

Oxycodone reduced postoperative catheter-related bladder discomfort undergoing transurethral resection prostate. A prospective, double-blind randomized study

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Research article

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Abstract

Background: Catheter-related bladder discomfort (CRBD) is a common and distressing complication that often occurs caused by urinary bladder catheterization and urethral mucosa injury postoperatively. Oxycodone is a semi-synthetic opioids prepared from opium alkaloid the baine plant derivative. Its μ and κ dual-receptor agonism has a unique effect in the treatment of visceral pain. The aim of this study to observe the efficacy of oxycodone for the treatment of CRBD undergo trans-urethral resection prostate (TURP).

Methods: Patients with ASA I-III received trans-urethral resection prostate under general anesthesia were enrolled. Patients who complained CRBD were randomized allocated to the control group (n=42) received placebo and the observed group (n=41) received 0.03mg/kg of oxycodone. The severity of CRBD assessed by NRS were assessed at 0, 5min, 1/2h, and 2h after administration of the study agents. VAS scores were used to assess pain intensity during the same period. Postoperative PCA analgesic sufentanil dose during of PACU times and the incidences of agitation, nausea, vomiting, dizziness, over sedation were recorded in these patients.

Results: Compared with the control group, the incidence of CRBD was significantly lower in the oxycodone group at 5min and 1/2h. Compared with the controlled group, VAS scores and incidences of agitation were lower in oxycodone group and significantly decreased sufentanil dosage within 6h ($P<0.01$). There were no significant differences in the incidence of postoperative adverse effects and during of PACU between two groups($P\geq 0.05$).

Conclusion: Oxycodone 0.03mg/kg effectively reduced patients with CRBD after TURP without incurring serious adverse effects.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-IPR-16008814.

Background

Catheter-related bladder discomfort (CRBD) is a common and distressing complication that often occurs caused by urinary bladder catheterization and urethral mucosa injury postoperatively ^[1]. CRBD could be partly responsible for high levels of violence reported against healthcare workers and lead to patient injury in postoperative recovery unit (PACU). Furthermore, CRBD could represent hyperactive delirium that associated with longer hospital stays and increased morbidity, mortality, and need for institutionalisation. Many risk factors for CRBD have been indentified in previous studies such as male sex, diameter of the Foley catheter, and types of operations ^[3, 4].

Because of a different underlying mechanism is involved, CRBD may be resistant to conventional analgesic therapy such as opioids. Many agents, including the muscarinic receptor blockers such as

Oxybutynin, tolterodine, tramadol and butylscopolamine^[8-11] and central nerves system inhibitors such as ketamine and gabapentin^[12, 13], have been investigated as approaches in the prevention or treatment of CRBD. But these agents with various side-effects and shortages limited the use.

Oxycodone is a semi-synthetic opioids prepared from opium alkaloid the baine plant derivative^[14]. Its μ and κ dual-receptor agonism has a unique effect in the treatment of visceral pain^[15-17]. We have reported that oxycodone IV. before the end of operation was effective for the preventive of CRBD after TURP^[5]. But the effects for treatment of CRBD has no investigated. We conducted a prospective, double-blind randomized, single-center study to investigate whether oxycodone has preventive effects on early postoperative CRBD after TURP.

Materials And Methods

This prospective, randomized, double-blind and placebo controlled study was performed after approval from ethic committee of Wenzhou people's hospital, number: 2016003. The protocol for this clinical trial was registered at CHICTR.ORG.CN (ChiCTR-IPR-16008814).

During preoperative visit, all patients were provided informed consents and educated about the symptoms of CRBD (characterized as a burning sensation with an urge to void or as discomfort in the suprapubic area) and numerical rating scale (NRS) Severity of CRBD was recorded using an NRS ranging from 0 (no discomfort) to 100 (most severe discomfort).

From July to December 2019, male patients with an ASA physical status I to III, who were scheduled to transurethral resection prostate were included. Patients were excluded if they were unable communicate, refused join the study, had a history of severity heart disease, lung disease, psychiatric disease, chronic pain or long-term administration of analgesics.

