

Comparison of the postoperative analgesic effects of intrathecal Clonidine and Fentanyl as adjuvant: Meta Analysis of randomized control trials

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Abstract

Background: Intrathecal clonidine and fentanyl added to bupivacaine prolongs the postoperative analgesic effects for below umbilicus surgery. However, the overall effect of clonidine and fentanyl mixed with spinal anesthesia is not harmonized. Therefore, the aim of this Meta - analysis was to assess the post operative analgesic effects of intrathecal clonidine and fentanyl for different randomized control trials of study.

Methods: Pubmed, Cochrane Review, EMBASE, and Google Scholar were searched and a total of four studies have been selected for Meta – Analysis. Three authors engaged independently to extract data on the efficacy of intrathecal clonidine and fentanyl for lower abdomen and limb surgeries. The statistical analysis was accomplished by RevMan (version 5.3) software. The overall efficacy of intrathecal clonidine and fentanyl were pooled by Forrest plot, table, and figure with 95% confidence interval.

Results: The pooled effect size mean difference of intrathecal clonidine versus fentanyl was 83.57(95 % CI, 29.33 to 137.82) minutes. Furthermore, the lowest and highest mean difference of effect size was 10.60 and 175.98 minutes respectively.

Conclusion: Intrathecal clonidine as adjuvant to bupivacaine gave the prolonged postoperative analgesia in comparison to intrathecal fentanyl. So it is recommended to use clonidine as intrathecal adjuvant when we consider the extended postoperative analgesia.

Background

Spinal anesthesia is the routine done procedure with bupivacaine for below umbilicus and lower limb Surgeries. This type of regional anesthesia is ensuring intraoperative and early postoperative period pain management, despite its restricted duration of action [1]. In turn, to increase duration of analgesia and quality of blockage, adjuvant of intrathecal clonidine and opioids are appropriate [2]. Different studies have been found that intrathecal midazolam, neostigmine, opioids and clonidine put together the prolongation of subarachnoid block and reduction of postoperative analgesic consumption [3-7].

Specifically, addition of low doses of clonidine and fentanyl in intrathecal could be associated with lesser incidence of adverse effects[8]. However, intrathecal opioids with bupivacaine connected with side effects of nausea, vomiting, pruritus, respiratory depression and urinary retention in favor of clonidine which has not this property[9]. Amongst the opioids, fentanyl could be the choice of adjuvant because of its potency, rapid onset and short duration of action with lesser incidence of respiratory depression[8, 10]. Even though rising number of published trials with small number of patients paying attention on post operative analgesic effects to intrathecal clonidine and fentanyl, full up to date evidence in larger population is lacking so far.

Therefore, it was the aim of this Meta analysis performed to confirm their conclusion using at large sample size.

Methods

Study selection

A literature search was conducted in Pubmed, Cochrane review, EMBASE and Google scholar data bases and articles which are relevant to our study were identified. The search was performed by three authors (FH, AH, SE) independently with asking the key words of intrathecal, clonidine, fentanyl and postoperative analgesia. In the middle of citation extracted, abstracts were reviewed to recoup the clinical studies of randomized control trials on intrathecal adjuvant of clonidine and fentanyl. Articles that were related, by title and abstract were right to used in full text to determine those that provided sufficient information to be included in our Meta-analysis.

Inclusion and exclusion criteria

The trials included in our Meta analysis: patients undergoing spinal anesthesia were assigned to at least two groups, including Clonidine alone as an adjuvant to local anesthetics and Fentanyl alone as an adjuvant to local anesthetics. So, all randomized control trial studies investigating the efficacy of intrathecal clonidine (50 µg) compared with intrathecal fentanyl (25 µg) for patients under went to lower abdomen and extremity surgery.

Table 1: characteristic of the included studies

Study	Year	Application (µg)	Sample size	Local anesthetics (mg)	Total volume (ml)	Operation
Ranju singh et al ¹⁸	2013	F25/C50/C75	35/35/35	Bup 10	2.0	Cesarean Section
Routray SS et al ¹⁹	2017	C50/F25	40/40	Bup 12.5	2.5	Lower limb orthopedic Surgery
Bajwa et al ²⁰	2017	C50/F25	50/50	Bup 12.5	2.5	Lower abdominal Surgeries
Hakim et al ²¹	2017	C50/F25/F12.5	30/30/30	Bup 12.5	2.5	Lower limb and hip Surgeries

Notes: * values are mean ± standard deviation.

