups was identical. No clear dose-response effect was seen when VAS was used as a measure of pain, but it was seen when area under the curve was used as a measure of pain.

In our study, there was statistically significant difference in VAS scores in 1st, 2nd and 24th h post-operative period. The statistically insignificant difference in the VAS scores in the intermediate period (i.e., at 6th and 12th post-operative hours) may have resulted from the supplemental analgesia that we had administered to the patients according to our study protocol. The time to first rescue analgesic in the post-operative period was higher in Group B and Group C patients than in Group A. Also, there was statistically significant less consumption of supplemental analgesia in the first 24 h in Group B and Group C patients than in Group A. As we had used equal amounts of IA bupivacaine in all our patients, so, we can conclude that higher dose of IA morphine appears to be having greater analgesic effect both in early and late post-operative period and results in less consumption of supplemental analgesics. In our study, no statistically significant difference was found between the three morphine groups for the complications such as pruritus, nausea and urinary retention but certainly the number of patients experiencing the side effects was higher with increasing dose of IA morphine. Hence, although 1 mg IA morphine had less pronounced analgesic effect, it had less number of side effects too.

The main limitation of our study was that subarachnoid block was administered in all our patients, as per the institutional practices, and may be a confounding factor in post-operative pain relief and complications like urinary retention. However, since all the patients were subjected to similar anaesthesia and post-operative pain relief was studied for 24 h; we believe that we countered the limitation to some extent. Another limiting factor was that both, diagnostic and therapeutic procedures were included, which might have confounded results, although the type of surgery in all three groups were similar. Small number of patients from single centre was another limiting factor and multicentric studies with large number of patients are required.

CONCLUSION

We conclude that IA dose of 3 mg and 5 mg morphine with 20 ml of 0.25% bupivacaine, provide superior analgesia as compared to 1 mg IA morphine following arthroscopic knee surgeries. Patients who received 3 mg IA morphine had fewer side effects as compared to 5 mg group patients, although the difference was not statistically significant. However, larger studies are required to establish the optimum IA dosage of morphine for post-operative pain relief.

Acknowledgement

We acknowledge Dr. Kailavani, Professor, Department of Biostatistics for the help in statistical analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Acute Pain Management: Operative or Medical Procedures and Trauma. (Clinical Practice Guideline.) Publication No. AHCPR 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health

and Human Services; February, 1992. Available from: http://archive.ahrq.gov/clinic/medtep/acute.htm. [Last accessed on 2015 Feb 10].
2. Georgopoulos G, Carry P, Pan Z, Chang F, Heare T, Rhodes J, *et al*. The efficacy of intra-articular injections for pain control following the closed reduction and percutaneous pinning of pediatric supracondylar humeral fractures: A randomized controlled trial. Bone Joint Surg Am 2012;94:1633-42.
3. Stein C. Peripheral mechanisms of opioid analgesia. Anesth Analg 1993;76:182-91.
4. Mauerhan DR, Campbell M, Miller JS, Mokris JG, Gregory A, Kiebzak GM. Intra-articular morphine and/or bupivacaine in the management of pain after total knee arthroplasty. J Arthroplasty 1997;12:546-52.
5. Stein C. The control of pain in peripheral tissue by opioids. N Engl J Med 1995;332:1685-90.
6. Gupta A, Bodin L, Holmström B, Berggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anesth Analg 2001;93:761-70.
7. Joshi GP, McCarroll SM, Cooney CM, Blunnie WP, O'Brien TM, Lawrence AJ. Intra-articular morphine for pain relief after knee arthroscopy. J Bone Joint Surg Br 1992;74:749-51.
8. Garcia JB, Barbosa Neto JO, Vasconcelos JW, Ferro LS, Silva RC. Analgesic efficacy of the intra-articular administration of high doses of morphine in patients undergoing total knee arthroplasty. Rev Bras Anestesiol 2010;60:1-12.
9. Denti M, Randelli P, Bigoni M, Vitale G, Marino MR, Fraschini N. Pre- and postoperative intra-articular analgesia for arthroscopic surgery of the knee and arthroscopy-assisted anterior cruciate ligament reconstruction. A double-blind randomized, prospective study. Knee Surg Sports Traumatol Arthrosc 1997;5:206-12.
10. Rao V, Sanjay OP, John L, Thomas I, Rajkumar, Sharma G. Intra-articular administration of morphine, bupivacaine and morphine with bupivacaine for post-operative analgesia following video knee arthroscopy. Indian J Anaesth 2003;47:265-8.
11. Yari M, Saeb M, Golfam P, Makhloogh Z. Analgesic efficacy of intra-articular morphine after arthroscopic knee surgery in sport injury patients. J Inj Violence Res 2013;5:84-8.
12. Elkousy H, Kannan V, Calder CT, Zumwalt J, O'Connor DP, Woods GW. Intra-articular morphine versus bupivacaine for postoperative pain management. Orthopedics 2013;36:e1121-7.
13. Woolf CJ, Chong MS. Preemptive analgesia – Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362-79.
14. Smith I, Van Hemelrijck J, Unite PF, Shively R. Effects of local anaesthesia after out-patient arthroscopy. Anesth Analg 1992;75:208-12.
15. Kalso E, Tramèr MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intra-articular morphine after knee surgery: A qualitative systematic review. Pain 1997;71:127-34.
16. Stein C, Comisel K, Haimerl E, Yassouridis A, Lehrberger K, Herz A, *et al*. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. N Engl J Med 1991;325:1123-6.

Announcement

CALENDAR OF EVENTS OF ISA - 2015

Certain important dates are given here for the members. All the applications should be sent by registered post (with Acknowledgement Due)

Date	Name of the Award/Post	Application has to be sent to
30th June 2015	Bhopal Award for Academic Excellence	Hony. Secretary, ISA
15th August 2015	Prof. A. P. Singhal Life Time Achievement Award	Hony. Secretary, ISA
31st October 2015	Dr. (Mrs.) Rukmini Pandit Award - Publication format along with Conference Presentation Certificate	Hony. Secretary, ISA
31st October 2015	Y. G. Bhoj Raj Award - Best Review Article in IJA	Hony. Secretary, ISA
31st October 2015	Dr. Kop's Award	Chairman Scientific committee of ISACON with a copy to Hony Secretary ISA
27th November 2015	Dr. TN Jha Memorial & Dr. KP Chansoriya Travel grant	Hony. Secretary, ISA
27th November 2015	Late Dr. Venkata Rao Memorial Oration	Hony. Secretary, ISA
27th November 2015	Ish Narani Best Poster Award	Chairman Scientific Committee ISACON
28th November 2015	ISA GOLDCON QUIZ Competition	Chairman Scientific Committee ISACON
28th November 2015	Awards for 1. Best City Branch 2. Best State Branch 3. Best Metro Branch 4. Public Awarness Individual 5. Public Awarness City 6. Public Awarness State 7. Ether Day State 8. Ether Day City 9. Membership Drive % (State) 10. Membership Drive No.s (State) 11. Individual Drive	Hony. Secretary, ISA

Dr. Venkatagiri K M
"ASHWATHI", Opp. Ayyappa Temple, Nullippady, Kasaragod - 671121, Kerala
Email: isanhq@gmail.com / secretaryisanhq@gmail.com/ isanhq@isaweb.in Mobile: 093880 30395