All patients had no premedicated, standard monitoring consisted of ECG, non-invasive arterial pressure (NIBP), and pulse oximetry (SpO₂). Anesthesia was induced with 0.05mg kg⁻¹ midazolam, 4 μ g/kg⁻¹ fentanyl, 1.5mg kg⁻¹ propofol and 0.6mg kg⁻¹ rocuronium. Intraoperative maintenance anesthesia relied on intravenous anesthesia; remifentanyl infusion was maintained at 0.2 μ g kg⁻¹ min⁻¹; intraoperative propofol infusion rate was adjusted to maintain BIS value within 40-60; rocuronium was intermittently injected. 16/18 Foley urinary catheter was inserted and 5 ml sterile normal saline was injected into the balloon at the end of operation. After the surgery, 0.5mg atropine and 1mg neostigmine were administered to antagonize residual muscle relaxation. These patients were transferred to PACU after the endotracheal catheter was removed. PCIA analgesia was postoperatively applied. the analgesic was 100 μ g sufentanil added to 100ml normal saline, the background infusion was 1ml per hour, the predetermined time was 8min and the volume of each press was 2ml.

After reporting CRBD, patients were randomly assigned to one of two groups (control or oxycodone) with the help of a computer generated random number table. The assignments were concealed in opaque

envelopes and opened immediately before induction by a nurse who was blinded to this study and was responsible for preparing the study drugs. All medications were administered in identical 2 ml syringes. patients were randomized into two groups using sealed envelopes by an anaesthesiologist responsible for the randomization. The group controlled received same volume normal saline, whereas the oxycodone group intravenous inject oxycodone 0.03mg kg⁻¹ (product batch number: AW259, Mundipharma, Britain).

The primary outcome was defined as the reduction in the severity of CRBD assessed by NRS ^[17]. Secondary outcomes were sufentanil consumption, during of PACU, incidences of agitation and requiring treatment of hypertension, heart rates (HRs), mean arterial pressure (MAP), and adverse effects included PONV, over sedation. All these outcomes were assessed at 0, 5min 1/2 h, and 2 h after administration of the study drug by blinded assessors. Times of duration of PACU were recorded. VAS scores were used to assess pain in these patients: 0 point, no pain; 10 points, unbearable pain. The Ramsay Sedation Scale was measured ^[18]. Patients with a sedation scale score of at least 4 were considered over sedation. The patients with severe vomiting received intravenous injection of 4mg ondansetron. Analgesic doses and anti-hypertension received by the two groups of patients within 6 hours after the operation were recorded. Agitation was defined as a Richmond Agitation Sedation Scale (RASS) score ^[19] of +3 or +4 during the PACU stay. If the patients' blood pressure higher 30% than baseline at the ward or more than 180mmHg must be used anti-hypertension agents.

The calculation of the sample size was based on our previous study, 60% of patients complain of CRBD postoperatively ^[20]. The severity of CRBD (NRS) of 10 patients was 80 at the time of reporting CRBD. Assuming that the severity of CRBD reduced from 80 to 50 (decrease of 30) after therapy with oxycodone. We calculated that 33 patients would be needed in each group to achieve statistical significance ($\alpha=0.05$ and $\beta=0.20$). Considering a 20% dropout rate, 80 patients per group were included.

All data were analyzed with SPSS16.0 software package (SPSS, Inc., Chicago, IL, USA). NRS, HR and MAP over time between the groups were analyzed by repeated measures analysis of variance (ANOVA) and then t-test was used to compare values at each time point. Rescue analgesic was analyzed by t-test. Analyses of categorical variables (incidence of side effects) were performed by χ^2 or Fisher's exact-tests. Data were analyzed according to the intention-to-treat principle. $P<0.05$ indicated statistically significant differences.

Results

162 patients were screened for inclusion in the study. 17 patients were excluded [not meeting inclusion criteria (n=9), declined to participate (n=6), cancelled operation (n=2)]. The remaining 145 patients comprised the study group. 83 patients complained CRBD in PACU (Fig 1). No differences in the patient characteristics surgery and anesthesia of two groups were observed (Table 1).