Abbreviation : C, Clonidine ; F, Fentanyl ; Bup, Bupivacaine

Outcome of interest

The primary outcome of interest was duration of Analgesia. The secondary outcomes of interest were duration of sensory and motor blockage.

Data extraction

Data from qualified studies were extracted independently by authors and summarized into a spreadsheet. Discrepancies were resolved by agreement. For each of the included studies, the following information was extracted; First author's name, year of the study, numbers of patients/study participants, total volume for spinal anesthesia, and types of surgery (Table 1).

- Sensory block: the time of regression to S1 from the maximum sensory block level
- Motor block: the time of regression to the modified Bromage score of 0
- Duration of analgesia: the time from intrathecal injection to the first time of compliant about pain or rescue analgesia

Three authors (FT, AH, SE) examine the full-text articles and they independently decided whether the retrieved trials met the inclusion criteria or not. The Two authors (FT, AH) carried out the data extraction using special standardized forms developed for the Meta analysis. These included titles, contact information of the authors, type of surgery, and types of intrathecal adjuvant. The outcome data were entered into RevMan 5.3 provided by the Cochrane Collaboration for further statistical analysis.

Quality control

Two authors (FT, AH) independently read and evaluated the methodological validity of all eligible studies using a set of prearranged criteria of research design, quality of paper, and engaged methods for intrathecal clonidine and fentanyl. Any discrepancies were resolved through joint discussion, if necessary a third researcher assisted in the decision.

Data analysis

A randomized effect model was used to determine the outcomes of analgesic effects of clonidine and fentanyl adjuvant with 95% confident interval. We evaluated the heterogeneity of study results with the use of I² test. Significant heterogeneity was considered $P < 0.10$ and $I^2 > 50\%$ [11, 12]. The overall effect size of time of first analgesic request for Intrathecal clonidine versus fentanyl was pooled by the forest plot with 95% CI. Statistical analysis was performed by the use of Cochrane review manager (RevMan 5.3).

Results

We have found 817 abstracts through electronic data base search. Among this studies 756 were excluded due to the abstracts or full text information did not related to the topic interest. Eventually, four articles fulfilled our eligibility criteria and were subjected to Meta analysis (Fig 1.)

Table 2: Summary of results from the individual studies

Study	Year	Application	Duration of Analgesia (minutes)*	Duration of Sensory Block (minutes)*	Duration of Motor Block (minutes)*
Ranju singh et al ¹⁸	2013	C	360.71± 86.51	189.57±11.40	224.71±35.22
		F	184.73 ± 68.64	122.27±23.39	210.33±32.37
Routray SS et al ¹⁹	2017	C	510.84±24.10	250.52±18.41	190.16±26.11
		F	439.95±19.16	205.16±19.55	171.31±24.58
Bajwa et al ²⁰	2017	C	497.20±139.78	136.56±12.67	184.58±12.07
		F	416.87±105.67	132.00±14.56	190.50±18.65
Hakim et al ²¹	2017	C	208.80±26.32	126.10±12.80	110.50±8.50
		F	198.20±21.92	86.00±10.50	86.20±6.48

Notes: * values are mean ± standard deviation.

Abbreviation : C, Clonidine ; F, Fentanyl.

Discussion

Spinal anesthesia is a type of neuraxial regional anesthesia which covers for lower limb and lower abdominal surgeries. However, plain local anesthetics associated with cardiac and neurological toxicities [13, 14]. For reduction of this, local anesthetics were mixed with other drugs, to decrease the dose requirement and potentiation of local anesthetics[15].

This Meta analysis of randomized control trials showed that 50 µg intrathecal clonidine as an adjuvant provided the prolonged postoperative analgesia compared with 25 µg intrathecal fentanyl as a mean difference of [83.57(95 % CI, 29.33 to 137.82), I2 = 97%, P < 0.00001] minutes. Different studies have been found that both clonidine and fentanyl added to spinal block with bupivacaine are effective for the persistence of postoperative analgesic time. [16, 17]

It was also supported by other different studies which gave the evidence of 50 µg clonidine to intrathecal bupivacaine made the lengthening of analgesic duration in comparison to 25 µg fentanyl with bupivacaine[18-20].

In regarding to secondary outcomes of interest Meta analysis study, the sensory and motor duration of block is significantly prolonged in intrathecal clonidine group compared to fentanyl. This was consistent with many different studies [19, 21, 22]. However, there was not considerable inter sub group differences of block duration between the motor and sensory.