Compared with the control group, NRS was significantly lower in the oxycodone group at 5 min, 1/2h and 2 h, respectively ($P<0.05$, $P<0.01$. table 2). The differences in VAS scores in 5 min and 10 min in group

Oxy was significance lower compared with group Con ($P<0.05$). Sufentanil dosage within 6 hours after the operation was lower in observation group than in control group ($P<0.01$). There were significant differences in HR between two groups at 5, 1/2h and MAP at 5 min after administration of the study drugs (Table 3). There was no significantly difference of stay times of PACU. The incidences of requiring treatment of hypertension and agitation in group Oxy were lower compared with group Con (Table 4).

1 cases in two groups respectively experienced over-sedation ($P=0.00$); There were no significant differences nausea [3(78%) vs. 2 (50%); $P=0.00$], and vomiting [3 (85%) vs. 1 (57%); $P=0.32$] between group Q and group C. The difference in dizziness between the groups had no significance (Table 4).

Discussion

We have demonstrated that oxycodone reduces the severity of postoperative CRBD and postoperative opioid requirements in patients undergoing TURP.

CRBD is one of the most important factors causing postoperative irritability. The incidence of CRBD in previous studies was reported with various ranges of 64 to 90% after general anesthesia in varies operations. In this study, 83 (57%) of 145 patients complain CRBD at 6 h postoperatively undergoing TURP, which is lower than the incidence of our previous study^[19]. Previous studies had shown that application of muscarinic subtype 3 receptor inhibitors Oxybutynin, tolterodine, can substantially reduce the risk or severity of CRBD. But these drugs have many adverse effects, such as dry mouth, dizziness and facial flushing, can't be fully avoided^[7-8, 10]. CNS acting drugs and opioids receptors agonists ketamine, pentazocine, tramadol, were effective for the prevention and treatment of CRBD, but these agents can cause sedation and PONV after operation^[11-13].

Oxycodone is μ and κ opioid receptor dual agonist^[14]. It can be used intraoperatively and postoperatively to relieve pain, especially with unique analgesic effect on visceral pain^[15-17]. The onset of iv. oxycodone is 2-3 min, with a peak effects at 5min, and a elimination half effects ranged from 4-6 h. In our study, we administered oxycodone 0.03mg/kg, which is used to treatment of acute pain postoperative single injection, reduced the postoperative incidence of CRBD at 0, 1, 2, and 6h respectively.

The causes for CRBD include urethral mucosa injury due to urethral catheterization and urologic procedures, the central nervous system is in the inhibitory state and the patients psychologically reject catheter-related discomfort. The peripheral nerves of lower urinary tract consist of sacral parasympathetic nerve, thoracolumbar sympathetic nerve and sacral-pudendal nerve^[18]. The mechanism by which oxycodone relieves CRBD may be explained by its central nervous system to regulate and control the central excitability of vesical afferent reflex and sacral reflex. Secondly, oxycodone activates κ receptor to effectively relieve pain induced by spasms of vesical neck and urethra mucosal injury in patients. Previous studies showed that tramadol, a drug similar to oxycodone, was able to inhibit M1 and M3 muscarinic receptors^[9] to effectively prevent the occurrence of CRBD in addition to its opioid receptor agonism. I.V. oxycodone was clinically effective for the treatment of CRBD as an antimuscarinic agent,

but an inhibitory action of oxycodone on the activity of the detrusor muscle has not been reported in animal or human studies.

This study showed that oxycodone could reduce VAS scores and PCA dosage in all postoperatively periods, suggesting that oxycodone was able to relieve postoperative pain and reduce postoperative analgesic dosage in addition to its efficacy on CRBD. 3 cases in the observed group and 1 case in the controlled group, had finger pulse oxygen saturation less than 90%, the condition returned to normal after oxygen inhalation through the mask. Compared with the controlled group, the incidence of nausea and vomiting was not higher in the oxycodone group. There were no significant differences in other adverse reactions such as dizziness and sedation between the two groups.