The means of clonidine related potentiation of spinal sensory block is reported to be reliant on presynaptic (decrease transmission) and postsynaptic (hyper polarization) action. It activates the α2 receptors with blocking of Aδ and C nerve fibers at substantia gelatinosa of spinal cord to generate

analgesia[23, 24]. Fentanyl is the preferred opioid drug for regional anesthesia with action on μ_1 and μ_2 receptor agonist. It is highly potent drug due to high lipid solubility[25, 26] despite some related complications of nausea, vomiting, and pruritus [27].

According to some study, even at higher dose of clonidine (450 μg) only in intrathecal, didn't result muscle weakness and motor block [28] , but combination to spinal bupivacaine caused significant enhancement of the strength and duration of motor block[29, 30]. Tilkar et al study compared clonidine and fentanyl added to intrathecal bupivacaine and reached as conclusion of clonidine was more helpful than fentanyl in pain-relieving properties[31].

Even though different studies have been used intrathecal clonidine from dose of 15 μg to 150 μg , the 50 μg intrathecal clonidine was provided the extended postoperative analgesia with minimal side effects compared to fentanyl[32-34].

There are a number of limitations to our Meta analysis. It was possible to miss some studies which satisfied the inclusion criteria, and number of studies to be excluded as the full text was unavailable. In addition, there was significant heterogeneity to duration of analgesia, duration of sensory block and duration of motor block with considering different doses of bupivacaine drug and types of surgery.

Conclusion

Addition of 50 μg clonidine to intrathecal bupivacaine, put forward the longer duration of postoperative analgesia than 25 μg of fentanyl. So, it is recommended to use clonidine when we consider the extended duration of postoperative analgesia.

Declarations

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Availability of data and materials

No additional data are required; all information is clearly presented in the main manuscript.

Authors' contributions

FT: Conception of research protocol, study design, literature review, data collection, data extraction, data analysis and interpretation, and drafting manuscript.

AH, SE: literature review, data collection and extraction, and reviewing manuscript. All authors have read and approved the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

We have meta-analyzed evidences obtained from randomized controlled studies.

Therefore, this study did not require approval from ethical committee.

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References

1. Rust, L.A., et al., *Intrathecal narcotics for obstetric analgesia in a community hospital*. American journal of obstetrics and gynecology, 1994. **170**(6): p. 1643-1648.
2. Nazareth, M., et al., *Addition of intrathecal fentanyl to bupivacaine clonidine mixture effect on quality of subarachnoid block and postoperative analgesia*. Anesthesia, essays and researches, 2013. **7**(1): p. 76.
3. Sites, B.D., et al., *Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty*. Anesthesia & Analgesia, 2003. **96**(4): p. 1083-1088.
4. Juliao, M. and G.R. Lauretti, *Low-dose intrathecal clonidine combined with sufentanil as analgesic drugs in abdominal gynecological surgery*. Journal of clinical anesthesia, 2000. **12**(5): p. 357-362.
5. Grace, D., et al., *Postoperative analgesia after co-administration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement*. Anesthesia & Analgesia, 1995. **80**(1): p. 86-91.
6. Prakash, S., et al., *Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery*. Regional anesthesia and pain medicine, 2006. **31**(3): p. 221-226.
7. Yoganarasimha, N., et al., *A comparative study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries*. Indian journal of anaesthesia, 2014. **58**(1): p. 43.

8. Benhamou, D., et al., *Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section*. *Anesthesia & Analgesia*, 1998. **87**(3): p. 609-613.
9. Bonnet, F., et al., *Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine*. *Regional anesthesia*, 1990. **15**(4): p. 211-214.
10. Selvaraju, K.N. and S.V. Sharma, *Comparison of forced expiratory spirometric flow changes following intrathecal bupivacaine and bupivacaine with fentanyl*. *Southern African Journal of Anaesthesia and Analgesia*, 2008. **14**(5): p. 33-37.
11. DerSimonian, R. and N. Laird, *Meta-analysis in clinical trials*. *Controlled clinical trials*, 1986. **7**(3): p. 177-188.
12. Rücker, G., et al., *Undue reliance on I 2 in assessing heterogeneity may mislead*. *BMC medical research methodology*, 2008. **8**(1): p. 79.
13. Cox, B., M. Durieux, and M. Marcus, *Toxicity of local anaesthetics*. *Best practice & research Clinical anaesthesiology*, 2003. **17**(1): p. 111-136.
14. Marri, S.R., *Adjuvant agents in regional anaesthesia*. *Anaesthesia & Intensive Care Medicine*, 2012. **13**(11): p. 559-562.
15. Sun, S., et al., *Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials*. *Drug design, development and therapy*, 2017. **11**: p. 3413.
16. Kothari, N., J. Bogra, and A.K. Chaudhary, *Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section*. *Saudi journal of anaesthesia*, 2011. **5**(1): p. 31.
17. Breen, T.W., et al., *Epidural anesthesia for labor in an ambulatory patient*. *Anesthesia and Analgesia*, 1993. **77**(5): p. 919-924.
18. Singh, R., D. Gupta, and A. Jain, *The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial*. *Saudi journal of anaesthesia*, 2013. **7**(3): p. 283.
19. Routray, S.S., et al., *Comparison of intrathecal clonidine and fentanyl as adjuvant to hyperbaric bupivacaine in subarachnoid block for lower limb orthopedic surgery*. *Anesthesia, essays and researches*, 2017. **11**(3): p. 589.
20. Bajwa, B.S., A.P. Singh, and A.K. Rekhi, *Comparison of intrathecal clonidine and fentanyl in hyperbaric bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing lower abdominal surgeries*. *Saudi journal of anaesthesia*, 2017. **11**(1): p. 37.

21. Hakim, A., A.A. Bhat, and M. Jan, *Effect of Clonidine and/or Fentanyl in Combination with Intrathecal Bupivacaine for Lower Limb Orthopedic Surgeries in Spinal Anaesthesia*.
22. Elia, N., et al., *Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials*. Regional anesthesia and pain medicine, 2008. **33**(2): p. 159-167.
23. Giovannitti Jr, J.A., S.M. Thoms, and J.J. Crawford, *Alpha-2 adrenergic receptor agonists: a review of current clinical applications*. Anesthesia progress, 2015. **62**(1): p. 31-38.
24. Sethi, B., M. Samuel, and D. Sreevastava, *Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine*. Indian journal of anaesthesia, 2007. **51**(5): p. 415.
25. Singh, H., et al., *Intrathecal fentanyl prolongs sensory bupivacaine spinal block*. Canadian Journal of anaesthesia, 1995. **42**(11): p. 987-991.
26. Unal, D., et al., *Selective spinal anaesthesia with low-dose bupivacaine and bupivacaine+ fentanyl in ambulatory arthroscopic knee surgery*. JPMA-Journal of the Pakistan Medical Association, 2012. **62**(4): p. 313.
27. Ben-David, B., et al., *Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery*. Regional anesthesia and pain medicine, 2000. **25**(3): p. 235-239.
28. Gecaj-Gashi, A., et al., *Intrathecal clonidine added to small-dose bupivacaine prolongs postoperative analgesia in patients undergoing transurethral surgery*. Canadian urological association journal, 2012. **6**(1): p. 25.
29. Dobrydnjov, I., et al., *Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study*. Anesthesia & Analgesia, 2003. **96**(5): p. 1496-1503.
30. Filos, K.S., et al., *Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study*. Anesthesiology, 1994. **81**(3): p. 591-601; discussion 27A-28A.
31. Tilkar, Y., S.A. Bansal, and G.S. Agnihotri, *Effect of adding clonidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in orthopedic procedures: A double blind controlled study*. Int J Med Sci Public Health, 2015. **4**: p. 458-62.
32. Thakur, A., et al., *Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy: A randomized double-blinded study*. Journal of anaesthesiology, clinical pharmacology, 2013. **29**(1): p. 66.
33. Nasr, I.A. and S.A. Elokda, *Safety and efficacy of intrathecal adjuvants for cesarean section: bupivacaine, sufentanil, or dexmedetomidine*. Ain-Shams Journal of Anaesthesiology, 2015. **8**(3): p. 388.