Several limitations of the current study should be considered. First, various agents are routinely used to decrease CRBD. In this study, however, a direct comparison between the effect of oxycodone and others agents on the incidence of CRBD was not performed. Secondly, a single dose of 0.03 mg/kg oxycodone was used in this study. We did not evaluate the dose-dependent effect of oxycodone for the prevention of CRBD. In our previous study, however, shown that increase dose of oxycodone could be added accident of omit and dizzy^[19]. On the other hand, patients complained CRBD is acutely onset, causing irritability, increasing the workload of health care workers in PACU. Study should be conducted to observe the correlation of the treatment of CRBD with different doses of drugs on efficacy. Thirdly, our observational study used NRS as a measure of CRBD severity, but many studies used severity as an observational indicator. Although there were no significant difference in the NRS scores of CRBD between two groups. The severity may be uneven within the group, so the same dose of injection may have different effects.

In conclusion, 0.03mg/kg oxycodone can effectively decreased the severity of CRBD, and reduced VAS scores without causing severe adverse reactions in these patients after the operation. Therefore, oxycodone seems to be an effective treatment for CRBD during the postoperative period.

Declarations

Authors' contributions

L.J and P. ZH. performed, recruited patients, clinical practice, W. CW. performed CRBD measurements, and contributed to the manuscript. L.J and X. JC. Contribute to the design of the study. L.J. and X. JC. initiate the study, wrote the study proposal for the ethics committee, calculated the final statistics, and wrote the main part of the final manuscript.

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CONFLICT OF INTEREST

No other competing interests declared.

References

1. Bai Y, Wang X, Li X, et al. Management of Catheter-Related Bladder Discomfort in Patients Who Underwent Elective Surgery. *J Endourol*. 2015, 29(6): 640-64
2. Tauzin-Fin P, Stecken L, Sztark F. Catheter-related bladder discomfort in post-anaesthesia care unit. *Ann Fr Anesth Reanim (French)*, 2012,31(7-8):605-608
3. Sun JL, Lu YP, Huang B, et al. Effect of a novel analgesic disposable urinary catheter in prevention of restlessness caused by catheter-related bladder discomfort in general anesthesia patients in recovery period. *Zhonghua Yi Xue Za Zhi (Chinese)*, 2008, 88(25):1750-1752.
4. Cong LI, Zheng LIU, Fan YANG et al. Predictors of Catheter-related Bladder Discomfort after Urological Surgery. *J Huazhong Univ Sci Technol [Med Sci]*, 2014, 34(4): 559-562.
5. Li J, Zhu CF, Xiong JC, et al. Effects of oxycodone in treatment of catheter related bladder discomfort. *Zhong Guo Yi Shi Za Zhi (Chinese)*. 2016, 18(5): 594-596.
6. Nielsen CK, Ross FB, Lotfipour S, et al. Oxycodone and morphine have distinctly different pharmacological profiles: radioligand binding and behavioural studies in two rat models of neuropathic pain. *Pain*, 2007, 132(1): 289-300.
7. Agarwal A, Dhiraaj S, Singhal V, et al. Comparison of efficacy of oxybutynin and tolterodine for prevention of catheter related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Br J Anesth*, 2006, 96(3): 377-381.
8. Tauzin-Fin P, Sesay M, Svartz L, et al. Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy. *Br J Anaesth*, 2007, 99(4): 572-57
9. Agarwal A, Yadav G, Gupta D, et al. Evaluation of intra-operative tramadol for prevention of catheter-related bladder discomfort: a prospective, randomized, double-blind study. *Br J Anesth*, 2008, 101(4): 506-510.
10. Ryu JH, Hwang JW, Lee JW, et al. Efficacy of butylscopolamine for the treatment of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Br J Anaesth* 2013; 111:932–937.
11. Agarwal A, Dhiraaj S, Pawar S, et al. An evaluation of the efficacy of gubapentin for prevention of catheter-related bladder discomfort—a prospective—randomized—placebo, controlled, double-blind study. *Anesth Analg*, 2007, 105(5): 1454-1457.
12. Agarwal A, Gupta D, Kumar M, et al. Ketamine for treatment of catheter related bladder discomfort: a prospective, randomized, placebo controlled and double blind study. *Br J Anesth*, 2006, 96(5): 587-591.