Figures

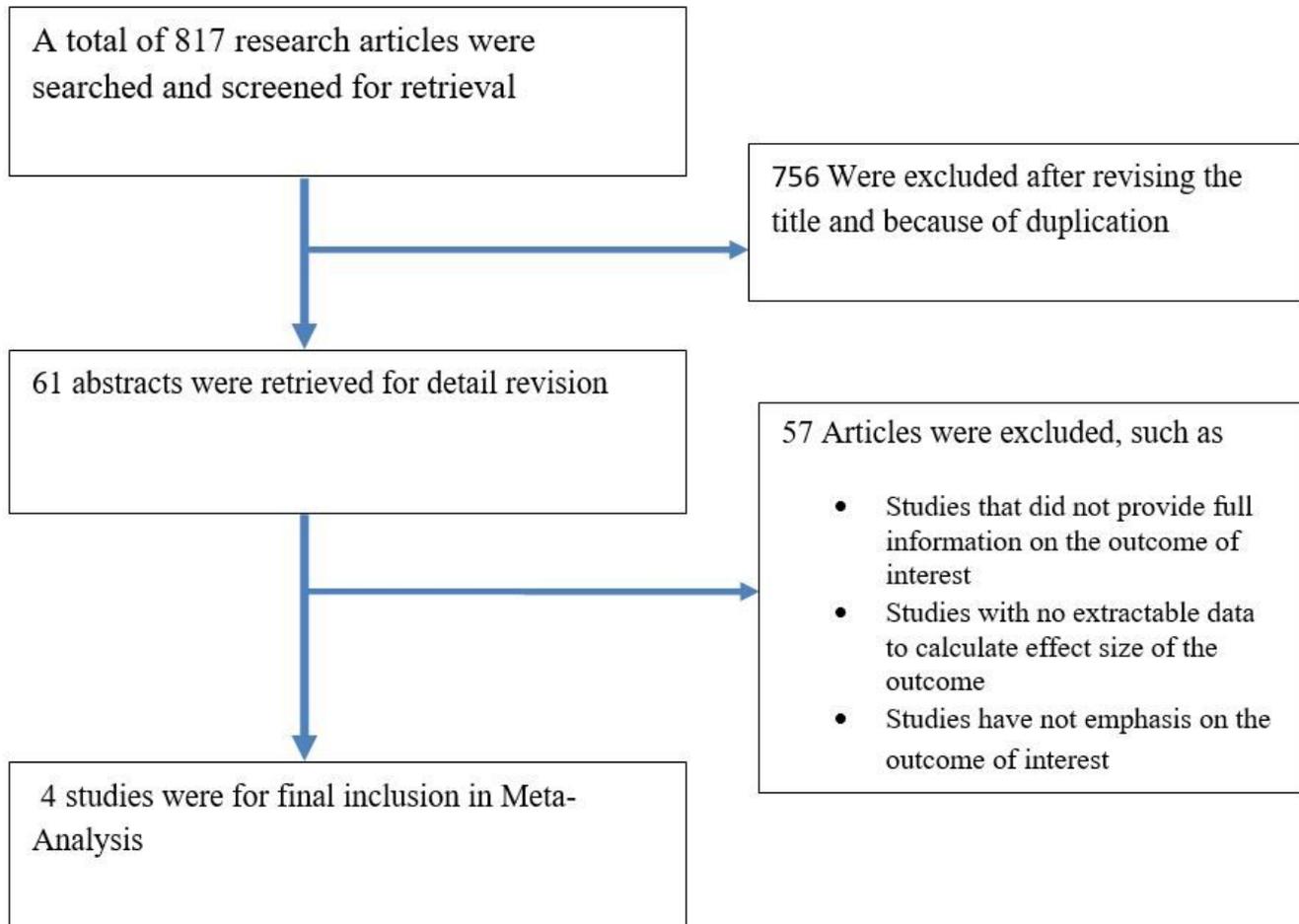


Figure 1

Flow chart shows selected articles for Meta Analysis

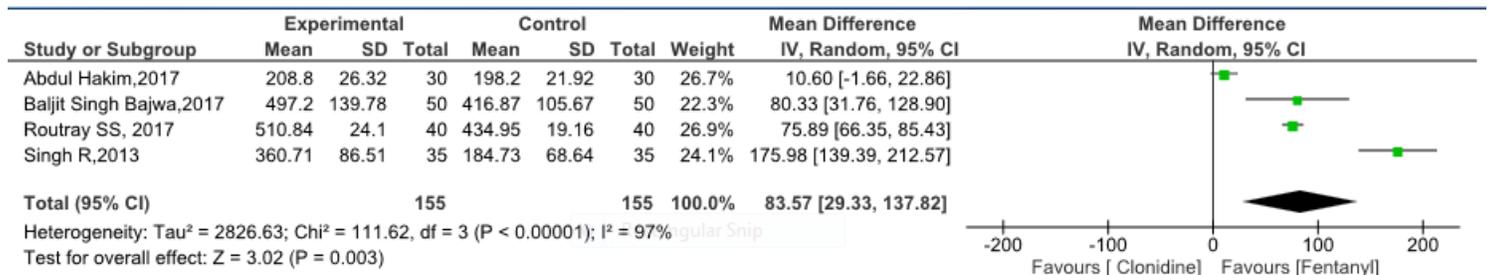


Figure 2

Forest plot of the pooled effect size of the intrathecal Clonidine versus Fentanyl for Postoperative analgesia underwent lower Abdomen and lower Limb Surgeries. Abbreviations: SD, Standard