13. [Lenz H, Sandvik L, Qvigstad E, et al.](#) A comparison of intravenous oxycodone and intravenous morphine in patient-controlled postoperative analgesia after laparoscopic hysterectomy. *Anesth Analg*, 2009, 109(4): 1279-1283.
14. McLaughlin JP, Myers LC, Zarek PE, et al. [Prolonged kappa opioid receptor phosphorylation mediated by G-protein receptor kinase underlies sustained analgesic tolerance.](#) *J Biol Chem*, 2004, 279(3): 1810-1818.
15. Staahl C, Dimcevski G, Andersen SD, et al. Differential effect of opioids in patients with chronic pancreatitis: an experimental pain study. *Scand J Gastroenterol* 2007; 42(2):383–390.
16. [Lenz H, Sandvik L, Qvigstad E, et al.](#) A comparison of intravenous oxycodone and intravenous morphine in patient-controlled postoperative analgesia after laparoscopic hysterectomy. *Anesth Analg* 2009; 109(4):1279-1283.
17. Friedman BW, Dym AA, Davitt M, et al. [Naproxen with Cyclobenzaprine, Oxycodone/Acetaminophen, or Placebo for Treating Acute Low Back Pain: A Randomized Clinical Trial.](#) *JAMA*. 2015, 314(15):1572-1580.
18. Yamanishi T. Chapple CR, Chess-Williams R. Which muscarinic receptor is important in the bladder? *World J Urol*, 2001, 19(2):299.
19. Xiong JC, Zhu CF, Li J, et al. effect of hydrocltic oxycodone with posteroperative pain after hysterscope. *Lin Chuang Ma Zui Xue Za Zhi (Chinese)*, 2015;31(9):607-608.
20. Xiong JC, Chen X, Weng CW, et al. Intra-operative Oxycodone Reduced Postoperative Catheter-Related Bladder Discomfort Undergoing Transurethral Resection Prostate: A Prospective, Double Blind Randomized Study. *Urology journal*, 2019, 16(4): 392-396.
21. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166: 1338-1344

Tables

Table1: Characteristics of patients, anesthesia and surgery.

Characteristics	Con group	Oxy group
Age[yr]	72±6	66±5
BMI[kg/m ²]	22±5	24±4
ASA class (□□/□)	33/8	30/11
Urinary catheter size(F16/F18)	29/12	26/14
Duration of anesthesia[min]	135±25	126±32
Duration of surgery[min]	99±24	95±18
Intraoperative remifentanil resumption[mg]	1.84±0.21	1.69±0.29
Intraoperative propofol resumption[mg]	697±185	731±223

Values are given as mean ±SD or number of patients (%)

Table 2Severity of postoperative CRBD, Anesthesia recovery course and treatment in PACU

Group Oxy					Group Con			
Time	0	5 min	1/2h	2h	0	5 min	1/2h	2h
NRS value	75±14	45±14#	32±14#	12±14*	82±14	72±14	45±14	28±14
Postoperative VAS value	3.15±0.12*	2.41±0.66*	1.69±0.67	1.73±0.17	5.72±0.21	2.89±0.14	3.52±0.33	3.06±0.41

Compared with group Con, * $P<0.05$ # $P<0.01$

Table 3.patient's vital signs of preoperative and postoperative

Index	Group	T0	T1	T2	T3
MAP [mmHg]	Group C	146±22	122±19	125±18	74±16
	Group Q	138±18	95±14*	76±16#	77±12
HR [bpm]	Group C	78±12	63±6	72±4	71±8
	Group Q	82±10	65±8	75±5	68±5
SpO2 [%]	Group C	97±1	98±2	99±1	98±2
	Group Q	98±1	96±2	97±2	98±1

Compared with group Con, * $P<0.05$ # $P<0.01$

Table4. Anesthesia recovery course and treatment in PACU and incidences of adverse reactions postoperative

	Control Oxy	Control Con
Sufentanil consumption(ug)	12.1±1.16*	9.2±0.85
Duration of PACU⏏min⏏	25±4 [#]	45±9
Agitation	0 [#]	5
Hypertension requiring treatment	2 [#]	6
Over-sedation	1	1
Nausea	3	2
Vomiting	3	1
Dizziness	2	0

Compared with group Con, * $P<0.05$ [#] $P<0.01$

Figures

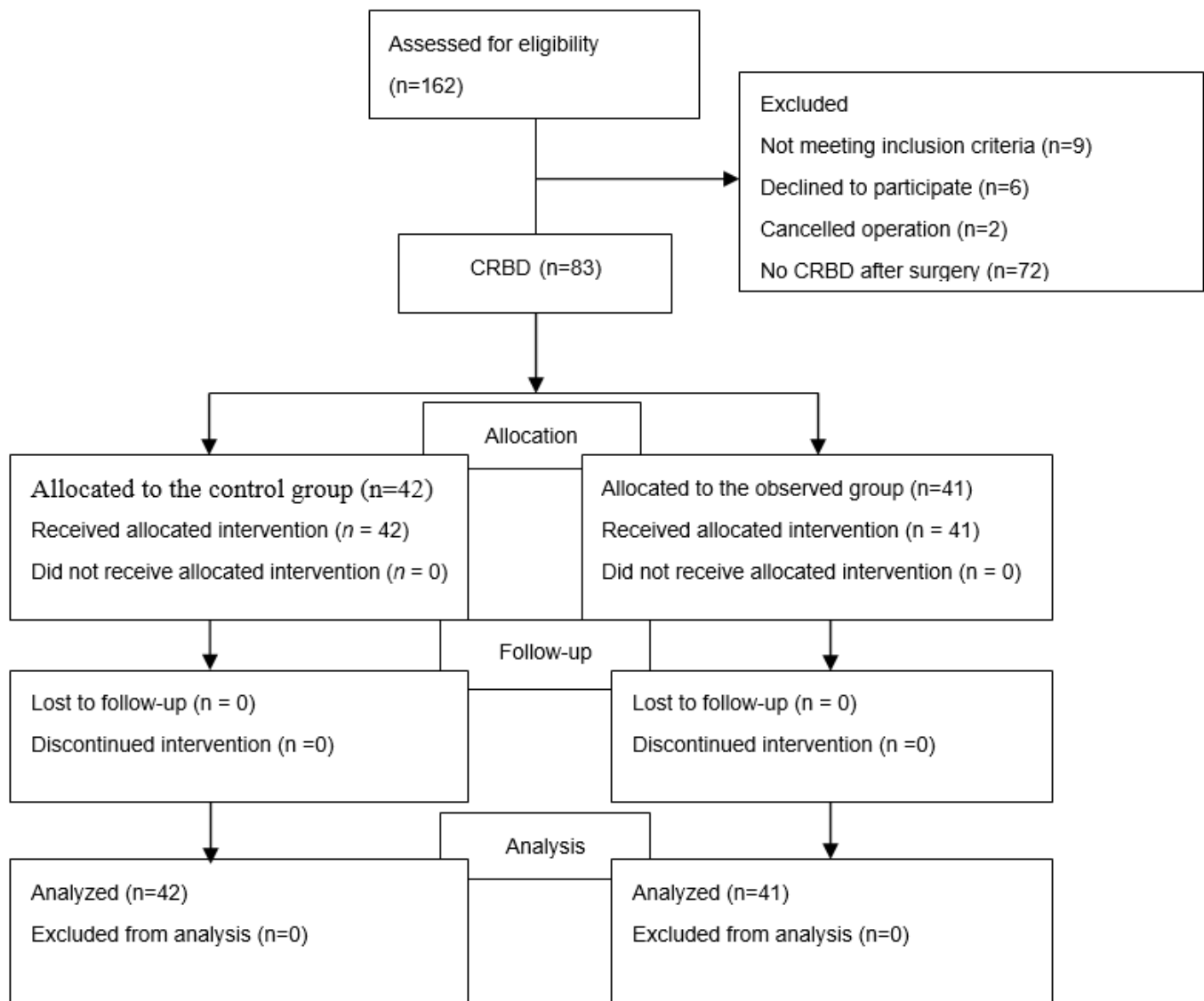


Figure 1

A consort diagram

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