deviation; CI, Confidence interval; IV, Inverse variance

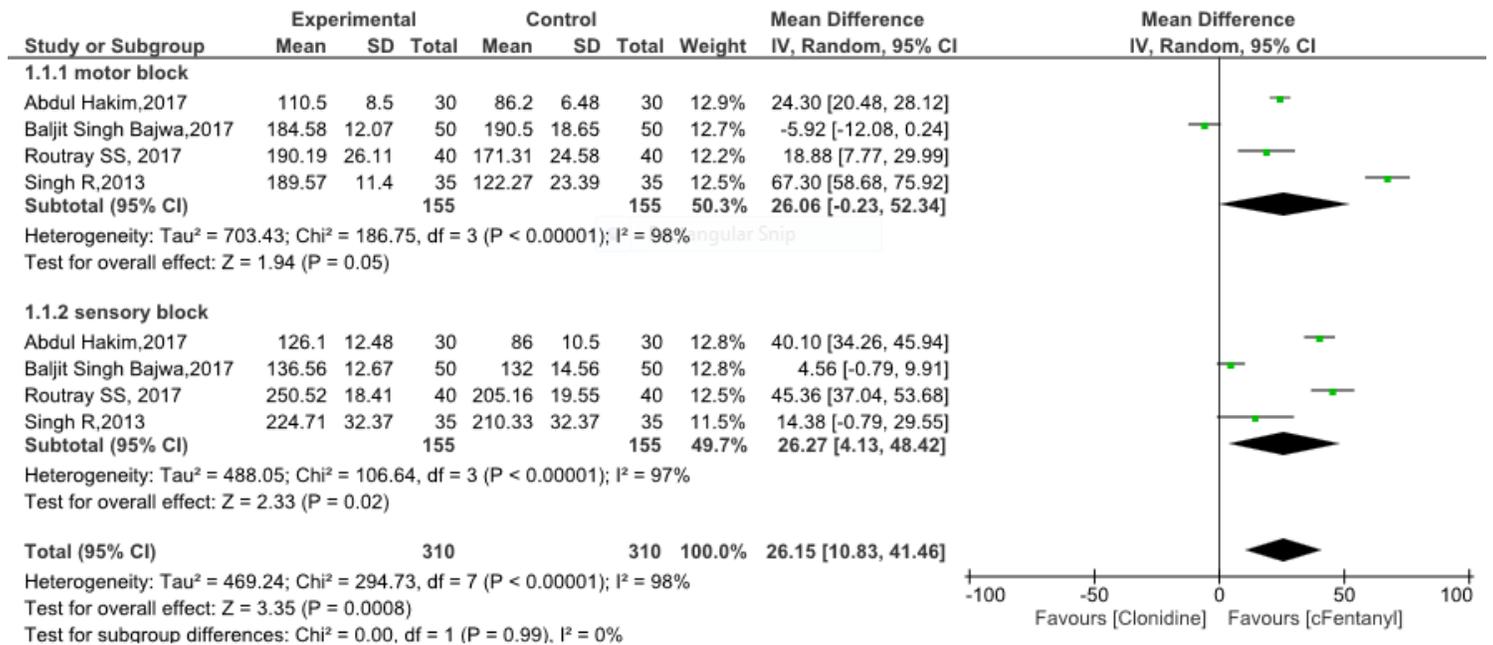


Figure 3

Forest plot of the pooled effect size of the intrathecal Clonidine versus Fentanyl for duration of motor and sensory block underwent lower Abdomen and Limb Surgeries. Abbreviations: SD, Standard deviation; CI, Confidence interval; IV, Inverse variance